CLINICAL PHARMACOLOGY REVIEW

NDA:	20-468 SE5, S-24
Brand Name:	Nasacort® AQ
Generic Name:	Triamcinolone Acetonide
Indication:	Seasonal and perennial allergic rhinitis for children 2 to 5 yrs of age.
Dosage Form:	Metered-dose pump spray suspension
Strength:	55 µg per spray
Route of Administration:	Nasal spray
Dosing regimen:	1 spray per nostril once daily
Applicant:	Sanofi-Aventis
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	November 19, 2007
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.
PM Reviewer:	Partha Roy, Ph.D.
PM Secondary Reviewer:	Christoffer Tornoe, Ph.D.

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1 Executive Summary

1.1 Background

Triamcinolone acetonide (TAA), a potent corticosteroid, is the active component of Nasacort® AQ. The focus of this sNDA is on the efficacy and safety of Nasacort® AQ Nasal Spray 110 µg once daily in pediatric patients 2 to 5 years of age with allergic rhinitis (AR) as an additional patient population. Nasacort® AQ Nasal Spray is currently approved for the indication of seasonal and perennial allergic rhinitis in adults and children 6 years and older. For adults and children ≥12 years, the recommended starting and maximum dose is 220 µg per day while in children 6 to 12 years of age, the recommended starting dose is 110 µg per day and the maximum recommended dose is 220 µg per day.

The clinical program consists of three studies: 1 PK/safety study (#1000), 1 large placebo-controlled efficacy/safety study (#3502), and 1 short-term growth study (#315). A separate 12-month growth study in children 3-9 years of age (#3503) is currently ongoing. The pivotal study (Study 3502) included a 6-month open-label safety extension following the completion of the initial 4-week double-blind portion. Sparse PK samples were collected from pediatric AR patients in the open-label segment at selected sites for population PK analysis. The systemic effect of the drug on the HPA axis was evaluated using low-dose cosyntropin stimulation test (CST) at screening, end of the 4-week double-blind period, and end of the open-label period. The selection of 110 µg once daily dose to be tested in the Phase III study for pediatric patients 2 to 5 years of age was based on the assessment of comparative exposure between children and adults in study 1000. The sponsor also pooled pediatric and adult PK data from study 1000 and pediatric PK data from study 3502 for a comprehensive population PK analysis using NONMEM.

1.2 Recommendation

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 20-468 SE5 S-24 originally submitted on November 19, 2007 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor

and the agency regarding the postmarketing study requirements and the language in the package insert.

1.3 Postmarketing Action

A dedicated HPA axis trial categorized as Post-Marketing Required (PMR) study would be needed. The design of this study should be consistent with the recommendations put forward in the FDA Draft Guidance for Industry (2000) for Allergic Rhinitis: Clinical Development Programs for Drug Products.

1.4 Comments to the Medical Team

The evaluation of systemic effects of 110 µg Nasacort® AQ administration on HPA axis function in children 2 to 5 years of age is deemed suboptimal and inconclusive. The conventional low-dose CST was employed in the Phase III study (Study 3502) to support this application. This method is not generally accepted as a sensitive method to assess systemic effects of intranasal corticosteroids on HPA axis function. While CST is not the preferred method to assess HPA axis function, results of this test did suggest that a real treatment effect can not be ruled out based on post-stimulation abnormal cortisol response in a subset of patients after 4-weeks and 6-months of chronic treatment with Nasacort AQ. For HPA axis evaluation, measurements of timed (24-hour) urinary free cortisol levels or serum cortisol AUC are the preferred methods of assessment.

The pharmacokinetics of TAA has been well characterized following intranasal administration of 110 µg of Nasacort AQ in children of 2-5 years of age (n=112) using population PK analysis of data from two studies (1000 and 3502). Therefore, HPA axis evaluation (i.e. cortisol suppression) only becomes important as a pharmacodynamic measure of safety in this patient population rather than a surrogate for systemic exposure.

The sponsor is currently conducting a long-term (12-month) growth study in children 3 to 9 years of age with PAR. Since, growth velocity is believed to be a more sensitive indicator of systemic corticosteroid effect in pediatric patients compared to tests of HPA axis function including low-dose CST, it is recommended that review of the data from the ongoing growth study would help obtain a more definitive conclusion about the long-term systemic effects of TAA in this pediatric patient population. In addition, it is also recommended that a dedicated HPA axis trial appropriately designed based on the recommendations from the FDA draft Guidance for Industry (2000) for Allergic Rhinitis: Clinical Development Programs for Drug Products, be undertaken to elucidate the HPA axis effect, if any.

1.5 Summary of Clinical Pharmacology Findings

PK in 2-5y old children vs. adults

Plasma PK samples of TAA were obtained using sparse sampling strategy from 2-5 year old pediatric AR patients participating in one clinical pharmacology trial (#1000) and the pivotal efficacy/safety trial (#3502). Study 1000 also included adult AR patients receiving 2 doses (high and low) of Nasacort® AQ that allowed comparison of systemic exposure between children and adults across doses within the same study.

In Study 1000, after both single and multiple dose (QD for 5 days) intranasal administration of Nasacort® AQ in adult and pediatric patients, the overall time course of systemic exposure to TAA produced by the 110 µg dose in the pediatric patients 2 to 5 years of age appears to be comparable to that produced by the 220 µg dose in adult patients. No significant accumulation is

apparent in pediatric as well as in adult patients following 5 consecutive days of once daily dosing.

In addition to conducting population PK analysis separately with PK data obtained in studies 1000 and 3502, the sponsor pooled pediatric and adult PK data from both studies for a comprehensive population PK analysis using NONMEM with FO estimation method. TAA disposition was described by a one-compartment model with first order input. The NONMEM covariate analysis revealed that the apparent total body clearance (CL/F) of TAA was correlated with age and body weight while the apparent volume of distribution (V/F) was strongly correlated with body weight only and not with age. Following the review of the sponsor's population PK data analysis and report, the Pharmacometrics reviewers in the Office of Clinical Pharmacology determined that the population PK analysis was not adequately performed in terms of estimation method, dataset preparation and mechanistic understanding of the covariate model. New analyses were conducted using pediatric and adult plasma concentration data from studies 1000 and 3502.

Based on FDA reanalysis using NONMEM with FOCE estimation method and the same structural model as the sponsor (i.e. one-compartment PK model with first-order elimination and absorption), apparent clearance and volume of distribution after intranasal administration of TAA were both dependent on body weight. In contrast to sponsor's analysis, age is not a significant covariate for clearance after correcting for bodyweight. The population predicted clearance and volume of distribution in pediatric patients were found to be approximately half of that in adults. Apparent intranasal clearance (CL/F) was estimated to be 70 L/hr in children compared to 141 L/hr in adults. Apparent volume of distribution (V/F) was calculated to be 275 L in children compared to 488 L in adults. This has resulted in children of 2-5 years of age exhibiting comparable mean systemic exposure (AUC) of TAA to that in adults following administration of half the approved dose in adults, i.e. pediatric dose of 110 µg is comparable to the adult dose of 220 µg.

PK in 6-11y old vs. adults

Based on the existing Nasacort AQ label as well as Clinical Pharmacology review by Dr. Brad Gillespie dated 3/31/1997, systemic exposure following intranasal administration of the same dose in adults and children 6-11 years of age was found to be comparable. The C_{max} and AUC_{0-6} estimates following multiple dose administration of 440 µg Nasacort AQ in children were about 31% and 7% greater than that observed after single dose administration of the same dose in adults. For further details, refer to Dr. Gillespie's review dated 3/31/1997 in the Action Package for NDA 20468 supplement 002.

HPA axis assessment

The effect of 110 µg of Nasacort® AQ on HPA axis function was assessed in a subset of children 2 to 5 years of age within the pivotal placebo-controlled parallel-group efficacy/safety trial (Study 3502). The systemic effects of TAA on HPA axis function was primarily assessed by low-dose (1 µg) CST conducted at study visit 1 (screening), study visit 4 (end of 4-week double-blind period), and study visit 8 (end of 6-month open-label period). In addition, AM serum cortisol data at baseline and at the end of double-blind and open-label periods was also available but was not reviewed due to limited value of such data for HPA axis evaluation.

The conventional low-dose CST is not generally accepted as a sensitive method to assess systemic effects on HPA axis function. Clinically, this test is useful in determining severe adrenocortical insufficiency but inadequate for detecting mild or short-term adrenal gland

suppression. Therefore, CST conducted in pediatric patients 2-5 years of age in study 3502 is not acceptable. For HPA axis evaluation, measurements of timed (24-hr) urinary free cortisol levels or serum cortisol AUC are the preferred methods of assessment. In addition, the study design employed in study 3502 involved 4 week double-blind placebo controlled treatment duration, which is shorter than the recommended minimum of 6-week treatment for HPA axis evaluation. In addition, HPA axis evaluation in the pediatric age group of 2 to 5 years was limited to one dose only preventing dose response evaluation.

Although there was no statistically significant difference between the post-stimulation changes in mean cortisol levels at the end of double-blind treatment period versus screening in the placebo and Nasacort® AQ groups (p=0.5432), numerically greater decrease from screening in post-stimulation change was observed in Nasacort® AQ compared to placebo treated patients (-43.13 nmol/L vs. -13.59 nmol/L). In addition, 54% of the Nasacort® AQ treated patients (18 out of 33) compared to only 39% of the placebo treated patients (11 out of 28) had a lower post-stimulation changes in cortisol levels at the end of double-blind period compared to screening baseline. Some patients (2 in placebo arm and 4 in Nasacort® AQ treatment arm) either failed to show the pre-specified increase (<193 nmol/L) in cortisol levels or did not reach the pre-specified level (<496 nmol/L) following cosyntropin stimulation. Based on these results, there appears to be a numerical trend towards greater suppressive effect on the HPA axis for Nasacort® AQ treated patients compared to placebo; therefore, a possible treatment effect on HPA axis can not be ruled out.

