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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00132925
		Study Code:	XRG5029C_3502
Generic drug name:	Triamcinolone acetonide	**Date:**	09/Aug/2007

Title of Study: A randomized, double-blind, parallel group, placebo-controlled, four-week efficacy and safety evaluation of NASACORT AQ 110 µg qd, followed by six-month open-label safety in children ages 2-5 years with perennial allergic rhinitis: XRG5029C/3502

Investigator: multicenter study

Study centres: 59 of 64 actively enrolling study centers (sites) in the United States (US)

Study period:

Date of first subject enrolled: 04/Mar/2004

Date of last subject completed: 06/Mar/2006

Phase of development: III (efficacy and safety)

Objectives: Primary objective: (a) to demonstrate the efficacy of administration of NASACORT AQ 110 µg once daily (qd), compared with placebo in children 2 to 5 years of age with perennial allergic rhinitis (PAR); and (b) to assess the safety of NASACORT AQ 110 µg qd in children 2 to 5 years of age with PAR **Secondary objectives:** (a) to evaluate the systemic effect of NASACORT AQ 110 µg qd on the hypothalamic-pituitary-adrenal (HPA) axis in a subset of children 2 to 5 years of age; and (b) to further characterize the steady-state exposure (pharmacokinetics [PK]) of NASACORT AQ µg qd in a subset of children 2 to 5 years of age

Methodology: multicenter, randomized, placebo controlled, parallel group during the 4-week efficacy and safety double-blind treatment period. Open-label during 6-month safety period with active investigational product

Number of subjects:

Planned: 400 (200/treatment arm) evaluable subjects during double-blind period. Over-enrollment to ensure 250 subjects by end of open-label period. A minimum of 40 (20/treatment arm) evaluable subjects for HPA axis

Randomized: 474 subjects randomized (238 placebo, 236 NASACORT AQ) during double-blind period

Treated: 474 subjects (238 placebo, 236 NASACORT AQ) treated during double-blind period. 428 subjects (NASACORT AQ) treated during open-label period

Evaluated:

Periods	Population types	Placebo (n)	NASACORT AQ 110 µg qd (n)	Total (N)
Double-blind	Intent-to-treat	233	231	464
	Completer	215	212	427
	Per-protocol	198	194	392
	Cosyntropin evaluable	28	33	61
Open-label	Intent-to-treat		410	410
	Completer		355	355
	Pharmacokinetics evaluable		111	111
	Cosyntropin evaluable		49	49

Diagnosis and criteria for inclusion: Male or female subjects, 2 to 5 years of age who had at least 1-year history of PAR with or without seasonal allergic rhinitis (SAR); positive or documented (in the past year) skin prick test or radioallergosorbent test (RAST) to a relevant perennial allergen in the subject's environment; and sum of symptom scoring for nasal stuffiness, nasal discharge, and sneezing of at least 18 out of 36 for 3 out of 5 days before randomization (Study visit 2), including the morning of Study visit 2 (ie, 3 symptoms x 3 maximum score x 4 days). Those subjects participating in the HPA axis assessment: screening morning serum cortisol of 5 µg/dL (138 nmol/L) and 30 minute post-stimulation (via cosyntropin stimulation test [CST]) of =18 µg/dL (496 nmol/L) confirmed by immunoassay

Investigational product: NASACORT AQ Nasal Spray

Dose: 110 µg/day during double-blind period. And, 110 µg/day during open-label period
Administration: Intranasally as 2 sprays qd (1 spray/nostril)

Duration of treatment: Double-blind period: approximately 4 weeks **Open-label period**: approximately 6 months **Duration of observation: Double-blind period:** approximately 6 weeks **Open-label period:** approximately 6 months and 1 week

Reference therapy: placebo

Dose: placebo during double-blind period only

Administration: intranasally as 2 sprays qd (1 spray/nostril)

Criteria for evaluation:

Efficacy: daily reflective (previous 24 hours) and instantaneous (immediately prior to dosing) ratings were performed upon arising in the morning before taking investigational product. For both the reflective and instantaneous symptom assessments, the symptoms rated daily were: nasal stuffiness, nasal discharge (anterior and/or posterior drainage), sneezing, nasal itching, and total eye symptoms of itching, tearing, and/or redness. The severity of each symptom was scored on a scale of 0 through 3, such that: 0 = symptom absent; 1 = mild (present but not annoying to self); 2 = moderate (present and annoying to self but does not interfere with sleep or daily living); or 3 = severe (interferes with/or unable to carry out activities of daily living or sleep).

