

<p><i>These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert</i></p>		
<p>For product information, please log-on to the web site www.nasacort.com or contact one of our Medical Information Specialists at (800) 633-1610.</p>		
<p>Proprietary Drug Name: NASACORT® AQ Nasal Spray</p>	<p>INN: Triamcinolone Acetonide Nasal Spray</p>	<p>Therapeutic area and FDA approved indications: For the treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 6 years of age and older.</p>
<p>Name of Sponsor/Company: Aventis Pharmaceuticals, Inc., Member of the sanofi-aventis group</p>		
<p>Title of Study: (XRG5029C/4004). Randomized, Double-blind, Placebo-Controlled, Crossover, Single Center Study Comparing the Effects of Nasacort® AQ 220 µg on Sleep Microarousals and Quality of Sleep in Subjects with Perennial Allergic Rhinitis – A Pilot Trial (SMART)</p>		
<p>Principal Study Investigators: David I. Bernstein, MD Bernstein Clinical Research Center, LLC 8444 Winton Road Cincinnati, Ohio 45231</p>		
<p>Study centre: 1 US center</p>		
<p>Publication: Bernstein D, Scharf M, Bernstein C, Diener P, Qiu C, Garcia J, Georges G. Effects of triamcinolone acetonide aqueous on sleep microarousals in perennial allergic rhinitis: a pilot study. <i>Proceedings of the American Thoracic Society</i> 2005;2:A329.</p>		
<p>Study period (years): (date of first enrolment) (date of last completed): 25 July, 2002 to 3 June, 2003</p>	<p>Phase of development: Phase IV</p>	
<p>Objectives: The primary objective of the study was to explore the potential of Nasacort® AQ 220 µg once daily to reduce microarousals [Cyclic Alternating Pattern Sequences (CAPS) rates] in sleep Stages 1 and 2, as measured by electroencephalography (EEG), in subjects with perennial allergic rhinitis (PAR) and moderate to severe nasal congestion.</p>		

<p>Methodology: Randomized, double-blind, placebo-controlled, crossover (Balaam's design: active-active, active-placebo, placebo-active, placebo-placebo), single center study.</p>
<p>Number of patients (planned and analyzed): 28 subjects were planned to complete the study; 7 subjects per sequence (4 sequences). To achieve this, assuming approximately a 10% dropout rate, 32 subjects were to be enrolled.</p> <p>35 subjects were enrolled, 34 were randomized. Of the 34 randomized subjects there were 34 subjects in the intention-to-treat (ITT) population, 34 subjects in the safety population, and 30 subjects in the per-protocol population.</p>
<p>Diagnosis and main criteria for inclusion: Subjects included in the study were male or female aged 18-55 years, who were on any intranasal corticosteroids (INS) ± H1 receptor antagonist and no decongestant for a minimum of 4 weeks or previously untreated subjects whose rhinitis symptoms, as diagnosed by the investigator, were sufficiently troublesome to require INS, and met the symptom scores for randomization. They had at least a one-year history of PAR, positive skin test to dust mite, and may also have had positive skin test to cat or dog dander with active home exposure.</p>
<p>Test product, dose and mode of administration, batch number:</p> <p>Nasacort® AQ Nasal Spray, 220µg (2 sprays / nostril once daily), batch # MN4886</p>
<p>Duration of treatment: Nasacort® AQ Nasal Spray for 4 weeks OR matching placebo Nasal Spray for 4 weeks</p>
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>Matching placebo Nasal Spray, (2 sprays / nostril once daily) batch # N10103B</p>
<p>Criteria for evaluation:</p> <p>Efficacy: Primary efficacy data was the % CAPS rates expressed in % epochs of NREM (non-rapid eye movement) sleep Stages 1 and 2 containing CAPS.</p> <p>Secondary efficacy data were the number of apneas and sleep latency, daily nasal rhinitis symptom scores [nasal congestion, nasal discharge (anterior and/or posterior drainage), sneezing, itchy nose], the Total Nasal Symptom Score (sum of the 4 nasal symptoms scores), acoustic rhinomanometry, NPIFR, nasal eosinophils, and the subjective Patient and Global Evaluations questionnaires.</p> <p>Safety: Safety was assessed primarily on the basis of clinical adverse events (AE).</p>
<p>Statistical methods: Summary statistics were presented to give a general description of the subjects and an overview of the subject disposition, baseline characteristics, and efficacy and safety data. In general, subject disposition summaries were based on the ITT (Intent-to-treat) population (all randomized subjects). Baseline and efficacy data analyses were based on per-protocol population.</p> <p>Safety data summaries were based on the safety population.</p> <p>Categorical variables [ie, sex, race, skin tests), physical examination, prior medication, concomitant medication, medical history, concomitant illness, adverse event] were summarized using the number and percentage of subjects in each category.</p>

Continuous variables were summarized to yield the number of subjects (n), mean, standard deviation/standard error, median, minimum, and maximum. Continuous variables included: age, weight, height, years with allergic rhinitis, medication compliance, vital signs, EEG variables, sleep quality, subjective estimate of numbers of awakenings, apneas index, hypopnea index, respiratory disturbance index, NPIFR, acoustic rhinomanometry, individual nasal symptom scores (nasal congestion, nasal discharge, sneezing, nasal itching), TNSS, patient and physician global evaluations questionnaires, Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI).