Since PK of TAA has been well characterized using population PK analysis, there is limited value for a separate HPA axis evaluation as a surrogate for systemic exposure. With regards to systemic effect of TAA, the results from the CST only indicated absence of severe adrenocortical insufficiency with Nasacort® AQ in most patients, although a real effect can not be ruled out in a subset of patients, who may be more sensitive to the effects of corticosteroids. However, long-term systemic effects of adult equivalent exposure of TAA in pediatric AR patients of 2-5 years of age remained undetermined at this time. The sponsor is currently conducting a long-term study (XRG5029C/3503) evaluating the effect of 12 month treatment with Nasacort® AQ Nasal Spray 110 µg once daily on the growth velocity of children, 3 to 9 years of age with PAR. Since growth velocity is believed to be a more sensitive indicator of systemic corticosteroid effect in pediatric patients than tests of HPA axis function including low-dose CST, it is recommended that review of the data from study 3503 would (b) (4) provide clarity to the possible long-term systemic effects of TAA in this pediatric age-group. In addition, since a real treatment effect on HPA axis function can not be ruled out in at least some pediatric patients, a separate dedicated HPA axis trial may (b) (4) be necessary to elucidate and quantify this effect.

2 Question Based Review

2.1 General Attributes/Background

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Triamnicolone Acetonide in pediatric patients?

Triamcinolone acetonide (TAA), a potent corticosteroid, is the active component of Nasacort® AQ. The focus of this sNDA is on the efficacy and safety of Nasacort® AQ Nasal Spray 110 µg once daily in pediatric patients 2 to 5 years of age with SAR and PAR as an additional patient

population. The original Nasacort® AQ Nasal Spray NDA 20-468 was approved on 20 May 1996 for patients 12 years of age and above with SAR and PAR. A pediatric supplement S-002 to NDA 20-468 was approved on 26 September 1997 for the indication of SAR and PAR in patients 6 to 11 years of age. At the time, pediatric patients down to the age of 4 years were enrolled but approval was not granted as their number (n=7) was considered insufficient to extend approval down to the age of 4 years. TAA in non-aqueous formulations has also been approved for other indications and other routes of application.

The clinical program consists of three studies: 1 PK/safety study, 1 efficacy/safety study, 1 short-term growth study. The efficacy and safety of Nasacort® AQ Nasal Spray 110 μg once daily in 2-5 years old pediatric patient population is based on one placebo-controlled clinical study (XRG5029C/3502). The design of study 3502 also included a 6-month open-label safety extension following the completion of the initial 4-week double-blind segment of the study. Plasma samples (sparse sampling) were collected at some selected sites in the open-label segment of the study for population PK analysis. The systemic effect of the drug on the HPA axis was also evaluated using low-dose CST at screening (baseline), end of double-blind (4-week) and end of open-label (6-month) periods of the study. This test is not generally accepted as a sensitive method to assess systemic effects on HPA axis function. The selection of a dose of 110 μg once daily as the appropriate dose to be tested in the Phase III study for pediatric patients 2 to 5 years of age is based on the PK study XRG5029C/1000. The dose was subsequently confirmed in a population PK analysis of the combined PK data from studies 1000 and 3502. The third study (RG5029Y-315) evaluated the pharmacodynamics of short-term effect on growth with Nasacort® AQ Nasal Spray 110 μg once daily in this patient population.

The sponsor is currently conducting a long-term study (XRG5029C/3503) evaluating 12 month effect of treatment with Nasacort AQ Nasal Spray 110 μg once daily on the growth velocity of children, 3 to 9 years of age with PAR. Data from this study is not in the current submission but expected to be available in the near future.

2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic characteristics of TAA in pediatric and adult allergic rhinitis patients?

The pharmacokinetics of TAA in 2 to 5 year old pediatric and adult allergic rhinitis patients were evaluated in a dedicated PK/safety study (#1000). The study involved dosing of 110 μg of TAA once daily for 5 days in pediatric patients and dosing of 110 μg and 220 μg once daily for 5 days in adult patients in a fixed-sequence (lower to higher dose), cross-over manner with a 7-day washout between the two treatment periods. PK blood samples were obtained from each pediatric patient according to a staggered, sparse sampling strategy: 4 blood samples collected on each of study days 1 and 5, for a total of 8 samples (pre-dose, 1, 2, 3, 4, 5, 6, and 8 hr) for the study. Rich PK sampling was done in adults.

The plasma concentration-time profiles of TAA appear to be similar between single and multiple dose intranasal administration in pediatric patients as illustrated in Figure 1. Exposure to TAA increased in a dose-proportional manner in adults across 110 μg and 220 μg doses, with no appreciable accumulation over 5 days of dosing (Table 1). TAA is rapidly absorbed with peak plasma concentration appearing in less than 45 minutes. The average terminal half life (2.3-2.9

hrs) and intranasal clearance (130-162 L/hr) remained unchanged across doses and upon multiple dosing.

Figure 1. Plasma concentration-time profile of TAA in pediatric patients at 110 µg once daily for 5 days.

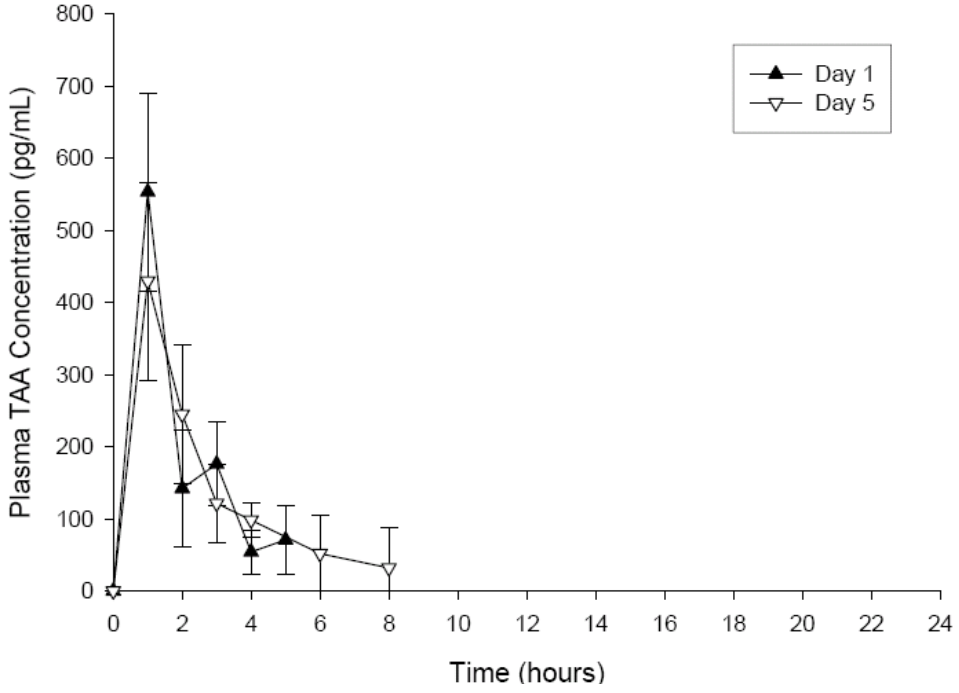

Table 1. TAA plasma PK parameters following single (day 1) and multiple (day 5) dose intranasal administration of Nasacort® AQ in adult AR patients.

PK parameters	Day 1		Day 5	
	110 mcg (n = 15)	220 mcg (n = 15)	110 mcg (n = 15)	220 mcg (n = 14)[a]
$AUC_{(0\text{-last})}$ (pg.h/mL)	585.7 ± 161.6	1350.7 ± 477.7	756.3 ± 185.2	1354.4 ± 361.5
C_{max} (pg/mL)	227.9 ± 80.6	403.7 ± 103.1	287.7 ± 67.7	441.8 ± 155.7
T_{max} (hr)	0.63 ± 0.30	0.70 ± 0.45	0.54 ± 0.13	0.61 ± 0.29
$T_{1/2}$ (hr)	2.34 ± 0.67	2.55 ± 0.54	2.61 ± 1.31	2.94 ± 1.00
CL (L/hr)	162 ± 41	158 ± 44	130 ± 30	151± 43

[a]One patient did not complete Day 5.

2.2.2 How does the systemic exposure in pediatric patients 2-5 years of age compare to that in adults including PK parameters estimated by population PK analysis using NONMEM?

There were two studies, one PK/safety trial (#1000) and the other efficacy/safety trial (#3502), where sparse PK blood sampling was conducted to evaluate the systemic exposure of TAA in 2-5y old pediatric PAR patients. Study 1000 also evaluated single and multiple dose

pharmacokinetics of TAA in adults following intranasal administration of Nasacort® AQ. The sponsor conducted population PK analysis using non-linear mixed effect modeling (NONMEM) with three different sets of data: 1) pooled sparse data from children and rich data from adults from study 1000, 2) sparse data from children from study 3502, and 3) pooled data for both adults and children from both the studies.

After single-dose intranasal administration of Nasacort® AQ in adult and pediatric patients, the PK profile of TAA produced by the 110 µg dose in the pediatric patients appears comparable to that produced by the 220 µg dose in the adult patients (Figure 2). However, the average peak plasma TAA concentration (C_{max}) appears to be greater in pediatric compared to adult patients. No significant accumulation is apparent in pediatric as well as in adult patients (Figure 1 and Table 1). Visual inspection of the plasma concentration data after administration of Nasacort® AQ 110 µg/day and/or 220 µg/day intranasally for 5 consecutive days in adult and pediatric patients, revealed that the overall time course of systemic exposure to TAA produced by the 110 µg dose in the pediatric patients appears to be generally more closer to the overall exposure to TAA produced by the 220 µg dose in adult patients compared to the 110 µg dose (Figures 3 and 4).

Figure 2. Mean (SD) TAA concentration-time profile on day 1 in pediatric (110 mg dose) and adult (220 mg) patients with allergic rhinitis.

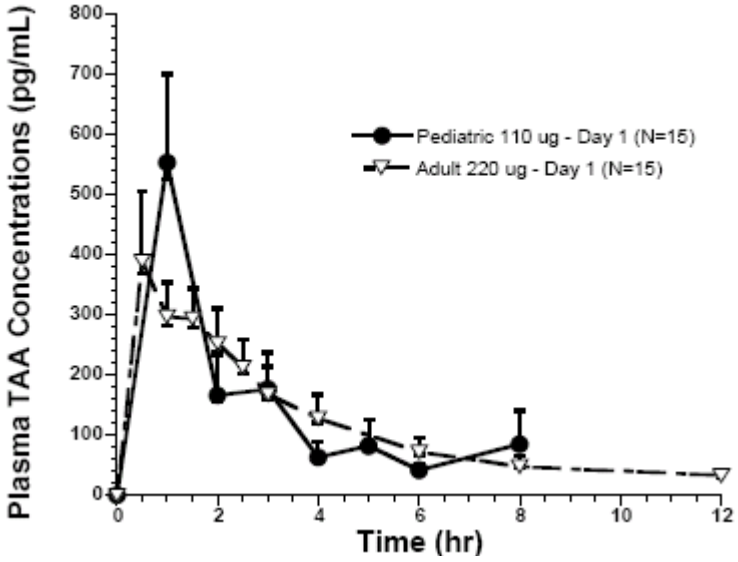

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Figure 3. Multiple-dose (day 5) individual TAA plasma concentration-time data for pediatric and adult patients, both receiving 110 µg Nasacort® AQ once daily.