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, nasal itching, and total eye symptoms of itching, tearing, and/or redness.

Efficacy variables were as follows: (a) adjusted mean change from baseline over the double-blind treatment period in the mean daily Total Nasal Symptom Score (TNSS) - instantaneous (immediately prior to dosing); (b) adjusted mean change from baseline over the double-blind treatment period in the mean daily TNSS - reflective (previous 24 hours); (c) adjusted mean change from baseline over the double-blind treatment period in the mean daily TNSS - instantaneous at Weeks 1, 2, 3, and 4; (d) adjusted mean change from baseline over the double-blind treatment period in the mean daily TNSS - reflective at Weeks 1, 2, 3, and 4; (e) adjusted mean change from baseline over the double-blind treatment period in the Total Symptom Score (TSS) - instantaneous; (f) adjusted mean change from baseline over the double-blind treatment period in the TSS - reflective; (g) physician's global evaluation of efficacy; (h) subject's global evaluation of efficacy; (i) treatment failure after 2 weeks of double-blind treatment; (j) number of subjects using rescue medication (CLARITIN® Children's fruit-flavored syrup); and (k) frequency of rescue medication use

Safety: adverse events (AEs) reported by the subject or noted by the investigator. Of these, subjects participating in the HPA axis assessment were required to have a set of on-treatment cortisol values. Physical examinations including vital signs

Pharmacokinetics: subjects participating in the PK assessment with adequate plasma TAA concentration-time data during open-label only

Pharmacokinetics sampling times and bioanalytic method: Sampling times: peripheral venous blood samples were obtained for measurement of triamcinolone acetonide (TAA) plasma concentrations according to a staggered, sparse sampling strategy. Each subject participating in the PK assessment was to have 4 blood samples collected during the open-label period only on Study visits 5, 6, 7, and 8. The investigator was instructed to draw blood for 2 of these 4 visits between 1 and 4 hours postdose; the remaining 2 visits were drawn between 4 and 8 hours postdose. **Bioanalytic method:** liquid chromatography assay method with tandem mass spectrometric detection (LC-MS/MS); assay range: 25 to 20 000 pg/mL

Statistical methods: For the double-blind period, the changes from baseline variables were analyzed by analysis of covariance (ANCOVA) with treatment and pooled site as class variables and the baseline value for the variable being analyzed as the covariate. From this model are presented the mean differences between treatments for the adjusted mean changes from baseline and their 95% confidence interval. Consistencies of effects across subgroups were examined using an ANCOVA model with treatment, pooled site, subgroup, and subgroup by treatment interaction as class variables and the variable being analyzed as the covariate. For these analyses, last observation carried forward (LOCF) was used to impute isolated missing symptom scores while the subject was taking investigational product. The physician's and subject's global evaluation of efficacy were analyzed using a Cochran-Mantel-Haenszel procedure (CMH) controlling for pooled site while using modified relative to an identified distribution (RIDIT) scores. CMH was used to evaluate the number of subjects with treatment failure after 2 weeks of double-blind treatment. An ANCOVA model similar to the one described above for the changes from baseline and descriptive statistics, means, medians, standard deviations and percentiles were used to evaluate the use of rescue medication. For the open-label period descriptive statistics, number and percent of subjects, were used to present the results for the physician's and subject's global evaluation of efficacy. Descriptive statistics were used to describe the results for the use of rescue medication. Numbers and percents of subjects were used to describe the results for adverse events, in particular the treatment-emergent adverse events (TEAEs).

For the double-blind period, ANCOVA models were used to evaluate the differences between treatments for the changes from baseline of the cosyntropin stimulation tests. In addition, numbers and percent of subjects were used to describe the number of subjects meeting particular cortisol thresholds before and after stimulation at screening and the end of the double-blind period. For the open-label period, numbers and percent of subjects were used to describe the number of subjects meeting particular cortisol thresholds before and after stimulation at screening and the end of the open-label period.

For the pharmacokinetics, nonlinear mixed effects modeling using NONMEM was used for the plasma concentration-time data to estimate the primary PK parameters for TAA in the pediatric population, including the associated inter-subject variability. Bayesian POSTHOC parameters for individual subjects were also estimated.

