1 THE STUDY IN SUMMARY

The objective of this multicenter, randomized, open-label study was to compare the safety and efficacy of Rhinocort (budesonide) Aqua Nasal Spray, versus Nasalcrom (cromolyn sodium), for the long-term (52-week) treatment of pediatric patients with perennial allergic rhinitis. Patients aged 6-17 years who had completed a six-week double-blind placebo-controlled Rhinocort Aqua study (Study No. 05-3039) were eligible for enrollment into the present study; in addition, pre-pubertal patients (male patients aged 11 years or younger, female patients aged 10 or younger) who did not participate in Study No. 05-3039 were also eligible for enrollment.

The study consisted of a four-week washout period (for 05-3039 patients only) and a one-week baseline period, which was followed by a 52-week treatment period. On entry into the treatment period patients were randomized in a ratio of 2:1 to receive either Rhinocort Aqua Nasal Spray, 256 µg administered once daily, or Nasalcrom, 10.4 mg administered four times a day. During the study patients were seen at the clinic on seven occasions: during the screening period, at randomization (Week 0) and at treatment period Weeks 4, 12, 26, 39 and 56.

Efficacy variables assessed in this study were the changes in nasal symptom scores (composite nasal index score and individual symptom scores), nasal cytology, and Quality of Life assessments.

Safety variables assessed in this study were: reported adverse events; physical exam findings, vital signs; laboratory safety tests; skeletal age (bone age), measured by X-rays of the hand and wrist; growth, measured by stadiometry at clinic visits; bone mineral density, measured by bone densitometry; and HPA-axis function, determined by measurement of basal and ACTH-stimulated plasma cortisol concentrations.

Differences between treatment groups in growth and growth velocity, bone mineral density, nasal and ocular symptom scores and Quality of Life scores were compared using analysis of variance methods. Differences between treatment groups in the percent of patients discontinuing from the study were compared using Fisher's exact test. Differences between treatment groups in baseline demographics, skeletal age, reported adverse events, physical exam findings, vital signs, laboratory safety tests and plasma cortisol levels, were compared using descriptive statistics.

A total of 313 patients were randomized and received study drug; 206 patients received Rhinocort Aqua, and 107 patients received Nasalcrom. The study population was primarily pre-pubertal (77%) and male (66%), with a mean age of 9.3 years. Patient demographics and baseline characteristics were generally similar between treatment groups; however, mean age and mean height were numerically lower in the Rhinocort Aqua group when compared to the Nasalcrom group (9.3 versus 9.4 years, and 138.1 versus 138.5 cm, respectively).

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Following 52 weeks of treatment mean changes from baseline in nasal index scores (0-9 scale) were -3.07 and -2.07 in the Rhinocort Aqua and Nasalcrom treatment groups, respectively; the greater reduction in Nasal Index Scores in the Rhinocort Aqua group was statistically significant (p<0.001), when compared to the Nasalcrom group. In addition, statistically significantly greater reductions over the 52-week treatment period in individual nasal and ocular complex symptoms were associated with Rhinocort Aqua, compared to Nasalcrom.

Nasal cytology results demonstrated that Rhinocort Aqua was associated with statistically significant reductions from baseline in eosinophils and basophils inflammatory cells, compared to Nasalcrom following 52 weeks of therapy. This contrasted with a statistically significant reduction from baseline in neutrophils associated with Nasalcrom, when compared to Rhinocort Aqua over the 52-weeks of treatment.

Improvements in mean changes from baseline in Quality of Life assessments (0-7 scale) were statistically significantly greater in several domains for the Rhinocort Aqua group than for the Nasalcrom group following 52 weeks of treatment. These domains included nonhayfever symptoms (p<0.001), practical problems (p<0.001), nasal symptoms (p<0.001), and overall score (p<0.001).

Analyses on growth data were performed on data that had been standardized using national standards obtained from the National Center for Health Statistics (NCHS) (1). Mean total growth in pre-pubertal patients over the 52-week treatment period was 5.23 and 6.02 centimeters over the one-year study period in the Rhinocort Aqua and Nasalcrom treatment groups, respectively. The observed difference in growth were statistically significant (p=0.0021) between treatment groups, reflecting a statistically significant (p=0.0133) difference in males. There was no statistically significant difference in growth among pubertal patients when all patients were analyzed. When the data for pubertal males were analyzed, a smaller (0.25 cm) difference over the one-year period was found to be statistically significant (p=0.0057), but the small sample size of this sub-population and the presence of significant treatment by center interaction make interpretation problematic.

Mean growth velocity in pre-pubertal patients over the 52-week treatment period was 5.20 and 5.98 cm/year in the Rhinocort Aqua and Nasalcrom treatment groups, respectively. The observed difference in growth velocity were statistically significant (p=0.0013) between treatment groups, again reflecting a statistically significantly (p=0.0031) difference in males.

There were no clinically or statistically significant differences between the Rhinocort Aqua and Nasalcrom treatment groups in changes in bone mineral density following 52 weeks of treatment regardless of pubertal status. In addition, changes in skeletal age, expressed as the difference
between chronological and skeletal age, were similar between the Rhinocort Aqua and Nasalcrom treatment groups regardless of pubertal status.

There were no clinically significant differences between the Rhinocort Aqua and Nasalcrom treatment groups in the mean change from baseline in basal or ACTH-stimulated plasma concentrations, or in the percent of patients who experienced a change in plasma cortisol concentrations from normal to abnormal, following 52 weeks of treatment.

Both treatments were well tolerated in this study. Six patients (3%) in the Rhinocort Aqua group were discontinued due to an adverse event, compared to five patients (5%) in the Nasalcrom group. Adverse events resulting in study discontinuation in the Rhinocort Aqua group included nasal irritation, dyspnea, bronchospasm, epistaxis/fungal infection, taste perversion, and rhinitis. Adverse events resulting in study discontinuation in the Nasalcrom group included rhinitis, sinusitis, nasal irritation, taste perversion, dyspepsia, and bronchospasm. Other adverse events reported in 10% or more of patients in either treatment groups were respiratory infection, sinusitis, pharyngitis, bronchospasm, flu-like disorder, and headache. The frequency of these adverse events was similar between treatment groups, except for a greater reported incidence of sinusitis (16% versus 8%) and pharyngitis (13% versus 7%) in the Rhinocort Aqua group compared to the Nasalcrom group.

There were no clinically significant changes in vital signs, physical exam, or laboratory finding that were considered attributable to study medication.

A total of 36 patients (17%) were discontinued prior to completion of the 52-week study in the Rhinocort Aqua treatment group, compared to 32 patients (30%) in the Nasalcrom group. The proportion of patient discontinuations in the Rhinocort Aqua group was statistically significantly (p=0.012) lower, when compared to the Nasalcrom group.

In conclusion, Rhinocort Aqua 256 μg daily did not effect HPA-axis, change in skeletal age, or change in bone mineral density differently from Nasalcrom. Males receiving Rhinocort Aqua had a statistically significantly lower growth than did those receiving Nasalcrom, but the long-term clinical significance of the estimated difference is unknown. Adverse event profiles between the two treatment groups were generally similar in kind and severity. Patients receiving Rhinocort Aqua reported statistically significantly better control of rhinitis symptoms and quality of life than did those receiving Nasalcrom.