CLINICAL REVIEW

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Established Name	Triamcinolone acetonide
Trade Name	Nasacort AQ
Therapeutic Class	Corticosteroid
Applicant	Sanofi Aventis
Priority Designation	S
Formulation	Aqueous Nasal Spray
Dosing Regimen	110 mcg once daily
Indication	Seasonal and Perennial Allergic Rhinitis
Intended Population	Children 2-5 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this supplemental NDA provide support for approval of the extension of the indication of Nasacort AQ (NAQ) nasal spray for the treatment of PAR and SAR for children 2-5 years from the current indication of adults, adolescents, and children 6-11 years of age. The adequate and well-controlled clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 mcg of NAQ nasal spray once daily provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo in children with PAR with or without SAR. Improvement in the instantaneous total nasal symptom score (iTNSS), which was the primary endpoint, while not statistically significant, did demonstrate a numeric advantage in children treated with NAQ over placebo as did most other secondary endpoints.

The extent of patient exposure to NAQ nasal spray during the development program for children 2-5 years of age was large compared to other clinical development programs for intranasal corticosteroids used to treat SAR and PAR in this young age group. Given its documented clinical efficacy and greater than 10 year history of approved use in children 6-11 years of age without major safety concerns, the safety profile of NAQ nasal spray as determined in the 2-5 year old population is acceptable. Adverse events attributable to the drug, such as epistaxis, were generally consistent with those observed for other intranasal corticosteroid products and were not significantly greater than found in the placebo. While there were no adverse reactions reported related to immunosupression or adrenal suppression in the clinical program, the results of the HPA-axis evaluation conducted as part of the pivotal clinical study could not rule out the potential for adrenal suppression in at least a subset of patients sensitive to the effects of corticosteroids.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant currently employs standard pharmacovigilance activities to monitor adverse events reported post-marketing for NAQ nasal spray. As NAQ is an intranasal steroid, a drug class with a well-known safety profile, has been marketed for over 10 years to adults and children 6-11 years of age, and no safety signals other than the known class effects of corticosteroids that were observed for NAQ in this NDA review, the current monitoring scheme remains acceptable.

1.2.2 Required Phase 4 Commitments

There are (b) (4) required Phase 4 commitments. Because of the potential negative effects of corticosteroids on growth, a required element of a pediatric clinical development program for nasal steroids is to assess the effects of the steroid nasal spray on growth in children (Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000). The Applicant is currently conducting a year long study to assess growth via stadiometry (b) (4) that was previously discussed with the Applicant. In addition, because the results of the HPA-axis evaluation conducted as part of the pivotal study could not rule out the potential for adrenal suppression in at least a subset of patients, a dedicated study to assess the HPA-axis whose design is consistent with the FDA Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, dated April, 2000 will (b) (4) be a required post-marketing commitment.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for the NAQ nasal spray program.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

NAQ nasal spray is a water-based, metered-dose pump spray formulation unit containing a microcrystalline suspension of the active drug substance, triamcinolone acetonide. Each actuation of the pump sprayer delivers 55 mcg of triamcinolone acetonide. NAQ was previously approved for the treatment of nasal symptoms of SAR and PAR in adults and adolescents 12 years of age and above on May 20, 1996. Additionally, a pediatric supplement subsequently submitted to support lowering the age range for which the drug is indicated to children 6-11 years of age was approved on September 26, 1997. This sNDA has been submitted to support the safety and efficacy of NAQ nasal spray, 110 mcg (2 sprays) once daily for use in children 2-5 years of age with PAR and SAR. The current approved dose of NAQ for adolescents and adults is 220 mcg once daily and for children 6-11 years of age the starting dose is 110 mcg once daily with the option of increasing to 220 mcg once daily if symptoms are not alleviated.

The clinical data submitted in support of this sNDA are derived from 3 studies performed in children 2-5 years of age, a 6-month pivotal safety and efficacy study in children 2-5 years old with PAR±SAR, a pharmacokinetic study used to support dose justification, and a knemometry study to assess the effect of NAQ on short-term bone growth.

Safety information in this application consisted primarily of safety information derived from the pivotal placebo-controlled study in children with PAR±SAR. This safety information included collection of adverse events, vital sign determinations, and HPA-axis assessments and a growth study.

1.3.2 Efficacy

The Applicant's data support the efficacy of NAQ nasal spray for the treatment of symptoms of PAR and SAR in children 2-5 years of age.

The efficacy of NAQ nasal spray 110 mcg once daily in children 2-5 years of age was demonstrated by virtue of achieving a statistically significant mean change from baseline over the entire treatment period in reflective total nasal symptom score (rTNSS) compared to placebo and showing a numerical difference in favor of NAQ over placebo in the primary endpoint of mean change from baseline in instantaneous total nasal symptom score (iTNSS).

1.3.3 Safety

The overall exposure in the NAQ nasal spray clinical development program is sufficient to allow for assessment of safety. The exposure, duration of exposure, and the proposed dose of NAQ nasal spray of 110 mcg once daily for children 2-5 years of age are also sufficient to allow for assessment of safety. The demographics of patients in the clinical program and exposure of subpopulations to NAQ nasal spray are adequate to provide an assessment of safety.

The safety of NAQ nasal spray for the treatment of symptoms associated with allergic rhinitis is supported by the Applicant's clinical studies. Known adverse events associated with local application of corticosteroids to the nasal cavity include epistaxis, nasal ulcerations, and nasal candidiasis. Epistaxis was observed in 5% of children in both the NAQ active treatment and placebo groups and remained at that approximate level during the 6-month open label extension period. Nasal ulceration and nasal candidiasis were not reported during either the 4-week double-blind or 6-month safety extension periods of the pivotal clinical study.

Adverse events associated with corticosteroid use in children include adrenal suppression and growth suppression. In this submission, the HPA-axis was studied in children as young as 2 years of age by assessing their blood cortisol levels in response to low-dose (1 mcg) cosyntropin stimulation. Although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at either the end of double-blind or open-label treatment periods versus screening in the placebo and NAQ groups, several children who received NAQ failed to show pre-specified increases in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation, suggestive of a possible treatment effect in a subset of subjects who may be more susceptible to the effects of corticosteroids.

In summary, NAQ nasal spray, at a dose of 110 mcg once daily was generally safe when administered to children 2-5 years of age. Adverse events were, for the most part, mild and infrequent and similar to those seen with the administration of other nasal corticosteroids. At the recommended dose and regimen, while NAQ nasal spray did not have a significant effect on changes in post-cosyntropin stimulation mean cortisol levels, suppression of the HPA-axis in a subset of children sensitive to the effects of corticosteroids could not be ruled out.

1.3.4 Dosing Regimen and Administration

A dose of 110 mcg once daily (one activation in each nostril) is recommended for children 2-5 years of age.

1.3.5 Drug-Drug Interactions

Drug-drug interactions were not assessed.

1.3.6 Special Populations

Special dosing is not recommended for NAQ nasal spray based upon gender, race, renal, or hepatic disease.

There are no adequate and well-controlled studies of NAQ in pregnant women. Therefore, NAQ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when NAQ Nasal Spray is administered to nursing women.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

NAQ nasal spray is a thixotropic, water-based metered-dose pump spray formulation unit containing a microcrystalline suspension of triamcinolone acetonide in an aqueous medium. Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0. Each actuation of NAQ delivers 55 mcg of triamcinolone acetonide from the nasal actuator.

The Applicant, Sanofi Aventis, submitted sNDA 20-468 on November 19, 2007, for Nasacort AQ nasal spray intranasal corticosteroid suspension, containing the active ingredient triamcinolone acetonide, for the treatment of nasal symptoms of SAR and PAR in adults and children ≥ 2 years of age. Nasacort AQ was previously approved for the treatment of nasal symptoms of SAR and PAR in adults and adolescents 12 years of age and above on May 20, 1996. A pediatric supplement subsequently submitted to support lowering the age range for which the drug is indicated to children 6-11 years of age was approved on September 26, 1997.

2.2 Currently Available Treatment for Indications

Including the product under review, there are currently 8 corticosteroid preparations formulated for intranasal administration indicated for the treatment of both seasonal and perennial rhinitis:

- Nasacort® AQ (triamcinolone) nasal spray and HFA aerosol
- Beconase® AQ (beclomethasone) nasal spray
- Flonase® (fluticasone propionate) nasal spray
    - Also available as a generic preparation
- Nasonex® (mometasone) nasal spray
- Rhinocort® Aqua (budesonide) nasal spray
- Nasarel® (flunisolide) metered nasal aerosol
- Omnaris® (ciclesonide) nasal spray
- Veramyst® (fluticasone furoate) nasal spray

They are all approved for patients 6 years of age or older with the exceptions that Flonase® is approved for children as young as 4 years, Nasonex® and Veramyst® for children as young as 2 years, and Omnaris® is not approved for patients < 12 years of age.

2.3 Availability of Proposed Active Ingredient in the United States

Nasacort AQ is marketed in 44 countries around the world, including the United States, Canada, and the European Union.

2.4 Important Issues With Pharmacologically Related Products

Because of limited systemic absorption when delivered intranasally and first-pass metabolism, NAQ nasal spray has low systemic bioavailability. However, as a potent corticosteroid it has the potential to produce the adverse events associated with corticosteroid administration. These adverse effects include adrenal suppression, the development of cataracts and glaucoma, and decreased growth in children.

2.5 Presubmission Regulatory Activity

An initial IND (39,306) for NAQ nasal spray was submitted on March 31, 1992 and NAQ was approved on May 20, 1996, for adult and adolescent patients 12 years of age and above with SAR or PAR. A pediatric supplement S-002 to NDA 20-468, consisting of two studies in a total of 542 children, (a 2 week study in children 6-11 years of age for SAR and a 12 week study in children 4-11 years of age with PAR) was approved on September 26, 1997, for the indication of SAR and PAR in patients 6 to 11 years of age. At the time, although pediatric patients down to the age of 4 years were enrolled, their number (a total of 7 children received NAQ at the proposed dose of 110 mcg/day) was considered insufficient to extend the approval down to 4 years of age. Subsequent to the approval of NAQ for children ≥ 6 years of age, the Division has had several discussions with the Applicant on the development plan for NAQ in children 2-5 years of age including:

- Agreement to the general content of the pediatric supplement to support approval for children 2-5 years of age is documented by Lydia McClain, MD in a "memo to file" dated August 27, 2003
- Correspondence dated June 14, 2005 in which the Division commented on the proposed pivotal study in children 2-5 years of age [(XRG5029C/3052), (see review dated January 15, 2004 by Tejashri Purohit-Sheth, MD)]
- Correspondence dated December 19, 2005, in which the Division and Applicant came to an agreement on the general content of this pediatric supplement
- Correspondence dated December 19, 2006 regarding clarification of the proposed statistical analysis plan

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Triamcinolone acetonide, USP, the active ingredient in NAQ nasal spray, is a synthetic fluorinated glucocorticoid chemically related to prednisolone. It has a molecular weight of 434.51 and the chemical designation 9-Fluoro-11ß, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with acetone ($C_{24}H_{31}FO_6$).

NAQ nasal spray is a thixotropic, water-based metered-dose pump spray formulation unit containing a microcrystalline suspension of triamcinolone acetonide in an aqueous medium. Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0. Each actuation of NAQ delivers 55 mcg of triamcinolone acetonide from the nasal actuator.

3.2 Animal Pharmacology/Toxicology

A full Pharmacology/Toxicology program was conducted for NAQ at the time of the initial NDA approval in 1996. No new additional data was submitted with this sNDA. A summary of animal pharmacology/toxicology data from the product label is included below.

In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg. In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg.

No evidence of mutagenicity was detected from in vitro tests (a reverse mutation test in Salmonella bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide. In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 15.0 mcg/kg. Triamcinolone acetonide caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 5.0 mcg/kg and above.

Triamcinolone acetonide is known to be teratogenic in rats, rabbits, and monkeys. In rats, TAA was teratogenic at inhalation doses of 20 mcg/kg and above, in rabbits, at inhalation doses of 20 mcg/kg and above and in monkeys at an inhalation dose of 500 mcg/kg (approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m2 basis). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in the monkey were cranial malformations.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data submitted in support of this NDA are derived from the studies performed as part of the Applicant's clinical development program. The application does not rely on reports in the medical literature or other sources of data. The review of efficacy was based exclusively on the reports of the clinical trials submitted with the original NDA application.

4.2 Tables of Clinical Studies

Study #	Design	Treatments Nasacort AQ QD	# of Subjects	Duration	Population	Study Objectives	Relevance to Review
XRG5029C/1000	PK study in 2-5 year olds	110 mcg	15	5 days	2-5 year olds with PAR±SAR	Pharmacokinetics	Dose Justification
RG5029Y-315	R, DB, PC, 2-week Crossover	110 mcg 220 mcg Flonase 200 mcg Placebo	56 55 51 55	2 week treatment periods	4-10 year olds with AR	Safety/assess for effects on growth	Knemometry Study
XRG5029C/3502*	R, DB, PC, PG Ages 2-5 years	110 mcg placebo	236 238	4 weeks for efficacy	2-5 year olds with PAR±SAR	Safety and efficacy (TNSS)	Pivotal PAR study

* Study 3502 also contained a 6-month open label extension in 428 subjects

4.3 Review Strategy

The Applicant identified three clinical studies in children 2-5 years of age as those that comprised the clinical development program for NAQ nasal spray (see table in Section 4.2, Table of Clinical Studies). These studies consisted of:

- A PK study used to support dose justification which compared the PK of NAQ in children 2-5 years of age who received NAQ 110 mcg/day to that of adults who received 220 mcg NAQ/day.
- A 2-week knemometry study to assess the effect of NAQ 110 and 220 mcg/day on short-term bone growth in children 4-10 years of age
- A 6-month pivotal safety and efficacy study in children 2-5 years old with PAR±SAR with efficacy determined at the 4-week time point and safety assessed through 6 months open-label exposure

The pivotal safety and efficacy study and knemometry studies are reviewed in depth in the Appendix to this review and form the primary basis for the assessments of safety and efficacy of FF nasal spray. Clinical pharmacology assessments that dealt with specific clinical safety issues such as the effect of NAQ on the HPA axis are summarized within the body of this review.

In addition to the three studies submitted to support the safety and efficacy of Nasacort AQ in children ages 2-5 years, Studies 312 and 314 (previously submitted with NDA 20-468 S-002 to support approval of NAQ for children ages 6-11 years of age) were also submitted as "supportive" studies. Only study 314 included children down to 4 and 5 years of age with PAR. However, in that study only one and six children four and five years of age, respectively, received the dose (110 mcg/day) of NAQ proposed for children 2-5 years of age in this application. These data on this small number of children, which have already been reviewed, do not make any meaningful contribution to the safety or efficacy of NAQ in children 2-5 years of age.

4.4 Data Quality and Integrity

Review of the data from the pivotal studies by the Biometrics reviewer (Dr. Feng Zhou) shows there is no for evidence of treatment-by-site interaction. Also, investigators that had a significant financial interest in the Applicant enrolled relatively few subjects in the trials. This would preclude them from having the ability to alter the outcomes of the pivotal studies. For these reasons, and because Nasacort AQ is already approved for the treatment of SAR and PAR and the efficacy data are as would be expected for the product, an audit by the Division of Scientific Investigation was not requested.

4.5 Compliance with Good Clinical Practices

The Applicant stated that they did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the application *[Module 1.3.3, other\debar.pdf]*. Clinical studies were conducted in compliance with recognized Good Clinical Practices.