Correlations were explored for any potential relationship among some of the secondary efficacy variables. Pearson correlation coefficients and the P-values to test significance of the correlation were calculated for specific secondary efficacy variables. Statistical tests for differences between treatment groups were presented as 2-sided P-values (4 decimal places). All statistical treatment group comparisons were carried out at a two-tailed significance level of 0.05, and statistical significance was defined at P-value of <0.05.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

% CAPS: Both Nasacort® AQ 220 µg/day and placebo significantly reduced the primary efficacy variable of % CAPS [Nasacort® AQ: mean change = -5.1 ($P = .0069$ vs baseline); placebo: mean change = -7.3 ($P = .0003$ vs baseline)] at the end of study. However, the difference in % CAPS between Nasacort® AQ and placebo was not significant [mean difference = 2.2 ($P > 0.2$)] at the end of study.

Secondary EEG Variables: Of the 16 secondary sleep variables, statistically significant differences between Nasacort® AQ and placebo were observed only for % Stage 1 sleep and subjective estimate of number of awakenings. The mean difference in % Stage 1 sleep between Nasacort® AQ and placebo was -3.0 ($P = 0.0021$). The mean change from baseline for Nasacort® AQ was -0.5 ($P > 0.5$); for placebo, it was 2.5 ($P = 0.0055$). For subjective estimate of number of awakenings, the mean difference between Nasacort® AQ and placebo was -0.9 ($P = 0.0155$). The mean change from baseline was 0.1 ($P > 0.6$) for Nasacort® AQ and 1.0 ($P = 0.0008$) for placebo.

Acoustic Rhinomanometry: There was no significant improvement from baseline for Nasacort® AQ in acoustic rhinomanometry variables ($P > 0.07$).

Nasal Eosinophils: Nasacort® AQ significantly reduced nasal eosinophils compared with baseline (mean change = -0.5, $P = .0017$); placebo mean change from baseline was not significant (mean change = -0.1, $P > .6$). The difference in mean change from baseline between Nasacort® AQ and placebo was statistically significant (mean difference = -0.4, $P = .0294$).

Nasal Peak Inspiratory Flow Rate (NPIFR): Both Nasacort® AQ and placebo significantly decreased the mean nasal peak inspiratory flow rate (NPIFR) weekly and overall compared with baseline ($P < 0.002$ for Nasacort® AQ; $P < 0.002$ for placebo). There was no significant difference in mean change from baseline in NPIFR between Nasacort® AQ and placebo ($P > 0.5$).

Total Nasal Symptom Score (TNSS): For TNSS, the change from baseline was -2.0 ($P < 0.0001$) for Nasacort® AQ and -1.8 for placebo ($P < 0.0001$). The difference between Nasacort® AQ and placebo was not significant ($P > 0.2$).

Patient & Physician Global Evaluations: Patient Global Evaluation of efficacy at the end of treatment was 1.6 for Nasacort® AQ ($P = 0.0153$ vs placebo) and 0.6 for placebo. The same scores

were observed for Physician Global Evaluation at the end of treatment ($P=0.0176$ v s. placebo).

SAFETY RESULTS: Over the course of the study, there were a total of 7 out of 34 subjects (21%) with 10 incidences of treatment-emergent adverse events (TEAE). There was 1 subject each who experienced at least one TEAE and they included: bee stings, bronchial infection, headache, nasal congestion, nasal discharge, nose bleeds, sinusitis, sinus pain, sore nose, and viral infection. All TEAE were moderate in intensity. Nose bleeds and sore nose were considered related to study medication as deemed by the investigator.

There were no deaths. There were no other serious adverse events.

One subject discontinued the study due to an adverse event (bronchial infection) on Day 33 of Nasacort® AQ treatment. The subject's adverse event resolved after 8 days after amoxicillin treatment. The investigator considered this adverse event not related to study medication.

Alert terms were not specified and there was no overdose observed with Nasacort® AQ.

Vital signs and physical examinations were not remarkable.

Date of the report: 11 March, 2003