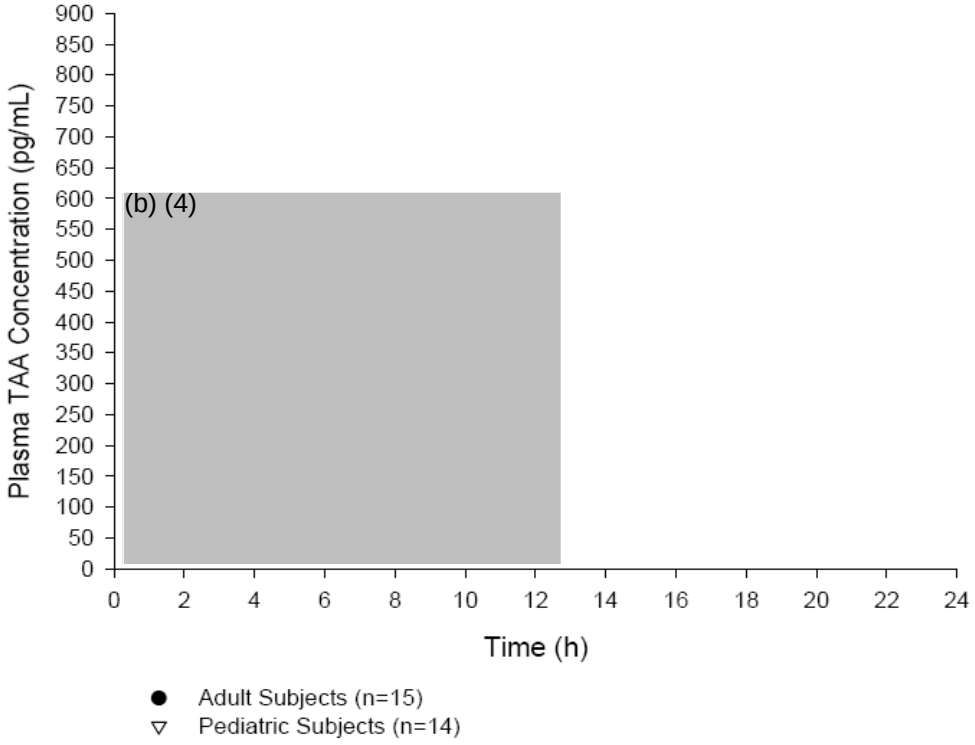
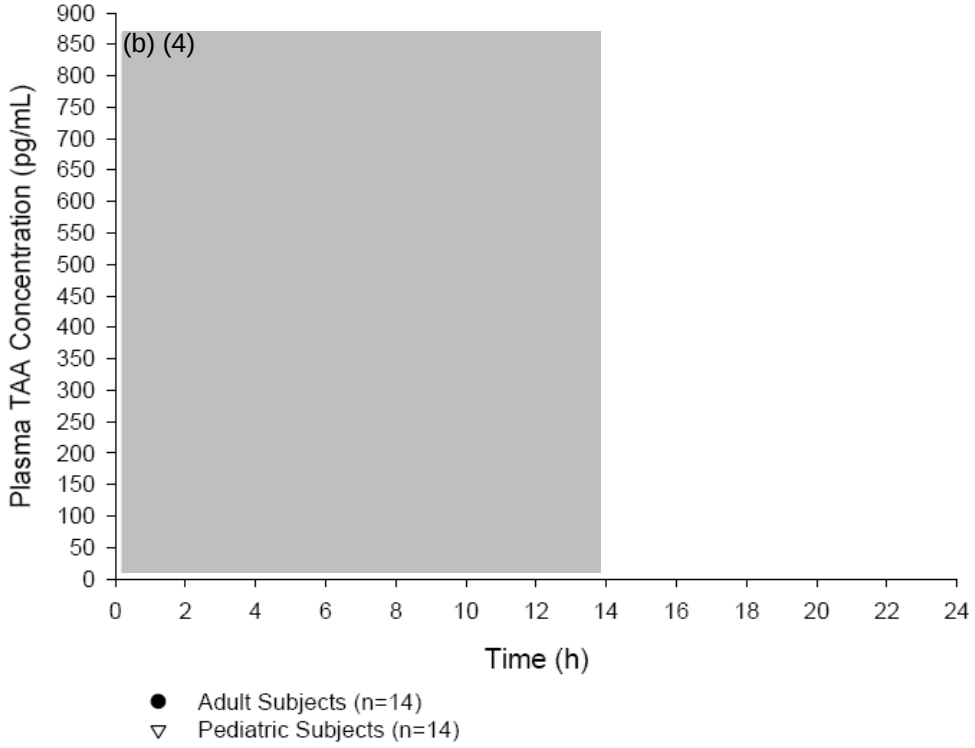


Figure 4. Multiple-dose (day 5) individual TAA plasma concentration-time data for pediatric and adult patients receiving 110 µg and 220 µg Nasacort® AQ once daily, respectively.



In order to quantify comparative exposure between adult and pediatric patients and support the proposed dose, the sponsor pooled and analyzed plasma TAA concentration-time data from study 1000 for both pediatric and adult subjects using NONMEM methods. TAA disposition was described by a one-compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters [clearance (CL/F) and volume (V/F)], while the residual variability was described by a proportional error model. The NONMEM covariate analysis revealed that apparent total body clearance (CL/F) was most strongly correlated with study population (pediatric or adult) while apparent volume of distribution (V/F) was strongly correlated with body size, with body weight being the preferred covariate over body surface area. According to the final PPK model, the CL/F in the typical pediatric subject 2 to 5 years of age was estimated as 83.6 L/h. Similarly, the CL/F in a typical adult subject was estimated as 148 L/h. The V/F was estimated as 195 L in a typical pediatric subject weighing 20 kg and 413 L in a typical adult subject weighing 70 kg.

NONMEM was again employed with data from study 3502 to estimate the primary PK parameters for TAA in the pediatric population, including the associated inter-subject variability. After administration of Nasacort® AQ 110 μg intranasally in pediatric patients, the PK of TAA was described by a one compartment model with first order input as described in study 1000. Age and body weight were strongly correlated with the apparent clearance (CL/F) following intranasal administration. Body weight was also strongly correlated with the V/F.

Finally, a population pharmacokinetic model (PPK) was developed using pooled data from studies 1000 and 3502 to assess the PK variability and the influence of demographic parameters (body weight, body mass index, age, height, gender, and race) on TAA pharmacokinetics in patients with PAR. A total of 1197 TAA concentrations in plasma collected from 15 adult and 120 pediatric patients were used in the NONMEM analyses: 821 concentration data points from study 1000, and 376 from study 3502. Again, TAA disposition was appropriately described by a one-compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters (CL/F, and V/F), while the residual variability was described by a combination of additive and proportional error model. The NONMEM covariate analysis revealed that the apparent total body clearance (CL/F) was correlated with age (AGE) and body weight (WT). The apparent volume of distribution (V/F) was strongly correlated with body weight (WT). Race and gender were not significant covariates in the analyses. The covariate age was correlated with body weight, and was chosen in combination with weight in the final model since incorporation of this covariate resulted in a greater drop in the objective function compared to body weight alone. TAA CL/F was dependent on age, with a decrease in CL/F associated with an increase in age. Overall, the sponsor concluded that age and body weight were strongly correlated with CL/F and the body weight was strongly correlated with V/F.

FDA's analysis

After reviewing the submitted data and analysis, the Pharmacometrics Reviewers in the Office of Clinical Pharmacology determined that the population PK analysis was not adequately performed in order to support the 110 μg dose for the pediatric age group of 2-5 years. According to the pharmacometric reviewer, the key deficiencies include 1) use of a less accurate estimation method (FO), 2) inadequate dataset cleaning, and 3) WT*Age covariate has limited physiologic understanding in children 2 years and older. New analyses were conducted using pediatric and adult plasma concentration data from studies 1000 and 3502.

Based on FDA's analysis of pooled data (see Pharmacometric Review, Appendix 1), the pharmacometrics reviewer concluded that apparent clearance and volume of distribution after intranasal administration of TAA were both dependent on body weight but constant within the pediatric and adult subgroups due to the limited body weight ranges studied (Figure 5). The population predicted clearance and volume of distribution in pediatric patients were found to be approximately half of that in adults. Intranasal clearance (CL/F) in children was estimated to be 70 L/hr compared to 141 L/hr in adults. Volume of distribution (V/F) in children was calculated to be 275 L compared to 488 L in adults. This has resulted in comparable mean systemic exposure (AUC) in children of 2-5 years of age and adults following intranasal administration of half the approved dose in adults (Figure 6 below). In contrast to sponsor's analysis, age is not a significant covariate for clearance after correcting for body weight. The inter-individual variability appears to be higher in 2-5 year old children compared to adults (Figures 5 and 6) although number of study participants was vastly different between the two groups (112 in pediatric group vs. 15 in adult group).

Figure 5. Individual Clearance vs. Body weight scatterplot in adults and pediatrics 2-5y of age: constant clearance within adults and pediatric sub-groups.