4.6 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54.

5 CLINICAL PHARMACOLOGY

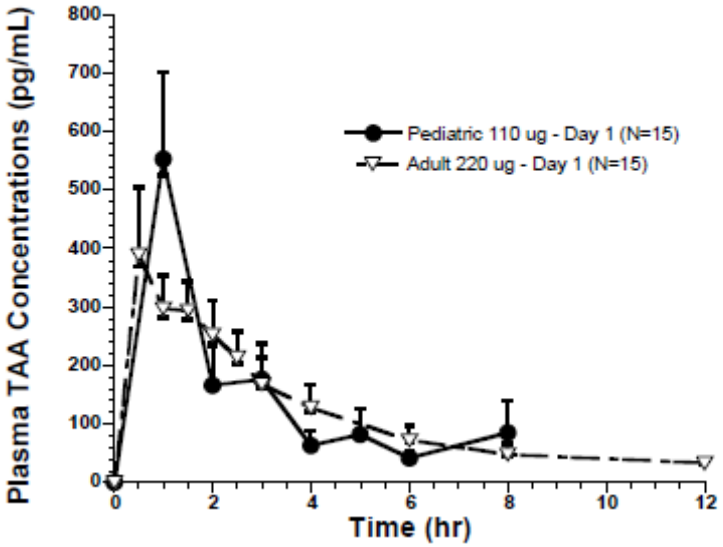
5.1 Pharmacokinetics

The pharmacokinetics of NAQ nasal spray 110 mcg once daily in the 2-5 year of age population were assessed in 2 clinical studies, study XRG5029C/1000 and study XRG5029C/3502. The objective of study XRG5029C/1000 was to compare the single dose and steady-state PK of triamcinolone acetonide (TAA) in pediatric patients 2 to 5 years of age who received NAQ nasal spray 110 mcg/day intranasally x 5 days to that of adult patients 18 to 50 years of age who received NAQ 220 mcg/day intranasally x 5 days with the goal of establishing that the systemic exposure of children who received 110 mcg/day of NAQ nasal spray would not exceed that of adults who received 220 mcg/day. The Applicant reasoned that comparable systemic PK determinations between children who received NAQ at a dose of 110 mcg/day and adults who received 220 mcg/day would support selection of the 110 mcg dose in the 2-5 year old population. A total of 30 patients (15 children; 15 adults) completed the study. Blood samples were obtained from each pediatric patient according to a staggered, sparse sampling strategy, prior to dose administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after dose administration one for day 1 and another for Day 5. Blood samples from adult patients were

obtained prior to dose administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after dose administration on Days 1 and 5 of each study period. Plasma was assayed for TAA with a validated liquid chromatography assay method with tandem mass spectrometric detection (LC-MS/MS) method.

The results demonstrated that the overall exposure to TAA produced by the 110 mcg dose in the pediatric patients was similar to the overall exposure to TAA produced by the 220 mcg dose in adults (see figure below). Additionally, no significant accumulation of TAA with multiple dosing in either pediatric or adult patients was apparent.

Study XRG5029C/1000: Mean triamcinolone acetonide concentration-time profile on Day 1 in pediatric (110 mcg dose) and adult (220 mcg dose) subjects who received Nasacort AQ once daily for 5 days



The pharmacokinetics of NAQ nasal spray was also determined in the pivotal study, XRG5029C/3502, a randomized, double-blind, parallel group, placebo-controlled, 4-week efficacy and safety evaluation of NAQ 110 mcg once daily, followed by a six-month open label safety extension in 474 children ages 2 to 5 years with PAR with or without SAR. The pharmacokinetic assessments were made only during the open-label extension portion of the study. Blood samples were obtained from each pediatric patient at 4 different study visits according to a sparse sampling strategy (2 samples between 1 to 4 hours and 2 samples between 5 to 8 hours). A population pharmacokinetic model was developed to assess the pharmacokinetic variability and the influence of demographic parameters (body weight, age, sex, and race) on TAA pharmacokinetics in pediatric patients from studies XRG5029C/1000 and XRG5029C/3502. The results demonstrated that TAA disposition was well described by a one compartment model with first order input. Covariate analysis revealed that the apparent total body clearance (CL/F) was correlated with age and body weight. The apparent volume of distribution (V/F) was strongly correlated with body weight. Race and sex were not significant covariates in the analyses *(see Module 2.7.2, Summary of Clinical Pharmacology Studies, Section 2.7, pages 20-27 and the Clinical Pharmacology review by Partha Roy Ph.D.).*

5.2 Pharmacodynamics

Assessments of the effects of NAQ nasal spray 110 mcg once daily on the HPA axis and short-term growth were performed in studies XRG5029C/1000, RG5029Y-315, and XRG5029C/3502. HPA axis assessments were made by determinations of AM serum cortisol levels (study XRG5029C/1000), change in 12-hour urinary cortisol/creatinine ratio (study RG5029Y-315), and by serum cortisol response to low-dose (1 mcg) cosyntropin stimulation test (study XRG5029C/3502). None of the HPA assessments were performed optimally. The serum cortisol assessments performed in study XRG5029C/1000 are of little value as they were determined after only 5 days of intranasal dosing. The 12 hour urinary determinations performed in study RG5029Y-315 were also not optimal for an assessment of HPA axis effects. The collection was for 12 hours rather than 24 hours and the short treatment period of 2 weeks precludes making any definitive conclusions of HPA axis effects.

While cosyntropin stimulation tests are not the preferred means to assess the effects of intranasal corticosteroids on the HPA axis outlined in the Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000), with respect to this sNDA for pediatric patients 2-5 years of age, the use of the low dose cosyntropin stimulation test as the method to assess a drug effect on the HPA axis in this young population, while not optimal, was appropriate. Among other reasons, which are discussed in Section 7.1.12 of this review, while the cosyntropin stimulation test may not be the preferred method to assess the HPA axis, it may be the only test that is practical for the youngest pediatric subjects. Presumably for this reason, in comments to the Applicant, DPAP has previously acknowledged the logistical problems with 24 hr urine or serum collections in very young children and has viewed the cosyntropin stimulation test as a reasonable alternative for this population (IND# 39,306 Medical Team Leader Memo by Lydia McClain, dated August 27, 2003).

Regarding the cosyntropin stimulation test results for study XRG5029C/3502, although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at the end of the 4-week double-blind treatment period versus screening in the placebo and NAQ groups or at the end of the open-label treatment period and screening, compared to placebo, more children who received NAQ failed to show pre-specified increases in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation. In addition, more children treated with NAQ during the 6 month open label safety extension failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation. These results are suggestive of a possible treatment effect in a subset of subjects who are more sensitive to the effects of corticosteroids.

Study RG5029Y-315 also assessed short-term lower leg growth using standard knemometric procedures and found that NAQ nasal spray at either 110 or 220 mcg administered once daily to children 4-10 years of age did not result in clinically meaningful suppression of lower leg growth.

A more in depth discussion of the results of HPA-axis assessments and growth assessment can be found in Sections 7.1.12 and 7.1.15, respectively and in the reviews of individual studies in the Appendix to this review.

5.3 Exposure-Response Relationships

Exposure-Response relationships were not formally addressed in this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Nasacort AQ nasal spray is currently indicated for treatment of nasal symptoms seasonal and perennial rhinitis in adults and children 6 years of age and older. This efficacy supplement proposes to extend the indication down to children 2 to 5 years of age.

6.1.1 Methods

Efficacy was assessed both on the basis of the submission of results from a single randomized, placebo-controlled, double-blind clinical trial in children 2-5 years of age as well as the previous demonstration of efficacy of NAQ in the treatment of PAR and SAR in children and adults 6 years of age and older.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for the pivotal efficacy and safety study in children 2-5 years of age was the mean change from baseline in daily instantaneous total nasal symptom score (iTNSS). The iTNSS was defined as the TNSS score determined immediately prior to dosing using the patients' parent/guardian assessments of four components (runny nose, stuffy nose, itchy nose, and sneezing), which were graded on a 4-point scale (absent, mild, moderate, and severe) with a maximum score of 12 and recorded in patient diaries. The primary analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) on the ITT population. Secondary efficacy endpoints prospectively identified by the Applicant included:

- Change from baseline over the double blind 4 week treatment period in mean daily reflective (previous 24 hrs) total nasal symptom scores (rTNSS).
- Weekly instantaneous TNSS
- Weekly reflective TNSS
- Instantaneous and reflective total symptom scores (TSS equals the TNSS score plus a score for total eye symptoms)
- Physician and subject global evaluation of efficacy (based on a 5 point (0-4) categorical scale

Reviewer's Comments: It should be noted that both the reflective TNSS score, while a secondary endpoint in the pivotal trial, is typically the preferred primary endpoint for allergic trials. Thus, positive findings for the rTNSS endpoint would likely be considered significant findings of efficacy. This is especially true due to the fact that the efficacy endpoints in the this phase 3 trial are based on parent/guardian assessments of the child's symptoms which introduces a level of

subjectivity and inconsistency in endpoint analyses not present in studies of adults with SAR or PAR thus making it more difficult to demonstrate statistical efficacy.

6.1.3 Study Design

The single pivotal study, labeled XRG5029/3502 (study 3502) was a randomized, double-blind, placebo-controlled, parallel group, multicenter, study of the efficacy and safety of Nasacort AQ nasal spray 110 mcg qd for 4 weeks in 474 pediatric subjects (236 Nasacort, 238 placebo) ages 2-5 years with PAR followed by a 6-month open-label safety extension. After a screening period of up to 14 days, subjects who met the specified symptom criteria (sum of symptom scores for nasal stuffiness, nasal discharge and sneezing of at least 18 out of a possible 36 for any 3 of the 5 days preceding the randomization visit (Visit 2) were randomized to 4 weeks treatment with Nasacort 110 mcg or vehicle placebo qd x 4weeks. Subjects were required to have at least a one year history of PAR with or without SAR. All subjects tested positive by prick test or RAST to at least one of the following perennial allergens: cat, dog, molds, dust mites, house dust, or cockroach. Subjects were seen in the clinic at screening, randomization and then every 2 weeks for a total of 4 visits during the efficacy phase of the study. Treatments were administered with the help of a parent/guardian once daily in the AM (one 55 mcg spray in each nostril). The use of loratadine (Claritin children's fruit flavored syrup) was allowed on an as-needed basis as a rescue allergy medication. The primary efficacy measure for the study was the mean change from baseline over the entire treatment period in daily instantaneous, total nasal symptom scores (iTNSS). Secondary measures included daily reflective, total nasal symptom scores (rTNSS) and physician and subject global efficacy scores. Subject compliance was assessed with the diary and by inspection of the medication bottles.

The duration of the trial was adequate to demonstrate efficacy; 4 weeks for PAR. Onset of action was not formally assessed.

6.1.4 Efficacy Findings

Disposition

A total of 762 subjects were screened for this study at the 59 investigative sites. Of these 762 subjects, 474 were randomized and received at least one dose of study drug and comprised the safety population of the double blind period.

Of these 474 treated subjects, 464 subjects (233 placebo, 231 NAQ) had at least one TNSS score recorded following double-blind treatment; thus, constituting the ITT population. Four hundred thirty two subjects (216 placebo, 216 NAQ) completed the double blind portion of the study and 427 subjects (215 placebo, 212 NAQ) met the criteria for the completer population. Premature withdrawals occurred in 22 (9.2%) of subjects in the placebo group compared with 20 (8.5%) in the NAQ group. The most common reason for subject withdrawal was lost to follow-up, with 7 and 6 subjects in the placebo and NAQ groups, respectively. Three subjects in the placebo group and one subject in the NAQ group discontinued due to lack of efficacy while 3 and 4 subjects discontinued due to AEs in the placebo and NAQ groups, respectively. *[Table 8 Study 3502 Study Report, page 73]*

For the open label period, 428 patients took at least one dose of NAQ while 357 (83.4%) completed the study. Of the 71 subjects who discontinued, 23 (32.4%) discontinued because they did not want to continue, 17 (23.9%) were lost to follow-up, and 15 (21.1%) discontinued due to an AE.

Treatment compliance was assessed by asking the subject or parent/guardian to note in the subject diary that a dose was given that day. Compliance was very similar across treatment groups with 98.3% of subjects in the placebo and NAQ treatment groups having compliance ≥ 80% *[Study 3502 Study Report, page 87]*.

For the open-label period, the mean number of days when subjects took NAQ was 152 days out of a total of 155 mean days.

Protocol Deviations

The definition of protocol deviation included failure to meet inclusion, exclusion, or randomization criteria, use of prohibited medications, and any other deviations deemed to have the potential to affect the interpretation of the primary efficacy variable. Reported deviations included not meeting the minimal symptom score requirement (18 subjects), lack of a 1 year history of PAR (1 subject), use of nasal or oral antihistamines within 3 days of screening (48 subjects, 24 each in the placebo and NAQ group), URI or sinus infection within 2 weeks of screening (7 subjects). There were no meaningful differences in the frequencies between the treatment groups. All subjects were excluded from the PP analysis. The most common deviation during the treatment period, other than the use of prohibited medications, was incorrect randomization of age stratum, which occurred in 2% to 4% of subjects in each treatment group *[Table 10 Study 3502 Study Report, page 76]*.

Primary and Secondary Endpoint Results

The primary efficacy endpoint was the change from baseline in the mean daily iTNSS over the 4 week double blind treatment period in the ITT Population. The key secondary endpoint from the point of determination of efficacy was the change from baseline in mean daily reflective TNSS (rTNSS) over the double-blind treatment period. This endpoint is often used (and is generally the preferred) primary endpoint in nasal corticosteroid SAR and PAR studies.

Total Nasal Symptom Score (TNSS) was calculated by adding the scores (0-3 for symptom absent, mild, moderate, and severe, respectively) for nasal stuffiness, nasal discharge, sneezing, and nasal itching. The TNSS did not include the score for the total eye symptoms (itching, tearing, and/or redness). Thus, the daily TNSS could range from 0 to 12.

The following table summarizes the mean changes in iTNSS and rTNSS from baseline and over the 4-week double blind treatment period.

Pivotal Study in Children 2-5 Years of Age with PAR±SAR after Treatment with Nasacort AQ Nasal Spray 110 mcg Once Daily *[Tables 18and 24, Study 3502 Study Report, pages 90 and 98]*

Study XRG5029/3502 Nasacort AQ 110 mcg Once Daily (ITT population)		
	Instantaneous Total Nasal Symptom Score (iTNSS)*	**Reflective Total Nasal Symptom Score (rTNSS)**
Mean Change from baseline: Placebo {n=233}	-1.92	-1.87
Mean Change from baseline: NAQ 110 mcg {n=231}	-2.28	-2.31
Difference from placebo, adjusted** mean change from baseline	-0.36	-0.44
p value	0.095	0.033

*iTNSS was identified as the primary endpoint
** ANCOVA with treatment and pooled site effects and the corresponding baseline values as covariate was used for the change from baseline (i.e., endpoint value – baseline value) with p values based on actual data

Reviewer's Comment: It is notable that in the allergic rhinitis clinical development program for fluticasone furoate (Veramyst), which was approved to treat SAR/PAR down to children 2 years of age, efficacy data in children 2 < 6 years of age were not included in analyses of the primary endpoints of the pediatric trials. It was, in general, supportive of results observed in the older children.