Summary: Overall, the results of the analyses of the efficacy variables support the efficacy of NASACORT AQ compared to placebo in pediatric subjects 2 to 5 years of age with a diagnosis of PAR.

Efficacy results: **Primary variable**: TNSS - instantaneous: Statistical significance was not observed

Total Nasal Symptom Score - instantaneous mean change from baseline over the double-blind period (intent-to-treat population)

	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

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. End of double-blind period was defined as Study visit 4. 95% CI = 95% Confidence interval for the differences of adjusted means; NAQ = NASACORT AQ 110 µg qd; PBO = Placebo; SE = Standard error
Source:
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Secondary variables: TNSS - reflective: Statistical significance was observed.

Total Nasal Symptom Score - reflective mean change from baseline over the double-blind period (intent-to-treat population)

	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. End of double-blind period was defined as Study visit 4. 95% CI = 95% Confidence interval for the differences of adjusted means; NAQ = NASACORT AQ 110 µg qd; PBO = Placebo; SE = Standard error
Source:
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The analyses of the TSS - instantaneous and TSS - reflective over the double-blind treatment period were consistent with the analyses of the respective TNSS; the treatment differences were 038 (p=0.1379) and 0.47 (p=0.0566), respectively. The analyses of the TNSS - instantaneous and TNSS - reflective by week showed improvements favoring NASACORT AQ for each week. Treatment differences tended to increase over time, particularly for the TNSS - reflective, where it reached statistical significance also at Week 4. Based on the physician's global evaluation of treatment efficacy, more subjects showed moderate, marked or complete relief at the end of the 4-week double-blind treatment with NASACORT AQ than with placebo. More subjects on placebo showed only slight or no relief at the end of the double-blind treatment period than on NASACORT AQ. The difference was statistically significant (p=0.0043). The results of the subject's global evaluation of treatment efficacy were similar to the physician's global evaluation with the exception of the percentages of subjects who reported marked relief, which were similar between the 2 treatment groups. The difference did not reach statistical significance (p=0.0658). The use of rescue medication was comparable between the 2 treatment groups during the double-blind period.

To further describe the treatment effects, exploratory subgroup analyses were performed. For age, sex, and baseline composite nasal symptom score for inclusion, there was no lack of consistency (p>0.25). Although the p value for race was p=0.0592 and the signs of the mean differences for white and non-white subjects were not the same, it was merely a quantitative interaction and the consistency of effect cannot be rejected. Thus, there was no lack of consistency for all subgroups investigated. Although the subgroup analyses by age (2, 3, 4, or 5 years old) did not reveal an interaction between the treatment responses and the variables, the treatment differences in the 2-year-old subjects favored placebo in the analyses of the TNSS - instantaneous and TNSS - reflective (ranked ANCOVA) in a more pronounced way than race. Therefore the primary and the majority of the secondary efficacy variables were analyzed in addition to the pre-specified analyses in the ITT population of 3- to 5-year olds.

Total Nasal Symptom Score - instantaneous mean change from baseline by subgroup (3- to 5-year-olds only) over the double-blind period (intent-to-treat population)

	Placebo		NASACORT AQ 110 µg qd		Difference			Treatment effect
	(N=181)		(N=188)			PBO - NAQ		p value
	Adjusted mean	SE	Adjusted mean	SE	Adjusted mean	95% CI	SE	
Baseline	7.65	0.165	7.56	0.162	0.09	(–0.33;+0.52)	0.217	0.6659
Change	–1.62	0.186	–2.25	0.182	0.63	(+0.15;+1.11)	0.244	0.0108

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. End of double-blind period was defined as Study visit 4. 95% CI = 95% Confidence interval for the differences of adjusted means; NAQ = NASACORT AQ 110 µg qd; PBO = Placebo; SE = Standard error
Source:
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Total Nasal Symptom Score - reflective mean change from baseline by subgroup (3- to 5-year-olds only) over the double-blind period (intent-to-treat population)

	Placebo		NASACORT AQ 110 µg qd		Difference			Treatment effect
	(N=181)		(N=188)			PBO - NAQ		p value
	Adjusted mean	SE	Adjusted mean	SE	Adjusted mean	95% CI	SE	
Baseline	7.90	0.158	8.00	0.154	–0.10	(–0.50;+0.31)	0.207	0.6367
Change	–1.61	0.179	–2.20	0.175	0.59	(+0.13;+1.05)	0.235	0.0129