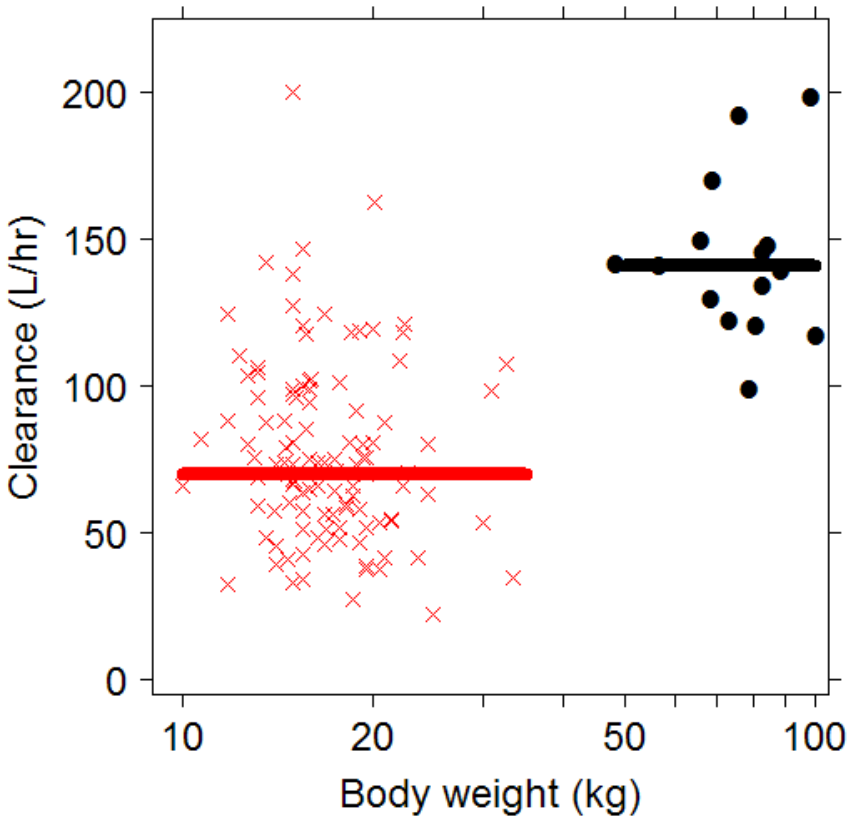
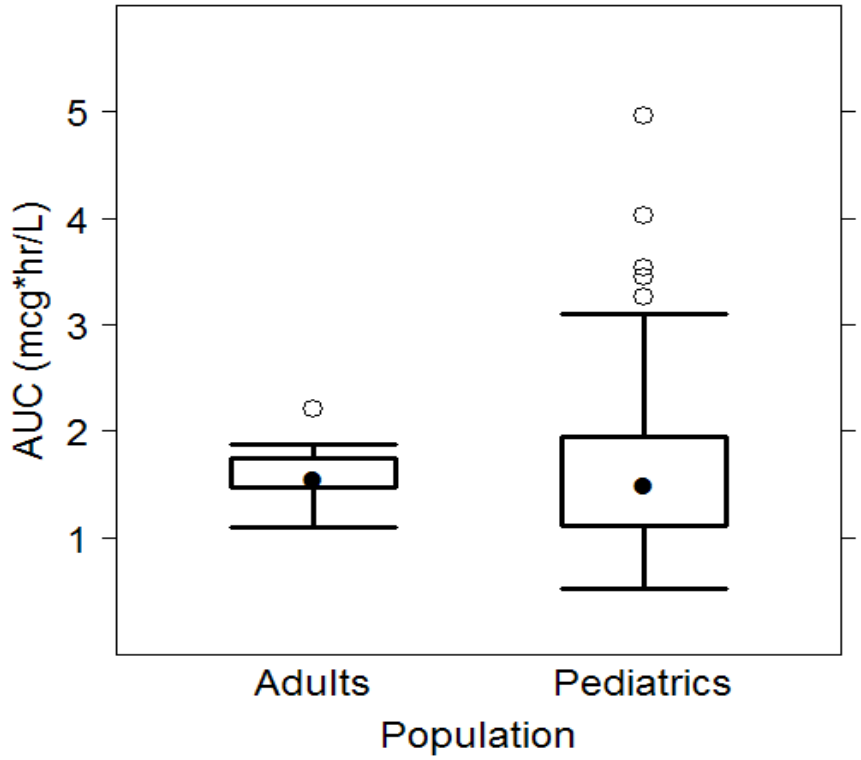


Figure 6. Boxplot of individual predicted AUC in adults receiving 220 mcg and pediatric patients receiving 110 mcg of Nasacort® AQ based on FDA's population PK analysis.



2.2.3 What is the effect of Nasacort® AQ intranasal administration on HPA axis function in pediatric allergic rhinitis patients 2-5 years of age?

The effect of Nasacort® AQ intranasal administration on HPA axis function in pediatric allergic rhinitis patients 2-5 years of age were evaluated in studies 1000, 315 and 3502. HPA axis assessments included determinations of AM serum cortisol levels (study 1000), change in 12-hour urinary cortisol/creatinine ratio (study 315), and serum cortisol response to low-dose CST (study 3502). Each of these determinations was less than optimal and deemed inadequate. The treatment periods for studies 1000 and 315 were for 5 days and 2 weeks, respectively, i.e. the duration of these studies were significantly less than 6-weeks, which is the minimum recommended for HPA axis evaluation. Therefore, cortisol data from these studies were of limited value and hence not reviewed in-depth. Study 3502, on the other hand, included a 4-week initial double-blind arm followed by a 6-month open-label safety extension, hence considered adequate duration-wise for HPA axis assessment.

The effect of 110 µg of Nasacort® AQ on HPA axis function was assessed in a subset of children 2 to 5 years of age within study 3502, a large safety/efficacy placebo controlled parallel-group trial. The systemic effects of TAA on HPA axis function was primarily assessed by low-dose (1

μg) CST, conducted at study visits 1 (screening), study visit 4 (end of 4-week double-blind period), and study visit 8 (end of 6-month open-label period). Subjects had to have a pre-stimulation cortisol level of least 5 μg/dL (138 nmol/L) and post-stimulation cortisol level of at least 18 μg/dL (496 nmol/L) at Study visit 1 in order to participate in the HPA axis evaluation.

Double-blind period (4-weeks)

Differences between the cosyntropin evaluable and safety populations were not generally observed for any demographic variable. The adjusted mean difference (SE) of the post-stimulation change at screening and end of double-blind period for morning serum cortisol was -13.59 nmol/L (39.64) in placebo and –43.13 nmol/L (37.229) in Nasacort® AQ subjects (cosyntropin evaluable population). The adjusted mean difference (SE) (i.e. placebo - Nasacort® AQ) of the post-stimulation change at screening was +32.84 nmol/L (±40.26); the adjusted mean difference (i.e. placebo – Nasacort® AQ) of the post-stimulation changes at the end of double-blind period versus screening was +29.54 nmol/L (±53.58). An ANCOVA, with treatment and pooled site effects and the corresponding screening value as covariate was used for the change from screening (i.e. difference: end of double-blind period value – screening value) with p values based on actual data, was performed. Treatment differences were not significant ($p>0.05$) as shown in Table 2.

Table 2. Analysis of Covariance (ANCOVA) on change from screening in Post – Pre-stimulation mean serum cortisol levels (nmol/L) at the end of double blind period (4-weeks)

Time-point	**Placebo (N=28)**	**Nasacort® AQ (N=33)**	**Difference (Placebo – Nasacort® AQ)**		**P value**
	Adjusted mean (SE)	**Adjusted mean (SE)**	**Adjusted mean (SE)**	**95% CI**	**Treatment effect**
Screening	369.65 (29.84)	336.81 (28.09)	32.84 (40.26)	(-47.9, +113.6)	0.4182
Change	-13.59 (39.64)	-43.13 (37.23)	29.54 (53.58)	(-78.0, 137.1)	0.5838

Cortisol levels categorized into pre- and post-stimulation criteria are presented in Table 3. One subject (#45) with borderline post-stimulation value of 490 nmol/L was allowed to participate in the Nasacort® AQ arm of the study, who subsequently exhibited normal post-stimulation value of 519 nmol/L after 4-weeks of treatment. Six subjects exhibited simultaneously cortisol post-stimulation level of <496 nmol/L (<18 μg/dL) and a post- minus pre-stimulation levels difference of <193 nmol/L (<7 μg/dL) at the end of double-blind period (Table 3). Individual cortisol data from these 6 patients are listed in Table 4. Five (5) out of 6 patients exhibited decrease in cortisol levels rather than the expected increase following cosyntropin administration. This seriously questions the reliability of this test. Of the 6, 5 subjects participated in the cortisol evaluation via CST during open-label period, of which 1 subject participated in the pre-stimulation CST and not post-stimulation CST. As shown in Table 4, out of the remaining 4 subjects, 3 exhibited normal post-stimulation level as well as normal pre- and post- difference at the end of open-label period (24-weeks).

Table 3. Descriptive statistics on serum cortisol via CST at the end of double-blind period (4-weeks)

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)

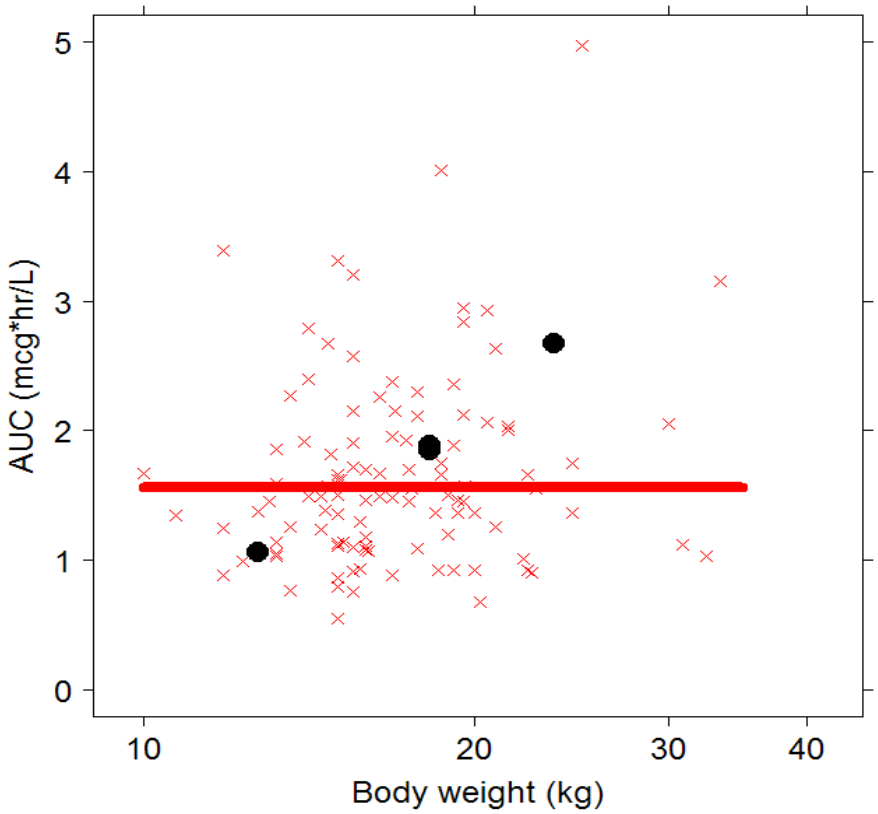
Table 4. Pre and post-stimulation plasma cortisol levels in pediatric patients who exhibited abnormal post-stimulation cortisol response.