Baseline mean daily iTNSS values were very similar across both treatment groups (7.61 placebo, 7.52 NAQ). The adjusted mean change (±SE) from baseline over the double-blind period was -1.92 (±0.157) for the placebo group and -2.28 (±0.157) for the NAQ treatment group in the ITT population (2-5-year-olds) for a difference of -0.36. A statistically significant treatment effect was not observed in the primary efficacy variable in the ITT population (p=0.0946). Subgroup analysis by age (2, 3, 4, 5 year old strata) did not demonstrate a statistically significant difference in iTNSS for any single age group but when an ad hoc analysis was performed for the primary endpoint on the 3-5 year old subgroup, a statistically significant difference was noted (p = 0.0108) *[Table 20 Study 3502 Study Report, page 93]*.

Baseline values for mean daily rTNSS (the key secondary endpoint, change from baseline in the mean daily rTNSS over the 4 week double blind treatment period) were very similar across both treatment groups (7.87 for placebo, 7.596 for NAQ). The adjusted mean change (±SE) from baseline over the double-blind period was -1.87 (±0.151) for the placebo group and -2.31 (±0.151) for the NAQ treatment group in the ITT population (2-5-year-olds) for a difference of -0.44 that was statistically significant (p = 0.033). Subgroup analyses revealed, similarly to the primary endpoint analysis that older children (3-5 yrs) generally demonstrated a greater difference in rTNSS compared to 2 year olds and that whites appeared to have a bigger treatment effect than non-whites. *[Table 27 Study 3502 Study Report (Supportive Material), page 373]*.

Other secondary endpoints for the study included:

- change from baseline in mean daily iTNSS and rTNSS at Weeks 1, 2, 3, and 4
- change from baseline in mean daily iTSS and rTSS
- physician's global evaluation of efficacy
- subject's global evaluation of efficacy

For the weekly instantaneous and reflective TNSS determinations, while treatment differences in favor of NAQ tended to increase over time, a statistically significant difference between placebo and NAQ treatment groups was only seen for rTNSS at week 4 ($p = 0.042$). There were no differences in instantaneous or reflective TSS *[Tables 26-28, Study 3502 Study Report, pages 100-103]*.

Physician and subject global evaluation scores were supportive in that they generally revealed greater improvement in patients who received active treatment compared to those who received placebo *[Tables 29, 30, Study 3502 Study Report, pages 103-104]*.

6.1.5 Clinical Microbiology

No microbiology was submitted as this drug product is not an antimicrobial.

6.1.6 Efficacy Conclusions

In pediatric subjects aged 2-5 years, NAQ nasal spray 110 mcg once daily demonstrated a numerical, but not statistically significant, difference over placebo in favor of a reduction in PAR symptoms for the primary endpoint of mean change from baseline in iTNSS over the 4 week double blind treatment period. However, for the key secondary endpoint of mean change from baseline over the double-blind 4-week treatment period in daily rTNSS (which is commonly used as the primary endpoint in allergic rhinitis studies) treatment with NAQ demonstrated a statistically significant, beneficial treatment effect over placebo ($p = 0.033$). Subgroup analyses for the instantaneous and reflective TNSS endpoints revealed that older children (3-5 yrs) generally demonstrated a greater difference in TNSS compared to 2 year olds and that whites appeared to have a greater treatment effect than non-whites. Other secondary endpoints lend support to the efficacy of NAQ in this population as they generally revealed greater improvement in children who received active treatment compared to those who received placebo.

In summary, Nasacort AQ, at a dose of 110 mcg once daily, as evidenced by demonstrating a statistically significant mean change from baseline in rTNSS, a numerical difference over placebo in favor of a reduction in PAR symptoms for the primary endpoint of mean change from baseline in iTNSS, and other supportive data has been shown to be effective in the treatment of nasal allergic rhinitis symptoms in pediatric subjects 2-5 years of age with PAR.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The original global clinical development program for intranasal NAQ nasal spray consisted of 12 studies safety and efficacy studies in adolescents and adults with PAR and/or SAR. On the basis of the results of these studies, NAQ nasal spray was approved to treat the nasal symptoms of PAR and SAR in 1996. Three additional safety and efficacy studies performed in children ages 4-12 years supported the approval in 1997 of NAQ nasal spray to treat children with allergic rhinitis 6-11 years of age.

In the current application three additional studies have been submitted to support the safety and efficacy of NAQ nasal spray in children 2-5 years of age at a dose of 110 mcg/day. They include a 5 day clinical pharmacology study (Study XRG5029C/1000), a knemometry study to assess the effects of NAQ on short-term bone growth (Study RG5029Y-315), and the pivotal, double-blind, placebo-controlled safety and efficacy study in children ages 2-5 years with PAR±SAR which also contained a 6 month open-label safety extension (Study XRG5029C/3502). Because of the dissimilar designs of the studies, the results have not been integrated. For this review, the safety of NAQ nasal spray in the 2-5 year old patient population is based on the one well-controlled clinical study XRG5029C/3502. Study RG5029Y-315 (knemometry growth study) is reviewed individually in the Appendix of this clinical NDA review; any relevant safety findings observed are incorporated into in the body of this review. For example, the effects of NAQ on short-term bone growth in children will be summarized in Section 7.1.15. Due to its design (5-day, open-label treatment period in only 15 children), the clinical pharmacology, study XRG5029C/1000, does not meaningfully contribute to the safety evaluation of NAQ. A summary of relevant pharmacology used to support dose selection for the 2-5 year old population is summarized in Sections 5.1 and 5.2.

Because of the extensive previous clinical trial experience and > 14 years history of use of NAQ in adults and children 6-11 years of age, minimal evaluations of vital signs and clinical chemistry/hematology were performed. However, in addition to adverse events, each of the 3 clinical studies included evaluation of serum cortisol levels, 12-hour urine cortisol excretion, or cosyntropin stimulation as assessments of HPA-axis suppression. The results of these evaluations are reviewed in Section 7.1.12.

Since approval in 1996, the cumulative patient exposure to NAQ nasal spray is estimated to be greater than (b) (4) patients (from February 1997 to March 2007), assuming each patient received one inhaler spray canister. Therefore, the Applicant conducted a postmarketing surveillance evaluation to assess the sponsor's current safety pharmacovigilance database for Individual Case Safety Reports (ICSRs) reported for children receiving NAQ nasal spray worldwide the results of which are summarized in Section 7.1.17.

7.1.1 Deaths

There were no deaths in any of the studies reviewed for this NDA.

7.1.2 Other Serious Adverse Events

No SAEs were reported during the 4 week double-blind portion of the study. During the open label period, 7 subjects experienced 8 SAEs that included: appendicitis, aseptic meningitis, adenoidal hypertrophy, asthma, tonsillar hypertrophy, lymphadenitis, foreign body trauma, and diabetic ketoacidosis. All recovered without sequelae. Causality cannot be assessed as all subjects were receiving NAQ.

7.1.3 Dropouts and Other Significant Adverse Events

Three (1.3%) subjects from the placebo group and 4 (1.7%) from the NAQ group withdrew from the study during the 4 week double-blind period because of an AE. AEs leading to withdrawal in the placebo group were URI (2) and asthma, rhinalgia, and pyrexia (1 each). In the NAQ group discontinuations were due to URI, bronchitis, rhinitis, and sinus congestion (1 each) *[Table 50, Study 3502 Study Report, page 141]*.

During the uncontrolled open label period 15 subjects (3.5%) receiving NAQ discontinued from the study due to an AE. Asthma (5 subjects) and URI (4) were the leading causes for discontinuation *[Table 52, Study 3502 Study Report, page 144]*.
Reviewer's Comment: Adverse events associated with drop-outs were generally consistent with adverse events seen in subjects with SAR/PAR such as URIs and rhinitis and not more common with placebo versus NAQ.

7.1.4 Other Search Strategies

No other search strategy was employed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In this NAQ nasal spray sNDA submission, an AE was appropriately defined as "any unfavorable and unintended sign, symptom, syndrome, or illness that developed or worsened during the period of observation in the study". During the trial, AEs were elicited by several methods. At every visit (weekly for the first 4 weeks then every 4 weeks during the safety extension) the investigator or appropriate designee interviewed the parent/guardian/caregiver (of the patient) regarding AEs. In addition, the parent/guardian/caregiver observed the child (the patient) for AEs and was to report any events that occurred during the study on the patient diary card. For the purposes of the study, the period of observation for each individual patient extended from the time the parent/guardian/caregiver gave informed consent until the final visit of the study.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The CRF text for AEs was coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were summarized and grouped by primary System Organ Class (SOC) and by AE (i.e., Preferred Term) within a primary SOC. Results were displayed in the order of decreasing frequency.

7.1.5.3 Incidence of common adverse events

One hundred and fifteen subjects (48%) in the placebo group, 120 subjects (51%) in the NAQ group experienced at least one AE during the 4 week double-blind treatment period. The most common AE was cough which was reported in 8-9% of subjects in each treatment group. Pyrexia was also reported fairly frequently (7-8%) across treatment groups. Epistaxis was reported equally (5%) across both treatment groups. There were no reports of nasal ulceration *[Table 3, Study 3502 Study Report (Supportive Material), pages 520-524]*.

Reviewer's Comment: For labeling, the Sponsor should submit a table of AEs that lists AEs with an occurrence rate ≥ 2% and is greater in subjects receiving NAQ. The Applicant's proposed label (b) (4) [redacted]

For the uncontrolled open-label period, pyrexia, again was the most frequent AE (22%). Epistaxis was reported in 4.2 % of subjects, consistent with what was seen during the double-blind treatment period *[Table 25, Study 3502 Study Report (Supportive Material), pages 590-596]*.

7.1.5.4 Common adverse event tables

Summary of AEs from the 4-Week Double-Blind Period of Pivotal Study XRG5029C/3502 **with a Prevalence ≥ 2% during Treatment (Safety Population)** *[Adapted from Table 46, Study XRG5029C/3502 Clinical Study Report, page 129]*

	Placebo (N=238)	**Nasacort AQ 110 mcg (N=236)**
Adverse event	Total (%)	Total (%)
Cough	22 (9)	18 (8)
Pyrexia	19 (8)	16 (7)
Headache	10 (4)	13 (6)
Pharyngolaryngeal pain	10 (4)	13 (6)
Epistaxis	12 (5)	12 (5)
Nasopharyngitis	9 (4)	12 (5)
Upper abdominal pain	2 (1)	11 (5)

Vomiting	8 (3)	8 (3)
Diarrhea	3 (1)	7 (3)
Asthma	5 (2)	6 (3)
Rash	4 (2)	6 (3)
Excoriation	0	6 (3)
Rhinorrhea	4 (2)	5 (2)
Sinusitis	5 (2)	3 (1)

Coding dictionary for adverse events is Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 8.1.

7.1.5.5 Identifying common and drug-related adverse events

The relatively common (≥ 2%) AE that could be considered drug related was epistaxis. Epistaxis is noted to be a class-related AE associated with intranasal steroid spray use. For the pivotal trial, however, the incidence of epistaxis was essentially the same (5%) in the placebo and NAQ treated children and its frequency did not increase with longer term use (4.2% in the open-label safety extension). This is consistent with the incidence of epistaxis seen in adults treated with NAQ 220 mcg/day (3%). Nasal ulceration and nasal candidiasis, other AEs known to be associated with intranasal steroid use were not reported during either the 4-week double-blind or 6-month safety extension periods.

7.1.6 Less Common Adverse Events

The uncommon AEs that are pertinent to this review are those related to local corticosteroid effects on the nose and eyes such as nasal candidiasis and formation of cataracts. There were no AEs reported related to nasal candidiasis or cataract formation in the clinical development program for 2-5 years old children. Note that even the 6-month safety extension is thought to be too short a time period to be able to evaluate for cataracts as a result of intranasal corticosteroid use.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The only clinical laboratory testing that was performed in the development program was at baseline and at the end of a 5 day treatment period in study XRG5029C/1000, the pediatric/adult comparative PK study in which 15 children ages 2-5 years participated. No clinically relevant abnormalities were detected.

7.1.8 Vital Signs

Vital signs (heart rate and blood pressure) were assessed at baseline and at the 2 and 4-week study visits during the double-blind treatment period of study XRG5029C/3502 and at the 10, 17, and 24 week study visits during the open-label safety extension. There was no evidence of a clinically meaningful effect of NAQ nasal spray on any vital sign.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not assessed in the clinical development program for 2-5 year olds. This is acceptable as corticosteroids do not generally have an effect on cardiac activity.

7.1.10 Immunogenicity

Immunogenicity was not assessed in clinical studies as NAQ is not a therapeutic protein.

7.1.11 Human Carcinogenicity

Intranasal corticosteroids are not considered to be carcinogenic. Carcinogenicity was not formally assessed in the clinical development program. There were no reports of malignancy in this program.

7.1.12 Special Safety Studies

Assessments for HPA-axis Suppression

Assessments of the effects of NAQ nasal spray 110 mcg once daily on the HPA axis were performed in studies XRG5029C/1000, RG5029Y-315, and XRG5029C/3502. HPA axis assessments were made by determinations of AM serum cortisol levels (study XRG5029C/1000), change in 12-hour urinary cortisol/creatinine ratio (study RG5029Y-315), and by serum cortisol response to low-dose (1 mcg) cosyntropin stimulation test (study XRG5029C/3502). None of the HPA assessments were performed optimally. The serum cortisol assessments performed in study XRG5029C/1000 are of limited value as they were determined after only 5 days of intranasal dosing. The 12 hour urinary determinations performed in study RG5029Y-315 were also not optimal for an assessment of HPA axis effects as the collection was for 12 hours only rather than 24 hours and the treatment period was for 2 weeks rather than the recommended 6 weeks. However, the inclusion of an active comparator, fluticasone propionate, which is approved for treatment of people with SAR/PAR down to the age of 4 years, does provide a comparison with another nasal corticosteroid that is generally regarded as safe for use in the pediatric population.

Cosyntropin Stimulation Test

While cosyntropin stimulation tests are not the preferred means to assess the effects of intranasal corticosteroids on the HPA axis outlined in the Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000), with respect to this sNDA for pediatric patients 2-5 years of age, the use of the low dose cosyntropin stimulation test as the

method to assess a drug effect on the HPA axis in this young population of children is appropriate for several reasons and, while not optimal, adequate. Those reasons include:

- HPA axis assessments using the cosyntropin stimulation test have been performed previously in adults and in children 6-12 years of age who received up to twice the maximum recommended daily dose of NAQ (440 mcg). The continued use of the test to assess the HPA axis in 2-5 year olds is consistent with evaluations in the older populations which allows for a meaningful comparison across age groups.
- The collection of 12 or 24 hour urine specimens in subjects who are not toilet trained is virtually impossible and collection of serum cortisol AUC is probably not doable in this young of a population

Thus, while not the preferred method to assess the HPA axis, the cosyntropin stimulation test may be the only assessment that is practical for the youngest pediatric subjects. Presumably for the same reasons mentioned above, in comments to the Sponsor DPAP has previously acknowledged the logistical problems with 24 hr urine or serum collections in very young children and has viewed the cosyntropin stimulation test as a reasonable alternative for this population (IND# 39,306 Medical Team Leader Memo by Lydia McClain, dated August 27, 2003).

Given the limitations noted above, in the pivotal study, XRG5029C/3502, an evaluation of whether NAQ demonstrated an effect on the HPA axis was performed by assessing serum cortisol levels before and after stimulation with 1 mcg of cosyntropin in a subset of subjects at screening and both at the end of the 4 week double blind treatment period and at the end of the 6 month open label safety period. For both the double blind and open label periods, the data are presented as adjusted mean group differences of post-stimulation measurements at screening and at the end of the respective treatment period. Other analyses performed that may indicate an effect on the HPA axis include the number of subjects who have a 30 minute post-stimulation cortisol level of <496 nmol/L (18 mcg/dL) and/or post-stimulation increases in cortisol level of <193 nmol/L (7 mcg/dL).
Reviewer's Comment: Because of the wide variability of what could be considered a "normal" response to cosyntropin stimulation, it would be highly unlikely to detect an effect on the HPA axis by comparing mean group differences.