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. End of double-blind period was defined as Study visit 4. 95% CI = 95% Confidence interval for the differences of adjusted means; NAQ = NASACORT AQ 110 µg qd; PBO = Placebo; SE = Standard error
Source:
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The analysis of the primary efficacy variable TNSS - instantaneous over the double-blind period in the ITT population of 3- to 5-year-olds demonstrated a between-treatment difference of 0.63 in favor of NASACORT AQ, which was also statistically significant (p=0.0108). The analysis of the TNSS - reflective over the double-blind period in the same ITT population showed a between-treatment difference of 0.59 in favor of NASACORT AQ, which also was statistically significant (p=0.0129). The analyses of other secondary efficacy variables also showed consistently larger and statistically significant treatment differences favoring NASACORT AQ.

Safety results: Treatment with NASACORT AQ 110 µg administered intranasally to 2- to 5-year-old pediatric subjects with PAR was generally safe and well tolerated. The analysis of TEAEs reported during the 4 weeks of double-blind treatment showed comparable reporting rates for placebo (48.3%) and NASACORT AQ (50.8%). The most frequently affected system organ classes, which also showed higher reporting rates for AEs on NASACORT AQ, were Gastrointestinal Disorders [placebo 16/238 (6.7%), NASACORT AQ 27/236 (11.4%)], Infections and Infestations [placebo 31/238 (13.0%), NASACORT AQ 38/236 (16.1%)], and Injury, Poisoning and Procedural Complications [placebo 4/238 (1.7%), NASACORT AQ 17/236 (7.2%)]. The most frequently reported TEAEs with higher frequencies on NASACORT AQ were headache, pharyngolaryngeal pain, nasopharyngitis, abdominal pain upper, diarrhea, asthma, rash, excoriation, and rhinorrhoea. There were no serious adverse events (SAEs) during the double-blind treatment period. Seven (1.5%) subjects (3 placebo, 4 NASACORT AQ) during the double-blind period discontinued due to TEAEs. In general, there was no apparent difference in the type, number, duration, severity, or resolution of TEAEs on NASACORT AQ between the double-blind and open-label components of the study in these pediatric subjects.

As expected for long-term studies and running over a prolonged period, upper respiratory tract infections and their symptoms dominate among the reported TEAEs during the open-label period. Seven (7) subjects reported SAEs during the open-label period: none of which were considered causally related to NASACORT AQ. Fifteen (3.5%) subjects on NASACORT AQ during the open-label period discontinued due to TEAEs.

The overall profile of AEs observed in the 2- to 5-year-old pediatric subjects studied was consistent with the known AEs associated with the use of NASACORT AQ in 6- to 12-year-old pediatric subjects.

In the cosyntropin stimulation test, 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). The comparison of the cortisol levels post-stimulation with cosyntropin at the end of the open-label treatment period and screening also did not reveal any statistically significant difference (p=0.1900). Based on these results, there appears to be no consistent suppressive effect on the HPA axis. However, some subjects did not show the pre-specified increase in cortisol levels or did not reach the pre-specified level following cosyntropin stimulation. A possible treatment effect can, therefore, not be excluded.

There were no clinically meaningful changes or observations for any of the vital signs analyzed in comparison to placebo at the end of the double-blind treatment period or over the course of the open-label treatment period. Especially, there was no effect of NASACORT AQ on the subjects' height.

Pharmacokinetics results: TAA plasma concentration-time data was pooled across sparse sampling strategies. NONMEM was used for the plasma concentration-time data to estimate the primary PK parameters for TAA in the pediatric population, including the associated inter-subject variability.

In pediatric subjects with PAR (with or without SAR), as in adults, the PK of TAA following intranasal administration of NASACORT AQ can be described by a one compartment model with first order input. Age and weight are strongly correlated with the apparent total body clearance (CL/F) following intranasal administration; weight is strongly correlated with the apparent volume of distribution (V/F). Population estimates of CL/F and V/F based on data from this study do not appear to be different, compared with the estimates obtained in another pediatric PK study (XRG5029C/1000) conducted by the sponsor. Based on differences in CL/F, a dose of 110 µg qd may be used in pediatric subjects 2 to 5 years of age in order to target exposures similar to those achieved with intranasal administration of NASACORT AQ at a dose of 220 µg qd in adults.

Date of report: 15-Jun-2007