Subjects	Trt	Screening		End of double-blind		End of open-level	
		Pre	Post	Pre	Post	Pre	Post
		Post - Pre		*Post - Pre*		*Post - Pre*	
00170003 3y black female	N	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	M
		193		***28***		_	
00380039 4y white female	N			(b) (4)	(b) (4)	M	M
		442		***- 413***		_	
00590038 5y white female	N	(b) (4)					
		276		***- 83***		*331*	
00730005 2y black male	N	(b) (4)				(b) (4)	(b) (4)
		552		***- 59***		*506*	
00730008 2y black male	P	(b) (4)		(b) (4)		(b) (4)	
		303		***- 166***		*238*	
00730009 3y black female	P	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
		662		***-138***		*520*	

N = Nasacort AQ, P = Placebo, M = missing
Note: Values in red are identified as abnormal.

Figure 7 presented the AUC values of the four subjects (black dots) who exhibited abnormal CST values at the end of the double-blind period following Nasacort® AQ administration. They do not appear to be the ones with the highest AUCs, i.e. lowest CL/F. These subjects are randomly scattered within the exposure range, i.e. no trend towards clustering of these subjects towards the higher end of the systemic exposure range for pediatric patients.

Figure 7. Individual AUC estimates for four pediatric patients (black dots) who exhibited abnormal CST results (two dots for two subjects nearly on top of each other around 20 kg body weight)



There were 29 subjects (11 placebo, 18 Nasacort® AQ) who had a lower post- minus pre-stimulation cortisol levels difference at end of the double-blind period compared to screening. Of the 11 placebo subjects with lower differences, there were three 2-year-old subjects, one 3-year-old subject, four 4-year-old subjects, and three 5-year-old subjects. Of the remaining 18 subjects (with Nasacort® AQ treatment), there were one 2-year-old subject, five 3-year-old subjects, five 4-year-old subjects and seven 5-year-old subjects. Therefore, it appears that this trend was randomly exhibited by subjects of all numerical ages within both placebo and Nasacort® AQ treated groups.

Open-label period (24-weeks)

An ANOVA with subject identifier and visit was used with p values based on actual data was performed. The adjusted mean (SE) post-stimulation change for cortisol value at screening was 363.57 nmol/L (±28.37) and at the end of open-label period was 310.23 nmol/L (±28.373) with Nasacort® AQ (of the cosyntropin evaluable population). Therefore, the adjusted mean difference in the post-stimulation change for cortisol at the end of the open-label period versus screening was -53.34 nmol/L (±40.13) in cosyntropin evaluable Nasacort® AQ subjects. This difference was not statistically significant (p=0.1900, based on chi-square test). The distribution of pediatric patients categorized by pre- and post- stimulation plasma cortisol level criteria is listed in Table 5.

Table 5. Distribution of pediatric patients categorized by serum cortisol via CST at the end of open-label period (24-weeks).

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)

Cortisol criteria of post-stimulation levels of <496 nmol/L (<18 µg/dL) and post-stimulation minus pre-stimulation difference of <193 nmol/L (<7 µg/dL) at the end of open-label period were observed concomitantly in 2 Nasacort® AQ subjects. There was no subject who met the cortisol criteria of post-stimulation levels of <496 nmol/L (<18 µg/dL) and post-stimulation minus pre-stimulation difference of <193 nmol/L (<7 µg/dL) concomitantly at the end both the double-blind and open-label periods.

There were 30 Nasacort® AQ subjects who had a lower post-stimulation minus pre-stimulation cortisol levels difference at the end of open-label period, compared with screening. Of the 30 subjects, 19 subjects (8 placebo, 11 Nasacort® AQ) also had a lower post-stimulation minus pre-stimulation cortisol levels difference during double-blind period, compared with screening.

Of the 30 Nasacort® AQ subjects, five were 2-year-old subjects, seven were 3-year-old subjects, eight were 4-year-old subjects, and ten were 5-year-old subjects. Therefore, a trend in any particular age distribution of subjects with greater cortisol suppression at the end of open-label period was not observed.

Reviewer's Comments

The conventional low-dose Cosyntropin stimulation test is not generally accepted as a sensitive method to assess systemic effects on HPA axis function. Clinically, this test is useful in determining severe adrenocortical insufficiency, however, it has been deemed sub-optimal and inadequate for detecting mild or short-term adrenal gland suppression or for detecting isolated central adrenal insufficiency. Therefore, CST conducted on pediatric patients 2-5 years of age in study 3502 is not acceptable for the purpose of determining systemic effects of short-term corticosteroid exposure. For HPA axis evaluation, measurements of timed (24-hour) urinary free cortisol levels or serum cortisol AUC are the preferred methods of assessment.

In addition, the study design employed in study 3502 involved 4 week double-blind placebo controlled treatment duration, which is shorter than the recommended minimum of 6-week treatment for HPA axis evaluation.

Although there was no statistically significant difference between the post-stimulation changes in mean cortisol levels at the end of double-blind treatment period versus screening in the placebo

and Nasacort® AQ groups (p=0.5432), numerically greater decrease from screening in post-stimulation change was observed in Nasacort® AQ compared to placebo treated patients (-13.59 nmol/L in placebo vs. –43.13 nmol/L in Nasacort AQ treated patients). In addition, the adjusted mean (SE) difference in the post-stimulation change for cortisol at the end of open-label period versus screening was –53.34 nmol/L (40.13), although this difference was not statistically significant (p=0.1900). Majority of the Nasacort® AQ treated subjects (18 out of 33) compared to only 11/28 placebo treated subjects had a lower post-stimulation minus pre-stimulation cortisol levels difference at the end of double-blind period (compared with screening). Also, some subjects (2 placebo, 4 Nasacort® AQ) did not show the pre-specified increase (<193 nmol/L) in cortisol levels or did not reach the pre-specified level (<496 nmol/L) following cosyntropin stimulation.

Overall, based on these results, there appears to be a numerical trend towards greater suppressive effect on the HPA axis for Nasacort® AQ treated patients compared to placebo, although no statistically significant effect was documented. Since HPA axis evaluation in the pediatric age group of 2 to 5 years was limited to one dose only, an assessment of dose response was not possible. Some subjects did not show the pre-specified increase in cortisol levels or did not reach the pre-specified level following cosyntropin stimulation; therefore, a possible treatment effect can not be ruled out in a sub-set of pediatric patients, who may be more susceptible to the effects of corticosteroids.

2.3 Analytical Section

2.3.1 Was the suitability of the analytical method used to measure TAA plasma concentrations supported by the submitted information?

Plasma samples from studies 1000 and 3502 were analyzed for TAA concentrations using a validated LC/MS/MS method at (b) (4) The assay involved quantitation of TAA in 0.5 mL of human plasma using (b) (4) as the internal standard and a calibration range of 0.025 to 20 ng/mL. A (b) (4) (b) (4) column at 40°C was used with an acetonitrile and water gradient both containing 2 mM ammonium acetate and 0.2% formic acid at 0.5 mL/min. The retention time of TAA and (b) (4) was approximately 2.0 minutes with a 3.5 minute total run time. A (b) (4) (b) (4) mass spectrometer was operated under the SRM mode; parent ions monitored were m/z 302 and (b) (4) for TAA and (b) (4) , respectively.

This assay fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. The method has been summarized per individual study in Table 6. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance. TAA was stable in human plasma following 3 freeze/thaw cycles, for 79 hours at room temperature, and for 22 months at -20°C. TAA was also found to be stable in human plasma for 48 hours in a refrigerator at ~4°C.

Table 6. Summary of bioanalytical method performance during validation and sample analysis from clinical studies 1000 and 3502.

Methods report	Matrix (Anti-coagulant)	Analytes	Type of method	Calibration range (ng/mL)	Precision (CV%)		Accuracy (A%)		Clinical studies
					Within run	Between run	Within run	Between run	
ORS Job number: 142634	Plasma	Triamcinolone acetonide	LC-MS/MS	0.025 to 20.0	3.11 to 9.11	2.95 to 10.5	-3.40 to -3.00	-11.6 to -2.80	
ORS Job number: 159971	Plasma	Triamcinolone acetonide	LC-MS/MS	0.025 to 20.0	3.99 to 6.15	NA	-3.40 to 3.33	NA	XRG5029C/1000
ORS Job number: 164513	Plasma	Triamcinolone acetonide	LC-MS/MS	0.025 to 20.0	2.83 to 6.05	NA	-1.33 to 4.40	NA	XRG5029C/3502

2.4 Detailed Labeling Comments

Here are the relevant sections from the proposed label with new text (in red) and edits that relates to Clinical Pharmacology:

(b) (4)

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3 Appendix 1 – Pharmacometric Review

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Pharmacometrics Review

NDA:	20468/SE5
Submission Date	19 Nov 2007
Type of Submission	Supplemental NDA for dosing in Pediatric Patients 2 to 5 years of age
Generic Name	Triamcinolone Acetonide
Brand Name	Nasacort® AQ
Dosage Form	Suspension; Nasal Spray
Sponsor	Sanofi Aventis
PM Reviewer	Partha Roy, Ph.D.
PM Secondary Reviewer:	Christoffer Tornoe, Ph.D.
PDUFA Date:	September 18, 2008

3.1 Executive Summary

Triamcinolone acetonide (TAA), a potent corticosteroid, is the active component of Nasacort® AQ. The focus of this sNDA is on the efficacy and safety of Nasacort® AQ Nasal Spray 110 μg once daily in pediatric patients 2 to 5 years of age with allergic rhinitis (AR) as an additional patient population. The original Nasacort® AQ Nasal Spray NDA 20-468 was approved on 20 May 1996 for patients 12 years of age and above with seasonal and perennial allergic rhinitis. A pediatric supplement S-002 to NDA 20-468 was subsequently approved on 26 September 1997 for patients 6 to 11 years of age.