For the 4 week double blind period, a total of 28 subjects who received placebo and 33 who received NAQ comprised the HPA axis population. There were 11 subjects in each group who were 2-3 years of age.

The following table summarizes the adjusted mean group differences of post-stimulation measurements at screening and at the end of the 4 week double blind treatment period.

Analysis of Covariance on Mean Serum Cortisol Levels at the End of the Four Week Double Blind Treatment Period (Cosyntropin Evaluable Population) *[Table 53, Study 3502 Study Report, page 146]*

Time-point (nmol/L)	Placebo (N=28)		NASACORT AQ 110 µg qd (N=33)		Difference PBO - NAQ			p value
	Adjusted mean	±SE	Adjusted mean	±SE	Adjusted mean	95% CI	±SE	Treat-ment effect
Screening	369.65	29.842	336.81	28.090	32.84	(−47.9;+113.6)	40.256	0.4182
Change	−13.59	39.640	−43.13	37.229	29.54	(−78.0;+137.1)	53.581	0.5838

Analysis of covariance (ANCOVA) with treatment and pooled site effects and the corresponding baseline value as covariate was used for the change from baseline (ie, difference = endpoint value – screening value) with p values based on actual data.

From the table above, the adjusted mean differences (±SE) (i.e., Placebo - NAQ) between the post-stimulation changes at screening and at the end of the 4 week double blind treatment period were +32.84 nmol/L ±40.256 and +29.54 nmol/L ±53.581, respectively. An ANCOVA, with treatment and pooled site effects as covariates showed that the treatment or pooled site effect differences were not significant ($p>0.05$). While the mean data did not demonstrate any significant differences between placebo and NAQ in cosyntropin stimulation testing of the integrity of the HPA axis, when cortisol levels were categorized into pre and post-stimulation criteria that could be representative of a blunted HPA axis response, more subjects treated with NAQ had cortisol levels that were below the pre-specified criteria of an adequate response (pre-stimulation values < 138 nmol/L (< 5 mcg/dL), post-stimulation values < 496 nmol/L (< 18 mcg/dL), or post minus pre-stimulation differences < 193 nmol/L (< 7 mcg/dL) (see table below).

Descriptive Statistics on Serum Cortisol Criteria for Cosyntropin Stimulation Tests at the End of the 4 Week Double Blind Period *[Table 54, Study 3502 Study Report, page 147]*

Time-point	Criteria	Placebo (N=28)		NASACORT AQ 110 µg qd (N=33)	
		Screening (n [%])	End of double-blind period (n [%])	Screening (n [%])	End of double-blind period (n [%])
Pre-stimulation	<138 nmol/L (<5 µg/dL)	0	0	0	4 (12.1)
	≥138 nmol/L (≥5 µg/dL)	28 (100.0)	28 (100.0)	33 (100.0)	29 (87.9)
Post-stimulation	<496 nmol/L (<18 µg/dL)	0	2 (7.1)	1 (3.0)	4 (12.1)
	≥496 nmol/L (≥18 µg/dL)	28 (100.0)	26 (92.9)	32 (97.0)	29 (87.9)
Post-minus pre-stimulation difference	<193 nmol/L (<7 µg/dL)	1 (3.6)	4 (14.3)	5 (15.2)	8 (24.2)
	≥193 nmol/L (≥7 µg/dL)	27 (96.4)	24 (85.7)	28 (84.8)	25 (75.8)

Cosyntropin stimulation test results for the open label period were similar to those from the 4 week double blind period in that the mean differences between the post-stimulation changes at screening and at the end of the open label 6 month treatment period were not statistically significant ($p = 0.190$) *[Section 9.4.2 Study 3502 Study Report, page 148.]* However, when categorized into per and post stimulation criteria as outlined above, once again, after 6 months treatment with

NAQ more subjects failed to meet criteria indicative of an adequate cosyntropin stimulation response than when tested at screening (see table below).

Descriptive Statistics on Serum Cortisol Criteria for Cosyntropin Stimulation Tests at the End of the 6 Month Open-Label Period *[Table 55, Study 3502 Study Report, page 149]*.

Time-point	Criteria	NASACORT AQ 110 µg qd (N=49)	
		Screening (n [%])	End of open-label period (n [%])
Pre-stimulation	<138 nmol/L (<5 µg/dL)	1 (2.0)	3 (6.1)
	≥138 nmol/L (≥5 µg/dL)	48 (98.0)	46 (93.9)
Post-stimulation	<496 nmol/L (<18 µg/dL)	0	6 (12.2)
	≥496 nmol/L (≥18 µg/dL)	49 (100.0)	43 (87.8)
Post-minus pre-stimulation difference	<193 nmol/L (<7 µg/dL)	4 (8.2)	5 (10.2)
	≥193 nmol/L (≥7 µg/dL)	45 (91.8)	44 (89.8)

Cosyntropin evaluable was those in the safety population during open-label period with an on-treatment set of values for cortisol.

In summary, although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at either the end of double-blind or open-label treatment periods versus screening in the placebo and NAQ groups, more children who received NAQ failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation, both suggestive of a possible treatment effect in a subset of subjects who are more sensitive to the effects of corticosteroids.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There was no evidence of drug dependence in these studies. No evidence of withdrawal phenomena or rebound was described post-treatment.

7.1.14 Human Reproduction and Pregnancy Data

As all subjects were children < 6 years of age, no pregnancies occurred.

7.1.15 Assessment of Effect on Growth

Since a class effect of corticosteroids is to decrease longitudinal growth in children, a formal, randomized, placebo-controlled, cross-over knemometry growth study was conducted in 59 pre-pubertal children ages 4-10 years of age with SAR/PAR (Study RG5029Y-315). The study was conducted using standard and accepted knemometric techniques with lower leg measurements obtained at baseline and at the end of 2 week treatment periods separated by 2 week washout periods. The primary endpoint was to determine if treatment with NAQ nasal spray at doses of 110 and 220 mcg/day had a clinically significant suppressive effect (reduction in lower leg growth velocity of ≥50%) on short term lower leg growth. Flonase nasal spray, a marketed product approved to treat allergic rhinitis containing the active ingredient fluticasone propionate,

was included as an active comparator at a dose of 200 mcg/day. For the ITT population, the growth velocity during placebo treatment was 0.51 mm/week. For NAQ nasal spray 110 mcg the treatment effect was -0.14 mm/week, a reduction of 27.5% in the estimate of total growth/length. The treatment effect for NAQ nasal spray 220 mcg was -0.16, a reduction of 31.4% Although the difference in growth velocity for NAQ nasal spray 220 mcg was statistically significant compared to placebo (p=0.036 estimated by regression), the treatment effect was below the predetermined clinically significant level of 50%. For Flonase nasal spray 200 mcg, the reduction in growth velocity compared to placebo was similar at 25.5%. Study RG5029Y-315 is reviewed in detail in the Appendix of this NDA review.
Reviewer's Comment: Per the Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, a short-term growth study such as a knemometry study, while helpful, is not adequate to assess growth over the long term. The Applicant is currently conducting a year long study to assess growth via stadiometry (b) (4) *that was previously discussed with the Applicant.*

It should be noted that height was measured during the double-blind and open-label treatment periods of study XRG5029C/3502 and data for each subject was compared to current stature-for-age tables. While the Applicant concluded that the distribution of subjects by stature-for age evaluation was comparable between the stature-for-age percentiles plotted at screening and the end of open-label period in NAQ-treated subjects, this evaluation is inadequate to assess the effects of NAQ on growth in children *[Sections 9.6.2.1 and 9.6.2.2, Study XRG5029C/3502 Clinical Study Report, pages 152-154]*.

7.1.16 Overdose Experience

No overdose was reported in the clinical program. However, the clinical effects of chronic over use of corticosteroids is well described (HPA axis suppression, immune suppression, hypertension, osteopenia, etc.).

7.1.17 Postmarketing Experience

There is a greater than 10 year history of post-marketing experience of NAQ nasal spray. Over this period of time, no new trends or risk factors have been identified from adverse reaction reports that would change the overall benefit-risk profile of NAQ for use as indicated in the prescribing information. This finding was confirmed by a recent search of the Applicant's safety data base performed by the Global Pharmacovigilance and Epidemiology at Sanofi-Aventis that was included in the safety update (see Section 7.2.9).

7.2 Adequacy of Patient Exposure and Safety Assessments

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

The designs of the studies in this application, patient demographics, exposure of subpopulations, and duration of exposure to NAQ nasal spray are sufficient to allow for assessment of safety. Adequacy of patient exposure and safety assessments are reviewed in depth below.

7.2.1.1 Study type and design/patient enumeration

The table of clinical studies provided in Section 4.2 provides a summary of the clinical studies that comprise the clinical development program for children 2-5 years including descriptive information on study type, treatment groups, design, patient population, subject numbers, dosing schedule, and indication.

7.2.1.2 Demographics

Children enrolled in the single pivotal study, XRG5029C/3502, comprise the population to support the safety and efficacy of NAQ nasal spray in children 2-5 years of age with PAR. Demographics were similar across treatment groups and study populations (safety, ITT, PP, completer). The mean age was 3.5 and 3.6 years for the placebo and NAQ groups, respectively with the age distribution fairly equally distributed (21, 26, 32, and 22% of subjects being 2, 3, 4, or 5 years of age). The majority of the subjects were White (66%) with 15% being Black, and 13% listed as "Other". Males comprised 57% of the population. The demographic profile did not substantially change during the open-label period *[Tables 13 and 14 Study 3502 Study Report, pages 80 and 82]*
Reviewer's Comment: The almost equal age distribution of subjects, especially for the 2 and 3 year old children is commendable.

The mean duration (±SD) of diagnosed PAR was 30.9 months (±13.11) in the placebo group and 29.8 months (±13.09) in the NAQ treatment group. All subjects tested positive by prick test or RAST to at least one of the following: cat, dog, molds, dust mites, house dust, or cockroach. Baseline iTNSS symptom scores were very similar across treatment groups with scores of 7.61 and 7.52 in the placebo and NAQ groups, respectively *[Study 3502 Study Report, pages 84 and 90]*.

In summary, the demographics of patients in the clinical program and exposure of subpopulations to NAQ nasal spray are adequate to provide an assessment of safety.

7.2.1.3 Extent of exposure (dose/duration)

For the pivotal study, XRG5029C/3502, which consisted of a double-blind, placebo controlled, 4-week study period followed by all eligible subjects entering an open-label safety extension period, approximately 428 children ages 2-5 years of age were exposed to the proposed dose of NAQ nasal spray of 110 mcg once daily for 4 months and 212 subjects were exposed for a total

of 6 months. Given the narrow age range of the study population (children ages 2-5 years) and the long history of product use in older children and adults, the extent of exposure to the proposed dose of NAQ nasal spray of 110 mcg once daily in children 2-5 years of age is adequate to support the safety its use in that population.
Reviewer's Comment: The safety database for this young (2-5 year of age) population is actually quite large compared to other programs.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

All pertinent studies performed for the NAQ nasal spray development program for children ages 2-5 years are provided in this NDA application.

7.2.2.2 Postmarketing experience

The cumulative patient exposure to NAQ nasal spray is estimated to be greater than [redacted] patients (from February 1997 to March 2007), assuming each patient received one inhaler spray canister.

A postmarketing surveillance evaluation was performed by the Applicant to assess its current safety pharmacovigilance database for Individual Case Safety Reports reported for children receiving NAQ nasal spray worldwide. The review summarized spontaneous case reports in patients younger than 6 years of age, patients 6 to 12 years of age, and adolescent patients 13 years of age and older and adults. In the course of the review no new or unpredicted, based on the mechanism of action, safety signals were identified that would influence the use of NAQ nasal spray in children 2-5 years of age with allergic rhinitis.

7.2.2.3 Literature

Two literature searches were conducted by the Applicant and submitted with the sNDA package for the use of NAQ in allergic rhinitis. The dates of the searches were both from the year of product approval (i.e., January 1996) to January 1, 2007. One search was conducted on the following (literal) terms: Nasacort AQ or triamcinolone acetonide; seasonal allergic rhinitis, SAR, perennial allergic rhinitis, or PAR; and children or pediatric and the second search used the terms: Nasacort AQ, triamcinolone acetonide, inhaled, or intranasal spray; plus, ocular pressure, cataract, or growth. A total of 43 citations were found. There was no unknown safety information found that was relevant to this application *[Module 2.7.4 Clinical Summary of Safety, pages 146-149]*. See section 8.6, Literature Review, for a more complete description of the literature search results.

7.2.3 Adequacy of Overall Clinical Experience

Given the extent of the clinical programs completed for adults and older children and the long period the product has been approved for use (> 10 years) program, the studies performed in children 2-5 years of age constitute a sufficient database to assess the efficacy and safety of NAQ

110 mcg once daily in that population. The pivotal study was double blind, randomized, and placebo-controlled. All of the subjects had an appropriate diagnosis of PAR with current evidence of allergy. All were symptomatic at the time or enrollment. The Total Nasal Symptom Score, an accepted instrument for measuring efficacy in allergic rhinitis was used as the primary efficacy variable. The statistical analysis was appropriate. In addition, there were an adequate number of subjects exposed to the drug, and adequate numbers within demographic subsets to allow for an assessment of safety (see Sections 7.2.1.2 and 7.2.1.3).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The drug is a corticosteroid about which the basic mechanism of action and range of toxicities are known. No special animal or in vitro studies were performed.

7.2.5 Adequacy of Routine Clinical Testing

In the pivotal study adverse events were collected daily by the parent/guardian and reviewed by the investigators at clinic visits. Vital signs were also collected at clinic visits. Minimal clinical laboratory testing (chemistry, hematology) was performed. Given that NAQ is in a class (corticosteroid) about which there is extensive information, the fact that the bioavailability of NAQ nasal spray is relatively low, and that the drug has been marketed for older children and adults for over 10 years without any new safety concerns becoming apparent, this degree of safety monitoring is sufficient.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Appropriate studies to assess the absorption, distribution, metabolism, and clearance of NAQ nasal spray were submitted by the Applicant in support of the original NDA for the use of NAQ nasal spray to treat adult and adolescent patients 12 years of age and above with PAR/SAR (approved May 20, 1996). Additional pharmacokinetic information was submitted with the first pediatric supplemental NDA for extension of the indication to children 6-11 years of age (approved September 26, 1997) as well as for this pediatric supplement (se Section 5, Clinical Pharmacology).

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

Overall, the clinical studies were adequate to assess for both local and systemic corticosteroid-related AEs. While adequate for approval, the effects of NAQ nasal spray on growth in children will be further evaluated (b) (4) .

7.2.8 Assessment of Quality and Completeness of Data

As noted above, the Applicant's safety assessments were adequate to conduct an appropriate safety review.

7.2.9 Additional Submissions, Including Safety Update

A safety update by the Global Pharmacovigilance and Epidemiology at Sanofi-Aventis covering the time period received between 20 February 20, 2007 and February 19, 2008, was submitted by the Applicant on April 17, 2008. During this reporting period, NAQ has not been withdrawn from the market, nor have restrictions been placed on its use.
An estimation of patient exposure during this time period is difficult to determine, however, based on IMS data available to the Applicant from the fourth quarter of 2006 through the third quarter of 2007, approximately (b) (4) canisters of NAQ nasal spray were distributed.

During the reporting period, 111 case reports (109 spontaneous, 1 literature, and 1 regulatory) were reported during the time period coincident with this report. Four cases contained at least one event(s) assessed as "serious and unlisted" (3 for cataract and 1 for osteopenia).
Reviewer's Comment: No new trends or risk factors were identified from the reports received that would change the overall benefit-risk profile of Nasacort AQ for use as indicated in the prescribing information. However, while the frequency, nature, and severity of the reported events in this one year interval do not reveal a new safety signal for nasally administered triamcinolone, the active drug substance in NAQ, the product label should be updated to include the "unlisted" serious adverse reaction reports of cataracts and (b) (4) *, which are known side effects of chronic corticosteroid use yet are not included in the current label.*

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

Adverse events associated with corticosteroid use include adrenal suppression, growth suppression in children, and cataract formation. Regarding the cosyntropin-stimulation evaluation of the HPA-axis conducted as part of the pivotal clinical study, although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at either the end of double-blind or open-label treatment periods versus screening in the placebo and NAQ groups, more children who received NAQ failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation, both suggestive of a possible treatment effect in a subset of subjects who are more sensitive to the effects of corticosteroids. For this reason, a dedicated HPA axis study should be performed as a post-marketing commitment.

Known AEs associated with local application of corticosteroids to the nasal cavity include epistaxis, nasal ulcerations, and nasal candidiasis. Epistaxis was observed in 5% of children in both the NAQ active treatment and placebo groups and remained at that approximate level during the 6-month open label extension period. Nasal ulceration and nasal candidiasis were not reported during either the 4-week double-blind or 6-month safety extension periods of the pivotal clinical study.

In summary, no new or different safety signals were seen regarding any known side effects of intranasal corticosteroids specifically, epistaxis, nasal ulcerations, or nasal candidiasis. Although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at either the end of 4-week double-blind or 6-month open-label treatment periods

versus screening in the placebo and NAQ groups, more children who received NAQ failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation. Thus an effect on the HPA axis in a subset of subjects who are sensitive to the effects of corticosteroids cannot be excluded. For this reason, a dedicated HPA axis study should be performed as a post-marketing commitment.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Due to the dissimilar nature of the clinical studies performed to support approval of NAQ nasal spray for use in children 2-5 years of age, pooling of or combining data was not appropriate.

7.4.2 Explorations for Predictive Factors

Due to the focused nature of the study population (children 2-5 years of age), the evaluation of a single 110 mcg dose of NAQ, and the single placebo-controlled, double-blind, parallel-group, 4-week treatment period used to support the safety and efficacy of NAQ nasal spray in children 2-5 years of age, explorations for dose and time dependency for adverse findings and demographic analyses could either not be performed or would not yield meaningful information.

7.4.3 Causality Determination

There were no unusual or rare adverse events that require a causality determination. All of the common adverse events (e.g., epistaxis) observed were those commonly seen in this class of drug, in this patient population and in this mode of administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for NAQ nasal spray in children 2-5 years of age is 110 mcg once daily (one activation/nostril). This is in contrast to the approved dose for children 6-11 years of age, in which a starting dose of 110 mcg is recommended with an option to increase the dose to 220 mcg once daily if not adequately responding, or the adult dose of 220 mcg NAQ/day. The proposed dose was arrived at by establishing the comparability of systemic exposure of 110 mcg NAQ in 2-5 year olds to that of adults receiving 220 mcg/day in order to avoid a higher systemic exposure to corticosteroids and then demonstrating the efficacy and safety of the 110 mcg dose in clinical studies.

8.2 Drug-Drug Interactions

Formal drug-drug interactions have not been studied for NAQ nasal spray.

8.3 Special Populations

Populations other than pediatric subjects 2-5years of age were not studied for this sNDA submission. It should be noted that for the entire NAQ clinical development program studies of NAQ nasal spray did not include sufficient numbers of subjects aged 65 and over to determine whether geriatric subjects respond differently from younger subjects.

8.4 Pediatrics

The treatment of children 2 to 5 years of age is covered in the body of the application.
The applicant requested and has been granted a waiver for studies in children < 2 years of age due to safety concerns with the use of corticosteroids via nasal inhalation in children < 2 years of age together with the fact that there are other treatments available for the treatment of symptoms of allergic rhinitis in this younger population.

8.5 Advisory Committee Meeting

NAQ is currently approved in patients 6 years of age and older for the treatment of nasal symptoms of SAR and PAR. Because this supplement proposes to extend the indication in children 2- 5 years of age, a Pulmonary Allergy Advisory Committee meeting was not held for this sNDA.

8.6 Literature Review

A general literature search was conducted by the Applicant and submitted with the sNDA package for the use of NAQ in allergic rhinitis. The dates of the search were from the year of product approval (i.e., January 1996) to January 1, 2007. The search was conducted on the following (literal) terms: Nasacort AQ or triamcinolone acetonide; seasonal allergic rhinitis, SAR, perennial allergic rhinitis, or PAR; and children or pediatric. The literature search was not restricted by language, as long as the abstract was available in the English language. A total of 28 citations were found. A second general literature search was conducted with the same date range with the following (literal) terms: Nasacort AQ, triamcinolone acetonide, inhaled, or intranasal spray; plus, ocular pressure, cataract, or growth. An additional 16 citations were found. The following online databases were searched for the indicated time period:

- MEDLINE
- Biosis Previews
- EMBASE
- International pharmaceutical abstracts
- Derwent Drug File

The sponsor then examined the results of the searches for clinical relevance and excluded one citation that related to CMC issues. The remaining 43 citations were reviewed and summarized by the Applicant's pharmacovigilance officer. Summaries of the citations confirmed that inhaled and intranasal corticosteroids have the potential to cause dose-related suppression of the HPA axis and growth retardation, generally at high doses. For example, Skoner et al., demonstrated that asthmatic children treated with 600 mcg triamcinolone acetonide by inhalation/day grew

0.79 and 0.59 cm less over the course of a year than asthmatic children not treated with steroids or normal children, respectively (J Allergy Clin Immunol 1999; 103:S61). However, there was no unknown safety information found that was relevant to this application *[Module 2.7.4 Clinical Summary of Safety, pages 146-149]*.

8.7 Postmarketing Risk Management Plan

The Applicant currently employs standard pharmacovigilance activities to monitor adverse events reported post-marketing for NAQ nasal spray. As NAQ is an intranasal steroid, a drug class with a well-known safety profile and has been marketed for over 10 years to adults and children 6-11 years of age, the monitoring activities were acceptable. As no safety signals other than the known class effects of corticosteroids were observed for NAQ in this NDA review, the current monitoring scheme remains acceptable.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

From a clinical perspective, the data submitted in this supplemental NDA provide support for approval of the extension of the indication of Nasacort AQ (NAQ) nasal spray for the treatment of PAR and SAR for children down to the age of 2 years from the current indication of adults, adolescents, and children 6-11 years of age. The adequate and well-controlled clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 mcg of NAQ nasal spray once daily provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo in children with PAR with or without SAR. While the rTNSS was not the pre-determined primary endpoint, it is a commonly used and accepted clinical primary endpoint in studies used to assess the effectiveness of therapies for allergic rhinitis. The iTNSS, which was the primary endpoint, while not statistically significant, did demonstrate a numeric advantage in children treated with NAQ over placebo as did most other secondary endpoints.

The extent of patient exposure to NAQ nasal spray during the development program for children 2-5 years of age was large compared to other clinical development programs for intranasal corticosteroids used to treat SAR and PAR in this young age group. Given its documented clinical efficacy and greater than 10 year history of approved use in children 6-11 years of age without major safety concerns, the safety profile of NAQ nasal spray as determined in the 2-5 year old population is acceptable. Adverse events attributable to the drug, such as epistaxis, were generally consistent with those observed for other intranasal corticosteroid products and were not significantly greater than found in the placebo. While there were no adverse reactions reported

related to immunosupression or adrenal suppression in the clinical program, the results of the HPA-axis evaluation conducted as part of the pivotal clinical study could not rule out the potential for adrenal suppression in at least a subset of patients sensitive to the effects of corticosteroids.

9.2 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this supplemental NDA provide support for Approval of the extension of the indication of Nasacort AQ (NAQ) nasal spray for the treatment of PAR and SAR for children down to the age of 2 years from the current indication of adults, adolescents, and children 6-11 years of age. The adequate and well-controlled clinical study performed in children 2-5 years of age demonstrated that the proposed dose of 110 mcg of NAQ nasal spray once daily provided a statistically significant improvement in reflective total nasal symptom score (rTNSS) compared to placebo in children with PAR with or without SAR. While the rTNSS was not the pre-determined primary endpoint, it is a commonly used and accepted clinical primary endpoint in studies used to assess the effectiveness of therapies for allergic rhinitis. The iTNSS, which was the primary endpoint, while not statistically significant, did demonstrate a numeric advantage in children treated with NAQ over placebo as did most other secondary endpoints.

Given its documented clinical efficacy and greater than 10 year history of approved use in children 6-11 years of age without major safety concerns, the safety profile of NAQ nasal spray as determined in the 2-5 year old population is acceptable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant currently employs standard pharmacovigilance activities to monitor adverse events reported post-marketing for NAQ nasal spray. As NAQ is an intranasal steroid, a drug class with a well-known safety profile, has been marketed for over 10 years to adults and children 6-11 years of age, and no safety signals other than the known class effects of corticosteroids were observed for NAQ in this NDA review, the current monitoring scheme remains acceptable.

9.3.2 Required Phase 4 Commitments

There are (b) (4) required Phase 4 commitments. Because of the potential negative effects of corticosteroids on growth, a required element of a pediatric clinical development program for nasal steroids is to assess the effects of the steroid nasal spray on growth in children (Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000). The Applicant is currently conducting a year long study to assess growth via stadiometry (b) (4) that was previously discussed with the Applicant. In addition, because the results of the HPA-axis evaluation conducted as part of the

pivotal study could not rule out the potential for adrenal suppression in at least a subset of patients, a dedicated study to assess the HPA-axis whose design is consistent with the FDA Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, dated April, 2000 will also be a required post-marketing commitment.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

The original label for Nasacort AQ Nasal Spray dates from the time of initial approval for the SAR and PAR indications in adults with allergic rhinitis in 1996. Due to the long length of time since the product has been approved, much of the labeling, while correct, is out of date when compared with current labels of recently approved nasal corticosteroid products used to treat SAR and PAR. Therefore, one of the principle goals for the Nasacort AQ label will be to ensure it is in the correct PLR format is as now required and to update each section to be as consistent as possible with DPAP's current labeling of intranasal corticosteroids indicated for SAR and PAR, while acknowledging that due to the age of the product and label, that complete consistency with the labels of newly approved locally active corticosteroid products indicated for treatment of SAR and PAR is not entirely feasible. The label issues that require revision include:

- Ensure the label has been appropriately converted into the new PLR format
- Reorganize Section 2, Dosage and Administration, to reflect the added indication for children with SAR/PAR 2-5 years of age and streamline and state explicitly dose-titration instructions.
- Update Section 5, Warnings and Precautions, to reflect the current class warnings for corticosteroid products.
- Revise Section 6, Adverse Reactions
    - Revise AE table to reflect AEs > 2% and greater than placebo
    - Add AE data from children 2-5 years of age
    - Insert a Postmarketing Experience Section which is completely lacking in the current label.
- Revise Section 8, Use in Specific Populations, to include updated use in pregnancy, pediatric, and geriatric class labeling.
- Revise Section 12, Clinical Pharmacology, to remove (b) (4) fro the mechanism of action section and update the pharmacokinetic and pharmacodynamics sections with new data in children 2-5 years of age.
- Revise Section 14, Clinical Studies, to better reflect the results of the clinical study demonstrating efficacy in patients 2-5 years of age.
- Expand Section 17, Patient Counseling Information. Note that at the time of this review, consultation regarding appropriate changes in the PPI is pending.

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

STUDY # XRG5029C/3502

A randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of NASACORT® AQ 110 mcg qd, followed by six-month open-label safety in children ages 2-5 years with perennial allergic rhinitis

Protocol

Administrative

Study initiated: March 04, 2004
Study completed: March 06, 2006
Clinical Centers: 64 study sites: all in the United States.
Study report dated: June 2007
Study Sponsor: Sanofi Aventis
Medical Officer: George Georges, M.D.

There were 5 amendments to this clinical study protocol: Protocol amendment no. 1, dated September 2, 2003; Protocol amendment no. 2, dated November 5, 2003; Protocol amendment no. 3, dated December 19, 2003; Protocol amendment no. 4, dated January 26, 2004; and Protocol amendment no. 5 dated July 25, 2005. Protocol amendment no. 1 increased the number of subjects from 40 to 80 for HPA axis evaluation, as requested by FDA. Only protocol amendment 5 (reduction in the number of subjects from 80 to a minimum of 40 for HPA axis evaluation, as permitted by DPAP) was introduced after patient enrollment was begun.

Objective/Rationale

The primary objectives of this study were to demonstrate the efficacy of administration of Nasacort AQ 110 mcg once daily (qd), compared with placebo in children 2 to 5 years of age with perennial allergic rhinitis (PAR) and to assess the safety of Nasacort AQ 110 mcg qd in children 2 to 5 years of age with PAR. Other objectives included evaluating the systemic effect of Nasacort AQ on the on the hypothalamic-pituitary-adrenal (HPA) axis in a subset of children 2 to 5 years of age.

Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group, multicenter, study of the efficacy and safety of Nasacort AQ nasal spray 110 mcg qd for 4 weeks in 474 pediatric subjects (236 Nasacort, 238 placebo) ages 2-5 years with PAR. The safety of Nasacort AQ was further characterized during a 6-month open-label safety extension.

After a screening period of up to 14 days, subjects who met the specified symptom criteria (sum of symptom scores for nasal stuffiness, nasal discharge and sneezing of at least 18 out of a possible 36 for any 3 of the 5 days preceding the randomization visit (Visit 2) were randomized to 4 weeks treatment with Nasacort 110 mcg or vehicle placebo qd x 4weeks. Subjects were seen in the clinic at screening, randomization and then every 2 weeks for a total of 4 visits during the efficacy phase of the study. Treatments were administered with the help of a parent/guardian once daily in the AM (one 55 mcg spray in each nostril). The use of loratadine (Claritin children's fruit flavored syrup) was allowed on an as-needed basis as a rescue allergy medication. The primary efficacy measure for the study was the mean change from baseline over the entire treatment period in daily instantaneous, total nasal symptom scores (iTNSS). Secondary measures included daily reflective, total nasal symptom scores (rTNSS) and physician and subject global efficacy scores. Subject compliance was assessed with the diary and by inspection of the medication bottles. Safety measures included AEs, physical examinations, vital signs, and an assessment of HPA axis using the low dose (1 mcg) cosyntropin stimulation test. Pharmacokinetic assessments of Nasacort AQ were also conducted. At the 4th study visit subjects were given the option to continue into the open-label period. There were four additional visits approximately every 6 weeks over the 24 week open-label safety phase of the study.

Study Population

A total of 474 subjects were enrolled in the study, 236 in the Nasacort 110 mcg qd group and 238 in the placebo group.