For pediatric patients 2-5y of age, the sponsor proposed a dosage regimen of 110 μg once daily i.e. one 55 μg spray per nostril. To support such proposal, the sponsor submitted pediatric sparse sampling PK data, which was obtained in one PK/safety study (#1000) and one (1) Phase III study (#3502) for the treatment of AR. Study 1000 also included adult AR patients receiving 2 doses (110 μg and 220 μg) of Nasacort® AQ that allowed comparison of systemic exposure between children and adults across doses within the same study. In addition to conducting population PK analysis separately with PK data obtained in studies 1000 and 3502, the sponsor conducted a comprehensive population PK analysis employing pooled PK data for both pediatrics and adults from these two studies. The sponsor claimed that the proposed pediatric dosing of 110 μg once daily will match the exposure observed in adults taking 220 μg once daily, i.e. two 55 μg sprays per nostril.

After reviewing the submitted data and analysis, the Pharmacometrics Group in the Office of Clinical Pharmacology has the following findings:

- The submitted PK data was well documented and adequate for benchmarking safety based on comparative systemic exposure assessment.

- The population PK analysis was not adequately performed due to following shortcomings: 1) the sponsor used FO as the estimation method instead of the more accurate FOCE, 2) improper dataset cleaning, and 3) WT*Age covariate has limited mechanistic (physiologic) understanding in children 2 years and older.

Therefore, new analyses were conducted using pediatric and adult systemic exposure data. The population predicted pediatric clearance and volume of distribution after intranasal administration of TAA were both dependent on body weight. In contrast to sponsor's analysis, age was not found to be a significant covariate for clearance after correcting for body weight.

Based on the results of these analyses, the proposed pediatric (2 to 5 years of age) dosage regimen of 110 μg once daily for Nasacort® AQ is acceptable as it was found to match the systemic exposure following a dose of 220 μg once daily in adults.

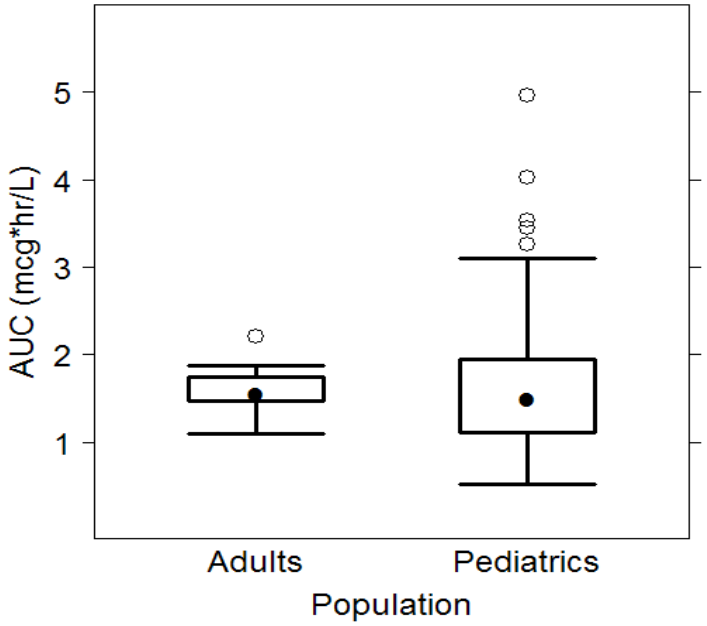
3.2 Key Questions

3.2.1 Does the exposure from pediatric dosing regimen of 110 mcg/day Nasacort® AQ match that from adult approved dose of 220 mcg/day?

The proposed pediatric dose of Nasacort® AQ 110 µg q.d. for treating AR achieved consistently measurable plasma TAA concentrations up to 8 hours. Study 1000 reported in adults peak plasma concentration of 287.7 (67.7) pg/mL and $AUC_{0\text{-last}}$ of 1354.4 (361.5) pg.hr/mL following multiple-dose administration of approved Nasacort® AQ dose of 220 mcg with an average terminal half life of 2.3-2.9 hrs and intranasal clearance of 130-162 L/hr.

The objective of pediatric dosing is to achieve exposure that does not exceed that observed in adults after multiple dosing of once daily 220 mcg of Nasacort® AQ. Such exposure is expected to provide a benchmark for safety based on which the medical officer would determine how much safety database (i.e. treatment duration and number of pediatric patients) they would like to see from the sponsor. FDA population PK analysis using NONMEM (see reviewer's analysis section) demonstrated that 110 mcg dose (1 spray per nostril) once daily will achieve same exposure as observed in adults taking 220 mcg dose (2 sprays per nostril) of Nasacort® AQ.

Figure 1. Boxplot of individual predicted AUC in adults receiving 220 mcg and pediatric patients receiving 110 mcg Nasacort® AQ.



3.2.2 Which covariates influence the PK of Nasacort® AQ?

Per FDA's reanalysis of pooled PK data from studies 1000 and 3502, pediatric clearance and volume of distribution after intranasal administration of Nasacort® AQ were both found to be dependent on body weight but constant within the pediatric and adult subgroups due to the limited body weight ranges studied. Population predicted intranasal clearance (CL/F) in children was estimated to be 70 L/hr compared to 141 L/hr in adults. Volume of distribution (V/F) in children was calculated to be 275 L which is about half of that in adults (488 L). In contrast to sponsor's analysis, age is not a significant covariate for clearance after correcting for body weight. Race and gender are also not found to be significant covariates for CL/F and V/F.

3.3 Background

Triamcinolone acetonide (TAA), a potent corticosteroid, is the active component of Nasacort® AQ. The focus of this sNDA is on the efficacy and safety of Nasacort® AQ Nasal Spray 110 µg once daily in pediatric patients 2 to 5 years of age with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) as an additional patient population. The original Nasacort® AQ Nasal Spray NDA 20-468 was approved on 20 May 1996 for patients 12 years of age and above with SAR and PAR. A pediatric supplement S-002 to NDA 20-468 was approved on 26 September 1997 for the indication of SAR and PAR in patients 6 to 11 years of age. TAA as non-aqueous formulations has also been approved for other indications and other routes of application.

To support the dosage of Nasacort® AQ in pediatrics that is sought to achieve exposures matching those of adults, the sponsor submitted PK data from two studies (1 PK/safety study and the other efficacy/safety study) in pediatric AR patients from 2 to 5 years of age. PK data following single and multiple dose intranasal administration of 110 mcg and 220 mcg doses of Nasacort® AQ in adult patients was also collected in study 1000 for comparative purposes. In addition to conducting population PK analysis separately with PK data obtained in studies 1000 and 3502, the sponsor pooled pediatric and adult PK data from both studies for a comprehensive population PK analysis using NONMEM. TAA disposition was described by a one-compartment model with first order input. Sponsor's NONMEM covariate analysis revealed that the apparent total body clearance (CL/F) of TAA was correlated with age (AGE) and body weight (WT) while the apparent volume of distribution (V/F) was strongly correlated with body weight only and not with age. Race and gender are not significant covariates of clearance and volume.

3.4 Reviewer's Comments on Sponsor's Analysis

The reviewer's identified several deficiencies of the sponsor's population PK analysis (see Appendix) that include:

1. The sponsor used FO as the estimation method in NONMEM. The preferred method would be FOCE, considered more accurate in the presence of large intra- and inter-individual errors.
2. Several places in the dataset, the sponsor set PK samples that were below the lower limit of quantification (BLOQ) to 0 instead of qualifying them as "missing" in the estimation.
3. There are few pre-dose PK samples that exhibited high concentrations, which were really not pre-dose as these samples were obtained immediately after dosing. These were not cleaned during dataset preparation.
4. WT*Age covariate has limited mechanistic (physiologic) understanding in children 2 years and older. WT covariate model appears adequate.

The identified deficiencies of sponsor's analysis will be addressed in the reviewer's analysis.

3.5 Reviewer's Analysis

3.5.1 Objective of the analysis

The objective of this analysis is to evaluate whether the Nasacort® AQ pediatric dose of 110 mcg once daily match systemic exposure in adults taking Nasacort® AQ 220 mcg q.d., i.e. the approved adult dose for treatment of allergic rhinitis.

3.5.2 Background

The clinical pharmacokinetic profile of TAA has been well documented from numerous studies conducted in healthy adults and allergic rhinitis patients. Based upon IV dosing of TAA phosphate ester in adults, the half-life of TAA was reported to be 88 minutes. The plasma half-life of corticosteroids does not correlate well with the duration of the drug's activity. The volume of distribution was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for TAA. The mean peak plasma concentration following single dose intranasal administration of 220 mcg in adults was approximately 0.5 ng/mL (range: 0.1 to 1.0 ng/mL) and occurred at 1.5 hours post dose. The average terminal half-life was 3.1 hours. The range of mean $AUC_{0-\infty}$ value was 1.4 ng•hr/mL to 4.7 ng•hr/mL between doses of 110 mcg to 440 mcg in both patients and healthy subjects. Dose proportionality was demonstrated in both normal adult subjects as well as in allergic rhinitis patients across single intranasal doses of 110 mcg to 220 mcg.

3.5.3 Data

Data from two clinical studies were used for this population pharmacokinetic (PK) analysis. The first study included sparse PK data obtained after intranasal administration of Nasacort® AQ at 110 mcg (adult and pediatric patients), 220 mcg (adult patients) for 5 days (Study 1000). The second study included sparse PK data obtained after intranasal administration of Nasacort® AQ at doses of 110 mcg over a 6-month period (Study 3502).

A population pharmacokinetic model (PPK) was developed to assess the PK variability and the influence of demographic parameters (body weight, body mass index, age, height, gender, and race) on TAA pharmacokinetics in patients with PAR. Data from studies 1000 and 3502 were pooled for this population analysis. Plasma TAA concentrations from 15 adult and 112 pediatric patients were used in the NONMEM analyses.

3.5.4 Pediatric and Adult Studies

XRG5029C-1000 (Phase I study)

This study was designed as an open-label, repeat dose, multicenter study with one treatment period for the pediatric subjects and two treatment periods for the adult subjects. The study involved dosing of 110 mcg of TAA once daily for 5 days in pediatric patients and dosing of 110 mcg and 220 mcg once daily for 5 days in adult patients in a fixed-sequence (lower to higher dose), cross-over manner with a 7-day washout between the two treatment periods. PK blood samples were obtained from each pediatric patient according to a staggered, sparse sampling strategy: 4 blood samples collected on each of study days 1 and 5, for a total of 8 samples (pre-dose, 1, 2, 3, 4, 5, 6, and 8 hr) for the study as shown below. Rich PK sampling was done in adults. A total of 30 subjects (15 children; 15 adults) completed the study.