Inclusion Criteria

1. Child of either sex, 2-5 years of age
2. At least 1-year history of PAR with or without SAR
3. No clinically relevant deviation from normal in either a general physical examination as determined by the investigator
4. Sum of symptom scores for nasal stuffiness, nasal discharge and sneezing of at least 18 out of a possible 36 for any 3 of the 5 days preceding the randomization visit (Visit 2) including the morning of Visit 2 (i.e., 3 symptoms x 3 maximum score x 4 days) [Symptoms scores were recorded on a diary card with assistance from responsible care provider.]
5. Positive or documented (in the past year) skin prick test or RAST to a relevant perennial allergen in the subject's environment [A test was considered positive if the wheal produced by the allergen was at least as large as that caused by a positive control (histamine), or was at least 3 mm greater than the wheal of a negative control (saline).]
6. Subjects undergoing cosyntropin stimulation test with a morning (8 AM±1 hour) pre-stimulation serum cortisol level ≥5 mcg/dL (138 nmol/L) and 30 minutes post-stimulation serum cortisol level ≥18 mcg/dL (496 nmol/L) at baseline

Exclusion Criteria

1. Asthma, requiring chronic use of inhaled or systemic corticosteroids in the previous 6 months
2. Upper respiratory tract infection or sinus infection requiring antibiotic therapy within 2

weeks prior to screening or viral upper respiratory tract infection within 7 days of screening
3. Nasal polyps, deviated septum, or nasal/facial anatomic abnormalities that interfere with symptom evaluation and/or use of intranasal corticosteroids
4. Treatment with more than 2 courses of systemic corticosteroids (each course not exceeding 14 days) within 1 year of screening
5. Intranasal or ocular corticosteroids use within 2 weeks of screening
6. Oral, inhaled, or intravenous corticosteroids use within 1 month of screening Intramuscular or intra-articular corticosteroids use within 3 months of screening
7. High potency dermatological corticosteroids use within 1 month of screening
8. Oral leukotriene modifiers use within 1 week of screening
9. Nasal or oral antihistamines or oral or nasal decongestants use within 3 days of screening
10. Current or history of cataract or glaucoma
11. Treatment with any investigational product or use of an investigational device within 1 month of screening
12. Immunotherapy, with the exception of a stable maintenance schedule, for at least 1 month prior to screening
13. History of hypersensitivity to glucocorticoids or to any excipients of the formulation

Any waiver of these inclusion and exclusion criteria had to be approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the subject.

All female subjects in this pediatric study were premenarchal; male subjects were prepubescent.

Withdrawal Criteria

Subjects could have been withdrawn from this study at any time for any of the following reasons:

- At their own request or at the request of their legally authorized representative.
- If, in the investigator's opinion, continuation in the study would have been detrimental to the subject's well-being.
- At the specific request of the sponsor.
- Occurrence of an intolerable treatment-emergent adverse event (TEAE) as determined by the investigator and/or subject
- At the request of the Sponsor

In all cases, the reason and date of withdrawal was to be recorded on the case report form (CRF) and in the subject's medical records. Whenever possible, all examinations scheduled for the final visit were to be performed on all subjects who received investigational product, but did not complete the study according to the clinical study protocol. Subjects who withdrew from study were not replaced.

Prohibited Medications

The following treatments were not allowed during the double-blind or open-label period:

- Treatments for breakthrough symptoms of AR (antihistamines, decongestants, topical vasoconstriction/decongestant eye preparations, anticholinergics), excluding the rescue

medication

- Systemic, nasal, ocular, inhaled, or high potency dermatological corticosteroids
- Nasal sprays or leukotriene modifiers
- Other medications that could have interfered with the study (e.g., centrally acting cardiovascular drugs, neuroleptics).

Study Treatments

The active investigational product was supplied by the Sponsor as the commercially available formulation of Nasacort AQ Nasal Spray. This was a metered-dose pump spray containing an unscented, thixotropic, microcrystalline suspension of triamcinolone acetate (TAA) in an aqueous medium. Each spray delivered 55 mcg TAA from the nasal actuator. One 16.5 gram bottle provided 120 actuations. The investigational product was to be stored at controlled room temperature (68°F to 77°F; 20°C to 25°C) and in a locked area with restricted access.

Placebo nasal spray was identical in composition to the active drug but without TAA. The parent/guardian/caregiver administered Nasacort AQ or placebo to the subject on participating days over the course of the study.

Additionally, Claritin Children's fruit-flavored syrup was provided as rescue medication. Claritin syrup contained 1 mg/mL micronized loratadine. Instructions for use were 1 teaspoonful qd as needed for control of breakthrough symptoms. One teaspoonful (5 mL) provided 5 mg of loratadine. Rescue medication was provided throughout the study. The manufacturer of the rescue medication was Schering-Plough Healthcare (Memphis, TN).

Dose Rationale

The Sponsor's rationale for the dose of Nasacort AQ for children ages 2-5 years (110 mcg/day) was based on demonstrating comparable systemic exposure to the active ingredient TAA as that for adults receiving the approved dose of 220 mcg/day with the argument being that systemic exposure determines the risk of systemic adverse effects such as adrenal suppression and growth suppression. Thus, prior to the initiation of this current study, the PK of TAA was characterized following intranasal administration of daily doses of 110 mcg qd in pediatric subjects 2 to 5 years of age with PAR, compared with 110 mcg and 220 mcg qd in adult subjects 18 to 50 years of age with PAR. The 110 mcg dose was studied in adult subjects 18 to 50 years of age to provide a reference database for interpreting exposure data in pediatric subjects 2 to 5 years of age since data with adults at this dose were not available. The overall exposure to TAA produced at the 110-µg dose in the pediatric subjects 2 to 5 years of age was similar to the overall exposure to TAA produced at the 220 mcg dose in the adult subjects 18 to 50 years of age.

Reviewer's Comment: No significant accumulation of TAA with multiple dosing in either pediatric or adult subjects was apparent. The apparent total body clearance (CL/F) and apparent volume of distribution (V/F) estimates for TAA in 2- to 5-year-old subjects were lower than those in adult subjects. While the "PK rationale" is valid, other factors will be assessed to decide if the Sponsor has selected an appropriate dose, including local nasal side effects/AEs and pharmacodynamics (HPA axis suppression).

Treatment Compliance

Proper use of the nasal spray was demonstrated to all subjects (including the parent[s]/guardian[s]/caregiver[s]) by the investigator or appropriate designee at the study site. The exact date and actual time of each treatment were recorded in the subject's daily diary and were captured on the appropriate pages of the CRF. Compliance was determined by reviewing the subject's diary and questioning the parent/guardian/caregiver. Details of discrepancies (such as reasons for missed dose, late dose) were to be documented in the subject's daily diary.

Demographic Assessments
Demographic assessments included age, sex, race, height, weight, PAR onset, skin prick test or RAST results, prior illnesses and surgeries, and rhinitis symptoms for inclusion in the study. All subjects also had a physical examination, vital signs assessment, and physical examination.

Efficacy Evaluations
All primary and secondary efficacy assessments were based on subject ratings.

The primary and secondary nasal endpoints for evaluation of efficacy were calculated from daily parent/guardian-rated nasal scores. The 4 individual nasal symptoms that each subject assessed throughout the study were:

- Nasal stuffiness
- Nasal discharge
- Nasal itching
- Sneezing
- Total eye symptoms of itching, tearing, and/or redness

The following scale was used to assess the severity of each of the 5 nasal and ocular symptoms:
0 = none (symptom is not present)
1 = mild (sign/symptom is clearly present but minimal awareness; easily tolerated)
2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable)
3 = severe (sign/symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Total Nasal Symptom Score (TNSS) was calculated by adding the scores for nasal stuffiness, nasal discharge, sneezing, and nasal itching. The TNSS did not include the score for the total eye symptoms (itching, tearing, and/or redness). The Total Symptom Score (TSS) was calculated by adding the scores for nasal stuffiness, nasal discharge, sneezing, nasal itching, and total eye symptoms of itching, tearing, and/or redness. Thus, the daily TNSS could range from 0 to 12. The daily TSS could range from 0 to 15.

Primary Efficacy Endpoint
The primary efficacy endpoint was the mean change from baseline over the double-blind 4-week treatment period in daily, instantaneous (immediately prior to dosing) total nasal symptom scores (iTNSS).

Secondary Efficacy Endpoints
Secondary endpoints for the study included:

- Change from baseline over the double blind 4 week treatment period in mean daily reflective (previous 24 hrs) total nasal symptom scores (rTNSS).
- Weekly instantaneous TNSS
- Weekly reflective TNSS
- Instantaneous and reflective total symptom scores
- Physician and subject global evaluation of efficacy (based on a 5 point (0-4) categorical scale

Safety Evaluation

The primary safety endpoints for the study consisted of the following assessments:

- Frequency and type of clinical adverse events
- HPA axis assessment by cosyntropin stimulation test
- Physical examinations
- Vital signs (systolic and diastolic blood pressures and heart rate)

Reviewer's Comment: Adverse events were to be noted in the patient diaries and were inquired about at study visits. Vital signs were performed at study visits and physical exams were generally performed at the beginning and end of the study. Given the relative safety of this drug class for this indication and the long history of use of NAQ in older children, this relatively low level of prospective safety monitoring is adequate.

Data Analysis

Sample Size

The planned sample size was based on the primary efficacy endpoint, the mean change from baseline in daily iTNSS over the 4 week double blind treatment period.

Four hundred (400) subjects were required to achieve a 90% power to reject the null hypothesis of no difference between Nasacort AQ Nasal Spray and placebo for the changes from baseline in iTNSS when the expected mean difference was no less than 0.65 units, assuming a common SD of 2.0 units. The estimated value of 2.0 units SD used in the calculation was obtained from a previous study on Nasacort AQ in 4- to 12-year-old subjects with PAR where the TNSS was the 24-hour reflective value. To ensure 200 evaluable subjects per treatment arm (400 subjects) by the end of double-blind period, at least 460 subjects (230 subjects/arm) were to be enrolled in the double-blind period.
This assumed a dropout rate of approximately 15%. Finally, approximately 350 subjects were to be enrolled in the open-label period to achieve approximately 250 subjects by the end of the 6-month open-label period.

Study Populations

There were 5 populations used for statistical analyses. The populations were defined as follows:
Safety: (a) during double-blind period, all randomized subjects to the double-blind period who received at least one dose of investigational product; and (b) during open-label period, all subjects who received at least one dose of Nasacort AQ during open-label period.
Intent-to-treat (ITT): (a) during double-blind period, all safety subjects during double-blind period who had a TNSS score recorded on the morning following any dose of double-blind

investigational product. All subjects in the ITT during the double-blind period were analyzed according to the investigational product to which they were randomized. And, (b) during the open-label period, all safety subjects who had ratings for the physician's and/or the subject's global evaluation of efficacy.
Completer: (a) during double-blind period, all ITT subjects during double-blind period who took investigational product for at least 25 days and had a TNSS assessment on a morning after any dose given on or after Day 25 (of double-blind period). And, (b) during the open-label period, all ITT subjects during the open-label period who took Nasacort AQ during open-label period for at least 141 days and had a rating for physician's and/or subject's global evaluation of efficacy on or after Day 141 (of open-label period).
Per-protocol (PP): all ITT subjects during the double-blind period with no major protocol deviation. Major protocol deviators were subjects whose deviation violated the clinical study protocol in a way that would affect the interpretation of the result of the primary efficacy variable. These deviations included: compliance rate of less than 80%, concomitant medication that interfered with the interpretation of the primary efficacy variable, or a medical procedure that interfered with the interpretation of the primary efficacy variable.
Cosyntropin evaluable: (a) during double-blind period, all safety subjects in the double-blind period with sets of cortisol data obtained at screening (Study visit 1) and at the end of double-blind period (Study visit 4) via CST and, (b) during open-label period, all safety subjects in the open-label period who participated in the CST component of the study with a sets of cortisol results at screening (Study visit 1) and at the end of the open-label period (Study visit 8).

In addition, all subjects during the open-label period who participated in the PK component of the study were considered evaluable and analyzed for demography.

Primary and Secondary Efficacy Analyses
The primary efficacy endpoint was the change from baseline over the double-blind 4 week treatment period in mean daily instantaneous TNSS (rhinorrhea, nasal congestion, nasal itching and sneezing), as evaluated on a 4-point categorical scale.

The primary analysis method was the pairwise comparisons of treatment groups (active vs. placebo) using analysis of covariance (ANCOVA) on the ITT population. The same model selected to analyze the primary efficacy variable was also used to present the results for the following secondary efficacy variables:

- Change from baseline for the mean daily rTNSS
- Changes from baseline at Weeks 1, 2, 3, and 4 of the double-blind period with LOCF for the mean daily iTNSS and rTNSS
- Change from baseline over the double-blind period for the mean daily instantaneous and reflective TSS

For the physician and subject global evaluation of (treatment) efficacy over the 4 week double blind period, descriptive statistics by treatment were calculated. These include mean, SD, median, range, and interquartile range. If required, an ANOVA included treatment, pooled site, subgroup, and subgroup by interaction was used to evaluate consistency of effect.

For the HPA axis (pharmacodynamic) endpoint, an ANCOVA, similar to the one used for the primary efficacy variable, was used to analyze the changes from screening to the end of double-blind period for the difference between post minus pre cosyntropin stimulation cortisol level(s).

Analyses also included the calculation of the proportion of subjects in each of the following categories at screening, end of double-blind period by treatment group, and end of open-label period as follows:

- a pre-stimulation cortisol level of (a) <138 nmol/L (5 mcg/dL) or (b) ≥138 nmol/L (5 mcg/dL)
- a 30 minute post-stimulation cortisol level of (a) <496 nmol/L (18 mcg/dL) or (b) ≥496 nmol/L (18 mcg/dL)
- a post-stimulation increase in cortisol level of (a) <193 nmol/L (7 mcg/dL) or (b) ≥193 nmol/L (7 mcg/dL)
- a combination of categories included (a) a 30 minute post-stimulation cortisol level of <496 nmol/L (18 mcg/dL) and (b) a post-stimulation increase in cortisol level of <193 nmol/L (7 mcg/dL)

The cortisol units were converted to the International System of Units (SI units).

Results

Study Population

Disposition

A total of 762 subjects were screened for this study at the 59 investigative sites. Of these 762 subjects, 474 were randomized and received at least one dose of study drug and comprised the safety population of the double blind period.

Of these 474 treated subjects, 464 subjects (233 placebo, 231 Nasacort AQ) had at least one TNSS score recorded following double-blind treatment; thus, constituting the ITT population. Four hundred thirty two subjects (216 placebo, 216 NAQ) completed the double blind portion of the study and 427 subjects (215 placebo, 212 NAQ) met the criteria for the completer population. Premature withdrawals occurred in 22 (9.2%) of subjects in the placebo group compared with 20 (8.5%) in the NAQ group. The most common reason for subject withdrawal was lost to follow-up, with 7 and 6 subjects in the placebo and NAQ groups, respectively. Three subjects in the placebo group and one subject in the NAQ group discontinued due to lack of efficacy while 3 and 4 subjects discontinued due to AEs in the placebo and NAQ groups, respectively. *[Table 8 Study 3502 Study Report, page 73]*

For the open label period, 428 patients took at least one dose of NAQ while 357 (83.4%) completed the study. Of the 71 subjects who discontinued, 23 (32.4%) discontinued because they did not want to continue, 17 (23.9%) were lost to follow-up, and 15 (21.1%) discontinued due to an AE.

Protocol Deviations

The definition of protocol deviation included failure to meet inclusion, exclusion, or randomization criteria, use of prohibited medications, and any other deviations deemed to have the potential to affect the interpretation of the primary efficacy variable. Reported deviations included not meeting the minimal symptom score requirement (18 subjects), lack of a 1 year history of PAR (1 subject), use of nasal or oral antihistamines within 3 days of screening (48 subjects, 24 each in the placebo and NAQ group), URI or sinus infection within 2 weeks of screening (7 subjects). There were no meaningful differences in the frequencies between the treatment groups. All subjects were excluded from the PP analysis. The most common deviation during the treatment period, other than the use of prohibited medications, was incorrect randomization of age stratum, which occurred in 2% to 4% of subjects in each treatment group *[Table 10 Study 3502 Study Report, page 76]*.

Demographics

Demographics were similar across treatment groups and study populations (safety, ITT, PP, completer). The mean age was 3.5 and 3.6 years for the placebo and NAQ groups, respectively with the age distribution fairly equally distributed (21, 26, 32, and 22% of subjects being 2, 3, 4, or 5 years of age). The majority of the subjects were White (66%) with 15% being Black, and 13% listed as "Other". Males comprised 57% of the population. The demographic profile did not substantially change during the open-label period *[Tables 13 and 14 Study 3502 Study Report, pages 80 and 82]*.

The mean duration (±SD) of diagnosed PAR was 30.9 months (±13.11) in the placebo group and 29.8 months (±13.09) in the NAQ treatment group. All subjects tested positive by prick test or RAST to at least one of the following: cat, dog, molds, dust mites, house dust, or cockroach. Baseline iTNSS symptom scores were very similar across treatment groups with scores of 7.61 and 7.52 in the placebo and NAQ groups, respectively *[Study 3502 Study Report, pages 84 and 90]*.

Treatment compliance was assessed by asking the subject or parent/guardian to note in the subject diary that a dose was given that day. Compliance was very similar across treatment groups with 98.3% of subjects in both the placebo and NAQ treatment groups having compliance ≥ 80% *[Study 3502 Study Report, page 87]*.

For the open-label period, the mean number of days when subjects took NAQ was 152 days out of a total of 155 mean days.

Efficacy Results

Primary Efficacy Outcome

The primary efficacy endpoint was the change from baseline in the mean daily iTNSS over the 4 week double blind treatment period in the ITT Population. The following table summarizes the mean change in iTNSS from baseline and over the 4-week double blind treatment period.

Mean Change from Baseline Over the Double Blind Treatment Period in iTNSS (ITT Population) *[Table 18 Study 3502 Study Report, page 90]*

	Placebo (N=233)		NASACORT AQ 110 µg qd (N=231)		Difference PBO - NAQ			Treatment effect p value
	Adjusted mean	SE	Adjusted mean	SE	Adjusted mean	95% CI	SE	
Baseline	7.61	0.142	7.52	0.142	0.10	(–0.28;+0.47)	0.192	0.6187
Change	–1.92	0.157	–2.28	0.157	0.36	(–0.06;+0.77)	0.212	0.0946

Baseline mean daily iTNSS values were very similar across both treatment groups (7.61 placebo, 7.52 NAQ). The adjusted mean change (±SE) from baseline over the double-blind period was -1.92 (±0.157) for the placebo group and -2.28 (±0.157) for the NAQ treatment group in the ITT population (2-5-year-olds) for a difference of -0.36. A statistically significant treatment effect was not observed in the primary efficacy variable in the ITT population (p=0.0946). Subgroup analysis by age (2, 3, 4, 5 year old strata) did not demonstrate a statistically significant difference in iTNSS for any single age group but when an ad hoc analysis was performed for the primary endpoint on the 3-5 year old subgroup, a statistically significant difference was noted (p = 0.0108) *[Table 20 Study 3502 Study Report, page 93]*.

Secondary Efficacy Outcomes

There were many secondary endpoints assessed in this clinical trial, however, the key secondary endpoint from the point of determination of efficacy was the change from baseline in mean daily reflective TNSS (rTNSS) over the double-blind treatment period as this endpoint is often used (and is generally the preferred) primary endpoint in nasal corticosteroid SAR and PAR studies.

The following table summarizes the mean change in rTNSS from baseline and over the 4-week double blind treatment period.

Mean Change from Baseline Over the Double Blind Treatment Period in rTNSS (ITT Population) *[Table 24 Study 3502 Study Report, page 98]*

	Placebo (N=233)		NASACORT AQ 110 µg qd (N=231)		Difference PBO - NAQ			Treatment effect p value
	Adjusted mean	SE	Adjusted mean	SE	Adjusted mean	95% CI	SE	
Baseline	7.87	0.136	7.96	0.136	–0.09	(–0.45;+0.28)	0.184	0.6412
Change	–1.87	0.151	–2.31	0.151	0.44	(–0.04; +0.84)	0.204	0.0328

Analysis of covariance (ANCOVA) with treatment and pooled site effects and the corresponding baseline value as covariate was used for the change from baseline (ie, difference = endpoint value – baseline value) with p values based on actual data.

Baseline mean daily rTNSS values were very similar across both treatment groups (7.87 for placebo, 7.96 for NAQ). The adjusted mean change (±SE) from baseline over the double-blind period was -1.87 (±0.151) for the placebo group and -2.31 (±0.151) for the NAQ treatment group in the ITT population (2-5-year-olds) for a difference of -0.44 that was statistically significant (p = 0.033). Subgroup analyses revealed, similarly to the primary endpoint analysis that older

children (3-5 yrs) generally demonstrated a greater difference in rTNSS compared to 2 year olds and that whites appeared to have a bigger treatment effect than non-whites. *[Table 27 Study 3502 Study Report (Supportive Material), page 373]*.

Other secondary endpoints for the study included:

- change from baseline in mean daily iTNSS and rTNSS at Weeks 1, 2, 3, and 4
- change from baseline in mean daily iTSS and rTSS
- physician's global evaluation of efficacy
- subject's global evaluation of efficacy

For the weekly instantaneous and reflective TNSS determinations, while treatment differences in favor of NAQ tended to increase over time, a statistically significant difference between placebo and NAQ treatment groups was only seen for rTNSS at week 4 ($p = 0.042$). There were no differences in instantaneous or reflective TSS *[Tables 26-28, Study 3502 Study Report, pages 100-103]*.

Physician and subject global evaluation scores generally revealed greater improvement in patients who received active treatment compared to those who received placebo *[Tables 29, 30, Study 3502 Study Report, pages 103-104]*.

Onset of Action

Onset of effect was not formally assessed in this pediatric study.

Safety

Extent of Exposure

For the 4 week double-blind treatment period, the median study drug exposure was 29 days for both the placebo and NAQ treatment groups with a range of exposure of 2-42 days for placebo and 2-41 days for NAQ.

During the open-label period the dose remained fixed at 110 mcg NAQ for all participating subjects. Four hundred twenty-eight subjects received at least one dose of NAQ for all participating open-label subjects, Compliance rate based on study duration of open-label period minus the number of days of any partial or missing dose(s) during open-label period 97.9%. The median study drug duration was 168 days during open-label period; the range of exposure was 1 day to 213 days exposure to NAQ.

Adverse Events

One hundred and fifteen subjects (48%) in the placebo group, 120 subjects (51%) in the NAQ group experienced at least one AE during the 4 week double-blind treatment period. The most common AE was cough which was reported in 8-9% of subjects in each treatment group. Pyrexia was also reported fairly frequently (7-8%) across treatment groups. Epistaxis was reported equally (5%) across both treatment groups. There were no reports of nasal ulceration *[Table 3, Study 3502 Study Report (Supportive Material), pages 520-524]*.

Reviewer's Comment: For labeling, the Sponsor should submit a table of AEs that lists AEs with an occurrence rate ≥ 2% and is greater in subjects receiving NAQ. This could be derived from Table 46 on page 129 of the Study 3502 Study Report (see below).

Number of treatment-emergent adverse events reported with at least 2% prevalence during double-blind period and their relationship to investigational product (safety population) *[Table 46 Study 3502 Study Report, page 129]*

MedDRA preferred term	Placebo (N=238)		NASACORT AQ 110 µg qd (N=236)	
	Total (n [%])	Possibly Related (n [%])	Total (n [%])	Possibly Related (n [%])
Total no. of subjects with TEAE (N [%])	115 (48.3)	20 (8.4)	120 (50.8)	13 (5.5)
Cough	22 (9.2)	3 (1.3)	18 (7.6)	2 (0.8)
Pyrexia	19 (8.0)	0	16 (6.8)	0
Headache	10 (4.2)	4 (1.7)	13 (5.5)	0
Pharyngolaryngeal pain	10 (4.2)	0	13 (5.5)	0
Epistaxis	12 (5.0)	7 (2.9)	12 (5.1)	9 (3.8)
Nasopharyngitis	9 (3.8)	0	12 (5.1)	0
Upper abdominal pain	2 (0.8)	0	11 (4.7)	0
Vomiting	8 (3.4)	0	8 (3.4)	0
Diarrhea	3 (1.3)	0	7 (3.0)	0
Asthma	5 (2.1)	0	6 (2.5)	0
Rash	4 (1.7)	0	6 (2.5)	0
Excoriation	0	0	6 (2.5)	0
Rhinorrhoea	4 (1.7)	0	5 (2.1)	0
Sinusitis	5 (2.1)	0	3 (1.3)	0

For the open-label period, pyrexia, again was the most frequent AE (22%). Epistaxis was reported in 4.2 % of subjects, consistent with what was seen during the double-blind treatment period *[Table 25, Study 3502 Study Report (Supportive Material), pages 590-596]*.

Deaths, Serious Adverse Events, and Events Leading to Withdrawal

No deaths or SAEs were reported during the 4 week double-blind portion of the study. During the open label period, 7 subjects experienced 8 SAEs that included: appendicitis, aseptic meningitis, adenoidal hypertrophy, asthma, tonsillar hypertrophy, lymphadenitis, foreign body trauma, and diabetic ketoacidosis. All recovered without sequelae. Causality cannot be assessed as all subjects were receiving NAQ.

Three (1.3%) subjects from the placebo group and 4 (1.7%) from the NAQ group withdrew from the study during the 4 week double-blind period because of an AE. AEs leading to withdrawal in the placebo group were URI (2) and asthma, rhinalgia, and pyrexia (1 each). In the NAQ group discontinuations were due to URI, bronchitis, rhinitis, and sinus congestion (1 each) *[Table 50, Study 3502 Study Report, page 141]*.

During the uncontrolled open label period 15 subjects (3.5%) receiving NAQ discontinued from the study due to an AE. Asthma (5 subjects) and URI (4) were the leading causes for discontinuation *[Table 52, Study 3502 Study Report, page 144]*.

Laboratory Results

Pharmacodynamics: Cosyntropin Stimulation Test

An evaluation of whether NAQ demonstrated an effect on the HPA axis was performed by assessing serum cortisol levels before and after stimulation with 1 mcg of cosyntropin in a subset of subjects at screening and both at the end of the 4 week double blind treatment period and at the end of the 6 month open label safety period. For both the double blind and open label periods, the data are presented as adjusted mean group differences of post-stimulation measurements at screening and at the end of the respective treatment period. Other analyses performed that may indicate an effect on the HPA axis include the number of subjects who have a 30 minute post-stimulation cortisol level of <496 nmol/L (18 mcg/dL) and/or post-stimulation increases in cortisol level of <193 nmol/L (7 mcg/dL).

Reviewer's Comment: The high or low dose cosyntropin stimulation tests are not the preferred means to assess the effects of intranasal corticosteroids on the HPA axis outlined in the Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products (April 2000). The Guidance instead mentions the use of timed urinary free cortisol or serum cortisol AUC before and after 6 weeks of treatment as the preferable methods of assessment. With respect to this sNDA for pediatric patients 2-5 years of age, I believe the use of the low dose cosyntropin stimulation test as the method to assess a drug effect on the HPA axis may be adequate for several reasons. First, HPA axis assessments using the cosyntropin stimulation test have already been performed in adults and in children 6-12 years of age who received up to twice the maximum recommended daily dose of NAQ (440 mcg). The continued use of the test to assess the HPA axis in 2-5 year olds is consistent with evaluations in the older populations which allows for a meaningful comparison across age groups. Second, the collection of timed urine specimens in subjects who are not toilet trained is virtually impossible and collection of serum cortisol AUC is probably not doable in this young of a population. Thus, while the cosyntropin stimulation tests may not be the preferred method to assess the integrity of the HPA axis, it may be the only test that is practical for the youngest pediatric subjects. Additionally, presumably for the same reasons mentioned above, in comments to the Sponsor DPAP has previously acknowledged the logistical problems with 24 hr urine or serum collections in very young children and has viewed the cosyntropin stimulation test as a reasonable alternative for this population (IND# 39,306 Medical Team Leader Memo by Lydia McClain, dated August 27, 2003).

For the 4 week double blind period, a total of 28 subjects who received placebo and 33 who received NAQ comprised the HPA axis population. There were 11 subjects in each group who were 2-3 years of age.

The following table summarizes the adjusted mean group differences of post-stimulation measurements at screening and at the end of the 4 week double blind treatment period.

Analysis of Covariance on Mean Serum Cortisol Levels at the End of the Four Week Double Blind Treatment Period (Cosyntropin Evaluable Population) *[Table 53, Study 3502 Study Report, page 146]*

Time-point (nmol/L)	Placebo (N=28)		NASACORT AQ 110 µg qd (N=33)		Difference PBO - NAQ			p value
	Adjusted mean	±SE	Adjusted mean	±SE	Adjusted mean	95% CI	±SE	Treat-ment effect
Screening	369.65	29.842	336.81	28.090	32.84	(−47.9;+113.6)	40.256	0.4182
Change	−13.59	39.640	−43.13	37.229	29.54	(−78.0;+137.1)	53.581	0.5838

Analysis of covariance (ANCOVA) with treatment and pooled site effects and the corresponding baseline value as covariate was used for the change from baseline (ie, difference = endpoint value – screening value) with p values based on actual data.

From the table above, the adjusted mean differences (±SE) (i.e., Placebo - NAQ) between the post-stimulation changes at screening and at the end of the 4 week double blind treatment period were +32.84 nmol/L ±40.256 and +29.54 nmol/L ±53.581, respectively. An ANCOVA, with treatment and pooled site effects as covariates showed that the treatment or pooled site effect differences were not significant ($p>0.05$). While the mean data did not demonstrate any significant differences between placebo and NAQ in cosyntropin stimulation testing of the integrity of the HPA axis, when cortisol levels were categorized into pre and post-stimulation criteria that could be representative of a blunted HPA axis response, more subjects treated with NAQ had cortisol levels that were below the pre-specified criteria of an adequate response (pre-stimulation values < 138 nmol/L (< 5 mcg/dL), post-stimulation values < 496 nmol/L (< 18 mcg/dL), or post minus pre-stimulation differences < 193 nmol/L (< 7 mcg/dL) (see table below).