Sampling Assignment	DAY 1				DAY 5			
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 1	Sample 2	Sample 3	Sample 4
A	1 hour	3 hours	5 hours	8 hours	pre-dose	2 hours	4 hours	6 hours
B	pre-dose	2 hours	4 hours	6 hours	1 hour	3 hours	8 hours	10 hours

XRG5029C-3502 (Phase III study)

This was a randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of Nasacort® AQ 110 mcg once daily, followed by 6-mo. open-label safety extension in children ages 2-5 years with PAR. The PK assessments were made only during the open-label segment of the study.

Peripheral venous blood samples for the measurement of plasma TAA concentrations were obtained from each child at 4 different study visits according to a sparse sampling strategy. These 4 separate blood collections spanned a total of ~20 weeks according to the following schedule:

Sample 1	Sample 2	Sample 3	Sample 4
Between 1 – 4 hours	Between 1 – 4 hours	Between 5 – 8 hours	Between 5 – 8 hours

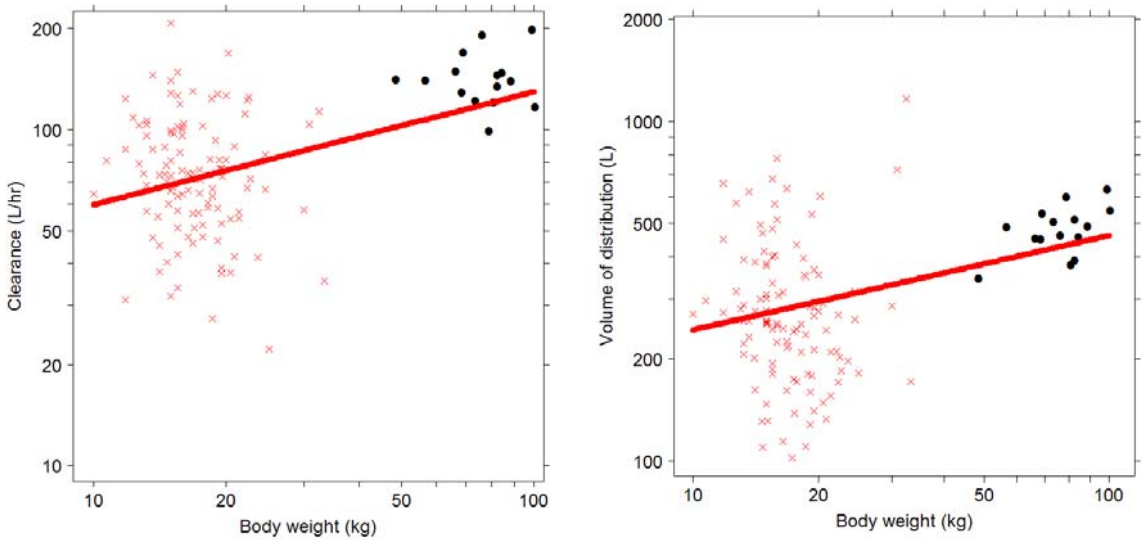
3.5.5 Results & Discussion

3.5.5.1 Population PK Model

TAA disposition was well described by a one-compartment model with first order absorption and elimination. Inter-subject variability was described by an exponential error model on the structural PK parameters (CL/F, and V/F), while the residual variability was described by a proportional error model. The NONMEM covariate analysis revealed that the apparent intranasal clearance (CL/F) was correlated with body weight (WT). The apparent volume of distribution (V/F) was also strongly correlated with body weight (see Figure 2). The population predicted adult clearance and volume of distribution are under predicted when using body weight as a continuous covariate for CL/F and V/F due to the lack of data between 30 and 50 kg and the low number of adult patients compared to pediatrics. CL/F and V/F both appear to be constant within the pediatric and adult subgroups and were therefore modeled using population (pediatric and adults) as a categorical covariate in the final model.

Race and sex were not significant covariates in the analyses.

Figure 2. Individual predicted clearance (left) and volume of distribution (right) vs. body weight scatter-plot in adults (black dots) and pediatrics 2-5y of age (red crosses) modeled with body weight as a covariate (solid lines).



The population predicted clearance and volume of distribution in pediatric patients were found to be approximately half of that in adults (see Table 1, Figure 3, and Figure 4). The inter-individual variability appears to be higher in pediatrics compared to adults although number of participants in each age group was vastly different (112 pediatric patients compared to 15 adult patients). The estimated population PK model parameters are shown in Table 1.

Table 1. Reviewer's Population PK Model Parameter Estimates.

Parameter	Unit	Population parameters		Inter-individual variability	
		Estimate	%RSE	Estimate (CV%)	%RSE
CL					
Adults	[L/hr]	141	4.61	50.4	12.2
Pediatrics	[L/hr]	69.8	5.96		
V	[L]				
Adults	[L]	488	4.36	57.4	12.2
Pediatrics	[L]	275	9.05		
Proportional residual error	[%]	38.0	8.13		

Figure 3. Individual predicted clearance vs. body weight scatter-plot (left) and box-plot (right) in adults (black dots) and pediatrics 2-5y of age (red crosses) modeled as constants within each group (solid lines).

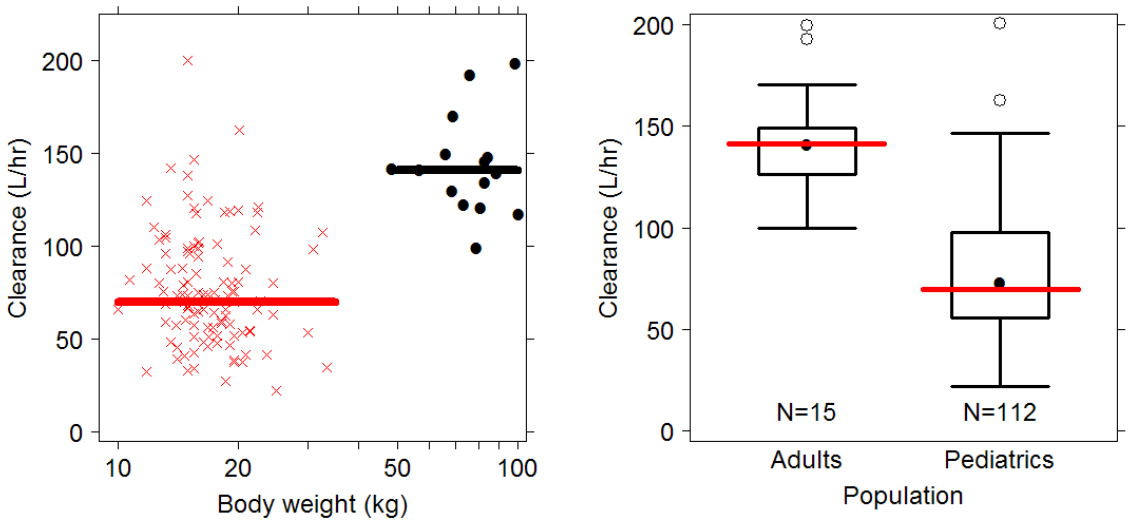


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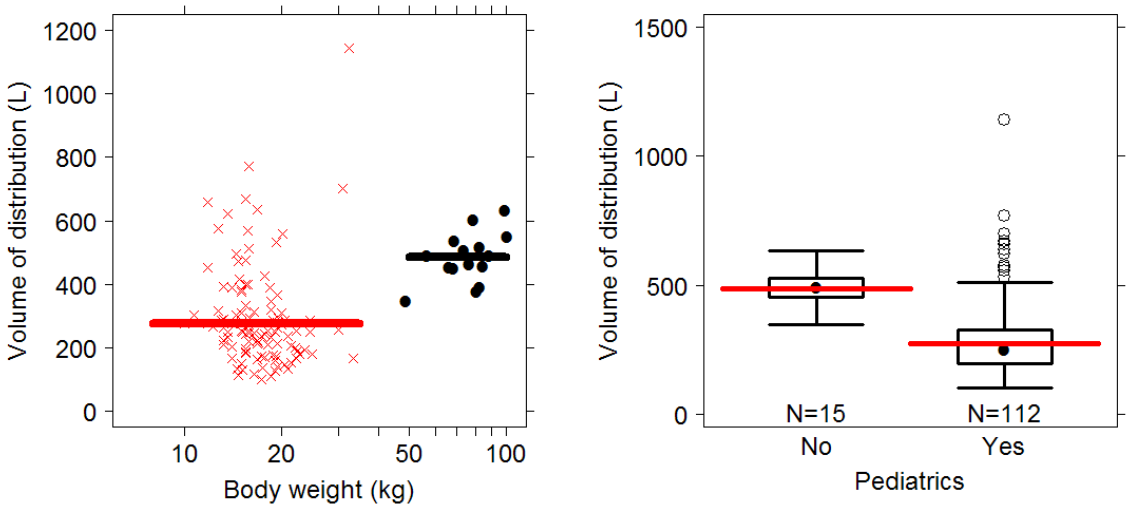
Figure 4. Individual predicted volume of distribution vs. body weight scatter-plot (left) and box-plot (right) in adults (black dots) and pediatrics 2-5y of age (red crosses) modeled as constants within each group (solid lines).