Descriptive Statistics on Serum Cortisol Criteria for Cosyntropin Stimulation Tests at the End of the 4 Week Double Blind Period *[Table 54, Study 3502 Study Report, page 147]*

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Time-point	Criteria	Placebo (N=28)		NASACORT AQ 110 µg qd (N=33)	
		Screening (n [%])	End of double-blind period (n [%])	Screening (n [%])	End of double-blind period (n [%])
Pre-stimulation	<138 nmol/L (<5 µg/dL)	0	0	0	4 (12.1)
	≥138 nmol/L (≥5 µg/dL)	28 (100.0)	28 (100.0)	33 (100.0)	29 (87.9)
Post-stimulation	<496 nmol/L (<18 µg/dL)	0	2 (7.1)	1 (3.0)	4 (12.1)
	≥496 nmol/L (≥18 µg/dL)	28 (100.0)	26 (92.9)	32 (97.0)	29 (87.9)
Post-minus pre-stimulation difference	<193 nmol/L (<7 µg/dL)	1 (3.6)	4 (14.3)	5 (15.2)	8 (24.2)
	≥193 nmol/L (≥7 µg/dL)	27 (96.4)	24 (85.7)	28 (84.8)	25 (75.8)

Cosyntropin stimulation test results for the open label period were similar to those from the 4 week double blind period in that the mean differences between the post-stimulation changes at screening and at the end of the open label 6 month treatment period were not statistically significant (p = 0.190) *[Section 9.4.2 Study 3502 Study Report, page 148.]* However, when categorized into pre and post stimulation criteria as outlined above, once again, after 6 months treatment with NAQ more subjects failed to meet criteria indicative of an adequate cosyntropin stimulation response than when tested at screening (see table below).

Descriptive Statistics on Serum Cortisol Criteria for Cosyntropin Stimulation Tests at the End of the 6 Month Open-Label Period *[Table 55, Study 3502 Study Report, page 149].*

Time-point	Criteria	NASACORT AQ 110 µg qd (N=49)	
		Screening (n [%])	End of open-label period (n [%])
Pre-stimulation	<138 nmol/L (<5 µg/dL)	1 (2.0)	3 (6.1)
	≥138 nmol/L (≥5 µg/dL)	48 (98.0)	46 (93.9)
Post-stimulation	<496 nmol/L (<18 µg/dL)	0	6 (12.2)
	≥496 nmol/L (≥18 µg/dL)	49 (100.0)	43 (87.8)
Post-minus pre-stimulation difference	<193 nmol/L (<7 µg/dL)	4 (8.2)	5 (10.2)
	≥193 nmol/L (≥7 µg/dL)	45 (91.8)	44 (89.8)

Cosyntropin evaluable was those in the safety population during open-label period with an on-treatment set of values for cortisol.

Reviewer's Comment: Since the sensitivity to corticosteroid effects varies with individuals with a minority being highly susceptible, it is not surprising that the mean data do not demonstrate HPA axis effects. However, when individual data are assessed these subjects are likely the ones who have blunted cosyntropin responses as defined in the criteria in the tables above.

Vital Signs

There were no clinically meaningful adverse changes from baseline in findings in vital signs in the active treatment group compared to placebo during the 4 week double blind period.

Summary and Discussion

In pediatric subjects aged 2-5 years, NAQ nasal spray 110 mcg once daily demonstrated a numerical, but not statistically significant, difference over placebo in favor of a reduction in PAR symptoms for the primary endpoint of mean change from baseline in iTNSS over the 4 week double blind treatment period. However, for the key secondary endpoint of mean change from baseline over the double-blind 4-week treatment period in daily rTNSS (which is commonly used as the primary endpoint in allergic rhinitis studies) treatment with NAQ demonstrated a statistically significant, beneficial treatment effect over placebo ($p = 0.033$). Subgroup analyses for the instantaneous and reflective TNSS endpoints revealed that older children (3-5 yrs) generally demonstrated a greater difference in TNSS compared to 2 year olds and that whites appeared to have a greater treatment effect than non-whites. Other secondary endpoints lend support to the efficacy of NAQ in this population as they generally revealed greater improvement in children who received active treatment compared to those who received placebo.

Cough and pyrexia were the most common AEs and did not substantially differ between active treatment and placebo. The incidence of epistaxis (5%), an AE associated with use of inhaled corticosteroid use, was not greater in the NAQ group than in placebo.

Regarding the effects of NAQ nasal spray 110 mcg once daily on the HPA axis, although there were no statistically significant differences between the post-stimulation changes in mean cortisol levels at the end of double-blind treatment period versus screening in the placebo and NAQ groups or at the end of the open-label treatment period and screening, compared to placebo, more children who received NAQ failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation. More children treated with NAQ during the 6 month open label safety extension also failed to show the pre-specified increase in cortisol levels or did not reach pre-specified cortisol levels following cosyntropin stimulation, all suggestive of a possible treatment effect in a subset of subjects who are more sensitive to the effects of corticosteroids.

In summary, Nasacort AQ, at a dose of 110 mcg once daily, as evidenced by demonstrating a statistically significant mean change from baseline in rTNSS, a numerical difference over placebo in favor of a reduction in PAR symptoms for the primary endpoint of mean change from baseline in iTNSS, and other supportive data has been shown to be effective in the treatment of nasal allergic rhinitis symptoms in pediatric subjects 2-5 years of age with PAR. No new patterns of adverse reactions were noted in the 2-5 year old population compared to those observed in older children or adults. Data from the cosyntropin stimulation tests are suggestive of a possible effect on the HPA axis in a subset of subjects sensitive to corticosteroids.

STUDY# RG5029Y-315

A Phase III, Single Center, Randomized, Cross-Over Pediatric Trial with Nasacort AQ Nasal Spray Assessing Short Term Growth in Patients with Allergic Rhinitis*

Protocol

Administrative

Study initiated: October 16, 1998
Study completed: September 22, 1999
Clinical Centers: Single Center, David Skoner, M.D., Principal Investigator, Children's Hospital of Pittsburgh
Study report dated: November 24, 1999 (original report), August 15, 2007 (updated report)
Study Sponsor: Sanofi Aventis
Medical Officer: Donald Banerji, M.D.

* This is an updated study report. The original clinical study report for study RG5029Y-315 was finalized on 24 November 1999, however subsequently no electronic version of the complete clinical study report was retained. In preparation of a supplemental New Drug Application for Nasacort AQ Nasal Spray the textual summary of Study 315 was transferred into a template compatible with the submission management system and edited using Microsoft Word. In addition, links to the appendices, available only as scanned documents were inserted.

Objective/Rationale

The primary objective of this trial was to determine if Nasacort AQ Nasal Spray (TAA Nasal Spray) at doses of 110 mcg and 220 mcg once daily has a clinically significant suppressive effect (reduction in lower leg growth velocity of ≥50%) on short term lower leg growth following a two week treatment period when compared to placebo in children aged 4 to 10 years with allergic rhinitis.

Secondary objectives included:

- Comparison of the effects of Flonase® (fluticasone propionate) Nasal Spray (FP Nasal Spray) 200 mcg once daily) with NAQ Nasal Spray (doses of 110 and 220 mcg once daily) and placebo on short term lower leg growth
- Comparison of the effects of NAQ Nasal Spray, FP Nasal Spray and placebo on HPA axis function as measured by 12 hour overnight urine cortisol/creatinine ratios, pre and post treatment

Study Summary

This was a randomized, four way crossover trial of two week treatment periods of once daily dosage with NAQ Nasal Spray 110 mcg or 220 mcg, FP Nasal Spray 200 mcg, and placebo group. Following a two week baseline period, patients received each of the four treatments in random order. During each treatment period, subjects made three clinic visits during which knemometric assessments of lower leg length were made. Each two-week treatment was followed by a two-week washout period. Patients were allowed to receive the antihistamine Triaminic Syrup® (chlorpheniramine maleate) as a rescue therapy for allergic rhinitis symptoms throughout the trial. See the following figure for a schematic of the study design.

Study Design Schematic

	Baseline	Treatment A	Washout	Treatment B	Washout	Treatment C	Washout	Treatment D	Final	Follow-up
Intervals		2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks		1 week
Visit No.	1	2,3,4	5	6,7,8	9	10,11,12	13	14,15	16	17

The following procedures were conducted at every visit after randomization: knemometry measurement of the lower leg; review of patient diaries; review of rescue medication use and dispensing rescue medication as needed. Study drug was dispensed at the beginning and collected at the end of each treatment period. The first dose of study drug in each treatment period was administered in the clinic following instruction of the patient on the correct dosing technique. At the end of every treatment or washout period, body weight was measured, urine samples for assessment of urinary cortisol levels were collected, patients were questioned about adverse events and use of concomitant medications, and diaries were dispensed for the next period.

Pertinent inclusion criteria included:

- Males 4 to 10.5 years of age or females 4 to 10 years of age
- Not greater than Stage 1 in the Tanner Classification of Sex Maturity
- Height within normal limits (5th to 95th percentile inclusive)
- At least a one year history of allergic rhinitis requiring regular treatment
- Clinical laboratory tests within normal limits or clinically acceptable limits
- Positive skin prick test (or historical test within 1 year) to allergen present in the patient's environment during the trial

Exclusion criteria included:

- History or evidence of abnormal growth
- Any disease or condition which may have substantially affected growth
- Received treatment with intranasal, inhaled or oral corticosteroids for 120 days prior to Visit 1
- Lack of sufficient symptoms of allergic rhinitis to require daily therapy during the trial
- Known hypersensitivity to any active ingredients in the study medications
- Nasal candidiasis, acute or chronic sinusitis, significant nasal polyposis (impairing nasal breathing), or other gross anatomical deformity of the nose sufficient to impair nasal breathing

Patients who experienced a febrile illness or who underwent a surgical procedure were to be discontinued from the trial, since such procedures or illnesses can have a significant negative impact on growth velocity. Likewise, any patients with swelling of the lower leg, including the knee, were to be discontinued. Patients must have been no greater than Tanner Stage I to be enrolled into the study. Patients, who advanced to Stage II during the course of the study were to be discontinued at that visit and all early termination visit procedures completed.

Lower leg growth was measured at each visit by measurement of the distance between the top of the knee and the bottom of the heel of the right or left leg of the sitting patient using knemometry. The patient was placed on a chair having adjustable vertical sitting height. The bare foot was placed on the knemometer footplate, which was covered by a standard piece of paper. The vertical sitting height of the chair was adjusted so that an angle of approximately 85 degrees was obtained at the knee of the leg being measured. The knee was moved passively under the measuring board first in the anterior-posterior direction and then in a transversal direction while the distance between the board and footplate was displayed continuously by a visual electronic display. The maximum distance, which could be reached during the movements of the patient's knee, was defined to be the actual lower leg length. The minimum distance, which could be discriminated by the device is 0.1 mm. Four measurements were taken at each visit using the above technique. The value utilized was the mean of the three values closest in range.
Reviewer's Comment: The measurements were performed according to standard knemometric guidelines.

Compliance was monitored through use of daily patient diaries. The parent or patient recorded the total number of sprays used each day. This information was reviewed at each visit by the medication dispensing person. Only patients maintaining 80% compliance were to be permitted to continue to the next two-week treatment period.

Twelve hour urinary cortisol collections were also obtained to assess for effects of study drugs on the HPA axis. The laboratory analyzed these samples for cortisol and creatinine and reported the individual values and as a ratio of urine cortisol to creatinine. Secondary safety endpoints included the frequency and type of clinical AEs and assessment of vital signs. There were no efficacy determinations made in the study.

Of the 59 patients randomized, 49 (83.1%) completed all 4 double-blind treatment periods. The most frequent reason for patient withdrawal was adverse event, accounting for 4 of the 10 withdrawals, 3 subjects were lost to follow-up. Two subjects were withdrawn due to noncompliance. Patients were to maintain an 80% compliance rate, as assessed by the daily diary, during each of the two-week treatment periods in order to continue to the next study treatment period.

Study Results

Demographics of the treatment groups were similar. The mean age of subjects was 7.2 years. Males comprised 71% of study subjects, 42% of the subjects were Caucasian and 58% were Black. Fifty-five per cent of subjects reported having allergic rhinitis for ≥ 3 years *[Table 10 Study 315 Study Report, page 33]*. Treatment compliance (> 80% of doses taken) was 94-98 % across treatment groups.

The primary objective of this trial was to determine if NAQ Nasal Spray at doses of 110 mcg and 220 mcg once daily had a clinically significant suppressive effect, defined as a reduction in lower leg growth velocity of ≥50%, on short term lower leg growth following a two week treatment period when compared to placebo in children aged 4 to 10 years with allergic rhinitis. For the ITT population, the growth velocity during placebo treatment was 0.51 mm/week. For NAQ Nasal Spray 110 mcg the treatment effect was -0.14 mm/week, a reduction of 27.5% in the

estimate of total growth/length. The treatment effect for NAQ Nasal Spray 220 mcg was -0.16, a reduction of 31.4% Although the difference in growth velocity for NAQ Nasal Spray 220 mcg was statistically significant compared to placebo (p=0.036 estimated by regression), the treatment effect was below the predetermined clinically significant level of 50%. For FP Nasal Spray 200 mcg, the reduction in growth velocity compared to placebo was similar at 25.5%. *Reviewer's Comment: Literature exists that supports both the sensitivity of knemometry as a means to assess the effect of corticosteroids on growth. It has been reported that the mean lower-leg growth rate for placebo-treated subjects is 0.40mm/wk to 0.50mm/wk and that a 50% or greater reduction in lower-leg growth rate would be considered a clinically significant effect (Wolthers OD, Pedersen S., Arch Dis Child, 1993b;68:673-6; Skoner DP, et al., Ann Allergy Asthma Immunol 2003;90:56-62).*

Twelve-hour overnight urine samples were collected for measurement of cortisol and creatinine and cortisol/creatinine ratios were calculated to asses for possible effects of study drugs on the HPA axis. Using the rank analysis of variance method, the difference in change in cortisol/creatinine ratio from the start to the end of a two week treatment period was not statistically significant between either NAQ nasal spray 110 mcg or 220 mcg and placebo. Rank ANOVA of the FP nasal spray data demonstrated statistically significant differences for FP Nasal Spray compared to the high dose NAQ nasal spray 220 mcg (p=0.037) and placebo (p=0.002). However, using the pairwise comparisons with Friedman rank sums, there was no statistically significant difference between groups *[Table 24 Study 315 Study Report, page 53]*. *Reviewer's Comment: The treatment period of just 2 weeks makes any conclusions of HPA axis effects suspect. Further, since effect on growth may be a more sensitive pharmacodynamic indicator of corticosteroid systemic effect than HPA axis suppression and there was no effect on growth seen, the HPA axis effect for FP is cast into doubt.*

Safety was also assessed by monitoring adverse events (AEs), and monitoring vital signs. During the treatment periods, 22-27% of subjects in each treatment group experienced at least 1 AE. The most common AEs were headache occurring in approximately 8-9% of subjects and pharyngitis which occurred in 4-9% of subjects. Epistaxis was reported in approximately 2% of subjects and did not differ between treatment groups *[Table 20 Study 315 Study Report, page 48-49]*. Four subjects discontinued due to AEs, 3 receiving NAQ 110 mcg (broken foot, asthma exacerbation, and nasal burning) and one receiving placebo (asthma exacerbation). There were 3 SAEs, all occurring during washout periods, straddle injury, asthma exacerbation, and behavioral (psychiatric) problem. There were no differences in vital signs between subjects in the two treatment sequences at any time point.

In summary, for this knemometry study in children ages 4-10 years, NAQ Nasal Spray, at 110 mcg/day (proposed dose for 2-5 year olds) and 220 mcg/day (labeled adult dose and maximum dose for children 6-11 years) did not have a significant effect on short term lower leg growth as defined by a reduction in short-term lower leg growth of ≥50% as determined by knemometry. Evaluation of the HPA axis was inadequate to make any conclusions regarding any drug effect. There were no safety issues in the study population in terms of AEs or vital signs.

REFERENCES

None

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

/s/

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I concur.