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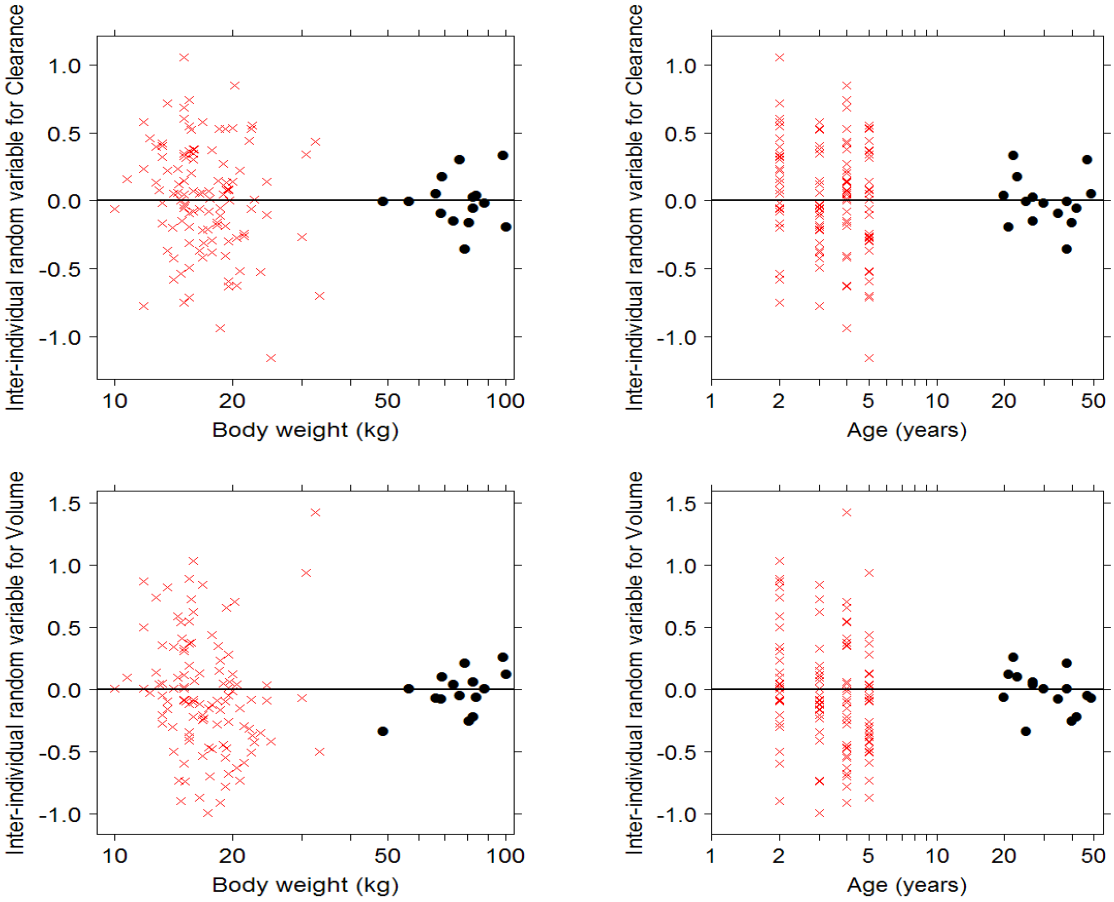
As illustrated in Figure 5, after including body weight in the clearance model, there was no apparent trend in the inter-individual random variables with age and bodyweight. Therefore, age was not considered a significant covariate for both CL/F and V/F.

Figure 5. Inter-individual random variables for clearance (top) and volume (bottom) against body weight (left) and age (right). The solid black dots are for adults and red crosses are for children.



3.5.5.2 Matching Adult and Pediatric Exposure

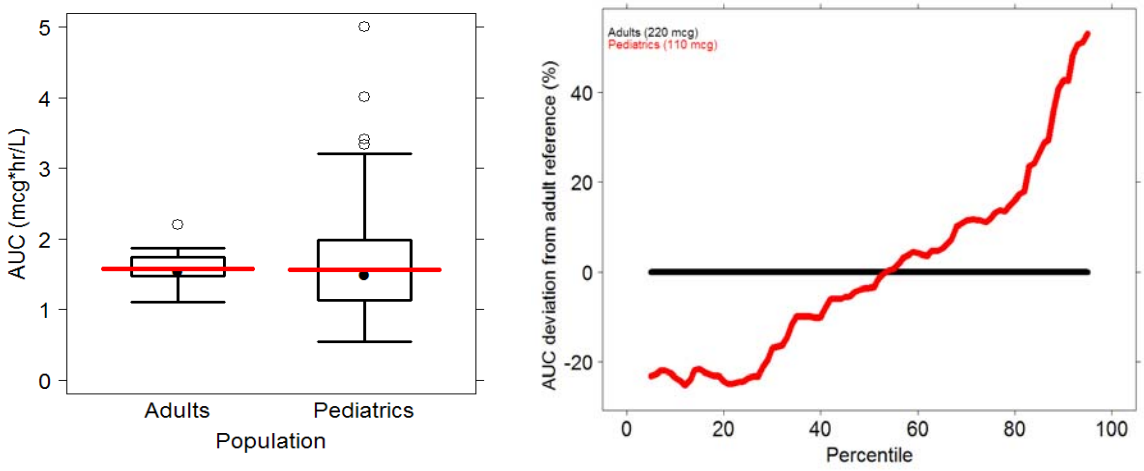
The individual AUCs were calculated using the individual predicted clearance estimates and the administered dose, i.e.

$$AUC = Dose/CL$$

The population mean predicted AUC in adults and pediatrics receiving 220 mcg/day and 110 mcg/day, respectively, are identical since the CL in adults is approximately twice that in pediatric patients receiving half the dose (see solid

red line in Figure 6 left). The median individual predicted AUCs in adults and pediatrics was similar while the tails of the AUC distribution in pediatric patients were found to be 20% lower to 50% higher than the adult exposure due to the higher variability in pediatric patients and the low number of adult patients (Figure 6 right).

Figure 6. AUC distribution in adults and pediatric patients receiving 220 and 110 mcg/day, respectively. (Left) Boxplot and (right) AUC deviation from adult reference.



3.5.5.3 Comparison of Sponsor's and FDA's population PK Analysis

FDA's population PK analysis of the data resulted in intranasal clearance estimates that are substantially different from the sponsor's estimates. From FDA's analysis, the intranasal clearance estimate for children is 70 L/hr compared to only 48 L/hr estimated by the sponsor. FDA's estimates of intranasal clearance for both adults and pediatrics closely match with the sponsor's earlier calculations from study 1000, as shown below.

Population (Protocol)	Apparent Nasal Clearance (L/h)
Adult Patients (XRG5029C-1000)	Mean (SD): 144.8 (29.5)
Pediatric Patients (XRG5029C-1000)	Mean (SD): 83.3 (28.0)

3.5.6 Conclusions

- Pediatric clearance and volume of distribution after intranasal administration of Nasacort® AQ were both dependent on body weight but constant within the pediatric and adult subgroups due to the limited body weight ranges studied.

- The sponsor's proposed pediatric (2 to 5 years of age) dosing regimen of 110 mcg Nasacort® AQ once daily was found adequate to match the adult exposure following a dose of 220 mcg once daily, i.e. the approved daily dose for treating allergic rhinitis in adults.

3.6 Synopsis of Sponsor's Population PK Modeling

Title

A population pharmacokinetic (PPK) study: A combined analysis of Phase I and Phase III studies after intranasal administration of an aqueous formulation of triamcinolone acetonide (TAA: Nasacort® AQ) in adult and pediatric patients with allergic rhinitis.

Protocols

Data from two clinical studies were used for this population pharmacokinetic (PK) analysis. The first study included sparse PK data obtained after intranasal administration of Nasacort® AQ at 110 mcg (adult and pediatric patients), 220 mcg (Adult patients) for 5 days (Study XRG5029C-1000). The second study included sparse PK data obtained after intranasal administration of Nasacort® AQ at doses of 110 mcg doses over a 6-month period (Study XRG5029C-3502).

Objectives

The primary objective of study 1000 was to characterize the single dose and steady-state pharmacokinetics of TAA in pediatric subjects 2 to 5 years of age compared with adult subjects 18 to 50 years of age following 5 days of intranasal dose administration and to evaluate the safety and tolerability of 5 days of intranasal TAA in pediatric subjects.

The primary objective of study XRG5029C-3502 was to demonstrate the safety and efficacy of once daily administration of Nasacort® AQ 110 mcg compared with placebo in children 2-5 years of age with allergic rhinitis. In addition, as one of the secondary objectives, plasma samples were collected to assess the pharmacokinetics (PK) of TAA using population analysis.

The objective of this population pharmacokinetic report was to assess the population PK of TAA in study XRG5029C-1000 (adult and pediatric patients with allergic rhinitis) and study XRG5029C-3502 (pediatric patients with allergic rhinitis).

Bioanalysis

Plasma samples were analyzed for TAA concentrations using a validated LC/MS/MS method with a lower limit of quantification (LOQ) of 25 pg/mL. The same method was used in both studies.

Data Analysis

Observed TAA plasma concentration data were analyzed by nonlinear mixed-effects modeling (NONMEM program, Version 5.0, Level 1.1) using a one-compartment structural pharmacokinetic model.

Results

A total of 1197 TAA concentrations in plasma collected from 15 adult and 120 pediatric patients were used in the NONMEM analyses: 821 concentration data points from Study 1000, and 376 from Study 3502.

TAA disposition was well described by a one-compartment model with first order input. Inter-subject variability was described by an exponential error model on the structural PK parameters (CL/F, and V/F), while the residual variability was described by a combination of additive and proportional error model. The NONMEM covariate analysis revealed that the apparent total body clearance (CL/F) was correlated with age (AGE), body weight (WT). The apparent volume of distribution (V/F) was strongly correlated with body weight. Race (RACE) and sex (SEX) were not significant covariates in the analyses. The covariate AGE was correlated with body weight, and was chosen in combination with weight in the final model since incorporation of this covariate resulted in a greater drop in the objective function compared to body weight alone.

According to the final model, CL/F in a typical adult subject was estimated to be 151 L/h (2.02 L/hr/kg) in adults aged 20-49 years and 48.3 L/h (2.87 L/hr/kg) in children aged 2-5 years. The CL/F of TAA was correlated with age and body weight:

$$CL/F\ (L/h) = 26 + 193 * (WT/70kg * AGE/25yrs)$$

V/F was estimated to be 456 L (6.05 L/kg) in a typical adult subject and 275 L (16.2 L/kg) in a typical pediatric subject. The V/F of TAA was correlated with WT:

$$V/F\ (L) = 785 * (WT/70\ kg)^{0.739}$$

In the final model, inter-individual variability of TAA CL/F was significantly related to body weight and age, and that of V/F was significantly related to body weight. Inter-patient variability associated with clearance was estimated to be 87.5%, while that with V/F was 68.8%. The residual variability for the final model was 52.8% with a SD of 15.9 pg/mL.

Conclusions

In pediatric subjects with allergic rhinitis, as in adults, the pharmacokinetics of TAA following intranasal administration of Nasacort® AQ can be described by a one-compartment model with a first-order input. Age and bodyweight is strongly correlated with CL/F and the bodyweight is strongly correlated with V/F. Based on differences in apparent total body clearance, a dose of 110 mcg daily may be used in pediatric subjects aged 2 to 5 years of age in order to target exposures similar to those achieved after administration of 220 mcg daily to adults.

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Partha Roy
8/8/2008 04:07:04 PM
BIOPHARMACEUTICS

Christoffer Tornoe
8/8/2008 04:14:48 PM
BIOPHARMACEUTICS

Wei Qiu
8/8/2008 04:18:02 PM
BIOPHARMACEUTICS