AstraZeneca

Clinical Study Report	
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Date:	28 August 2003

A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Long-term Treatment with RHINOCORT AQUA® (budesonide) Nasal Spray in Children with Perennial Allergic Rhinitis

Study dates: First patient enrolled: 20 January 2000
Last patient completed: 14 April 2003

Phase of development: IV

Sponsor's Responsible Medical Officer: Liza O`Dowd, M.D.

This study was performed in compliance with Good Clinical Practice.

Drug product:	RHINOCORT AQUA®	**SYNOPSIS**	
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A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Long-term Treatment with RHINOCORT AQUAP(P (budesonide) Nasal Spray in Children with Perennial Allergic Rhinitis

Study center(s)

This study was conducted in the USA (35 centers).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	20 January 2000	Phase IV
Last patient completed	14 April 2003	

Objectives

This study will determine whether the use of RHINOCORT AQUA® [1] (RAQ), at a fixed daily dose of 64 μg has any clinically significant effect on growth in children when compared to placebo following a 12-month treatment period.
The primary objective was to characterize the difference in 12-month growth velocity, as measured by stadiometry, of prepubertal children with PAR treated with RAQ 64 μg/day or placebo.
The secondary objectives of the study were

- To characterize the growth velocity of prepubertal children with PAR who were treated with RAQ 64 μg/day or placebo for 12 months
- To assess the safety of RAQ 64 μg/day when used to treat PAR in prepubertal children
- To assess the efficacy of RAQ 64 μg/day in the relief of symptoms of PAR in prepubertal children

Study design

This was a multi-center, randomized, double-blind, placebo-controlled study of the effect of long-term treatment with RAQ on growth in prepubertal children with perennial allergic rhinitis.

Target patient population and sample size

Approximately 240 prepubertal boys between 4 years and 8 $^{8/12}$ years of age and prepubertal girls between 4 years and 7 $^{8/12}$ years of age

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[1] RHINOCORT AQUA is a registered trademark of the AstraZeneca group of companies.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Budesonide (RHINOCORT AQUA) 64 μg intranasally once daily or matching placebo. Batch numbers are provided in **Error! Reference source not found.**.

Duration of treatment

The baseline period was 6 months, the treatment period was 12 months, and the follow-up period was 3 months.

Criteria for evaluation (main variables)

The primary variable and some secondary variables of the study (growth velocity and changes in patient height), are assessments of safety.

Growth velocity and patient height

Primary variable (safety): Growth velocity, as measured by stadiometry, from baseline to the end of treatment (at 1 year or early termination)

Secondary variables (safety):

The percentage of patients whose growth velocity was below the 3rd percentile at the end of treatment (at 1 year or early termination)

The percentage of patients whose percentile for height decreased during treatment (at 1 year or early termination)

The change in growth velocity percentile, by quartile, from baseline to the final on-therapy height measurement

Growth velocity during the follow-up period

Standard safety assessments (see below)

Efficacy

Secondary variables (efficacy):

Physician (investigator) and patient (or parent/guardian) global assessments of efficacy after 6 months (Visit 6) and 12 months (Visit 8) of treatment

Quality of life as assessed by The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) administered to the patients at baseline (Visit 3) and after 6 months (Visit 6) and 12 months (Visit 8) of treatment

Safety

Standard safety variables were also assessed and included any adverse events, serious adverse events, discontinuations of study treatment due to adverse events, vital signs, clinically significant findings on physical examination or on visual examination of the nasal cavity, and laboratory measurements derived from blood and urine samples. All randomized patients who received at least 1 dose of study medication were included in the safety analysis.

Statistical methods

Growth velocity was estimated using least squares estimates of linear regression slopes for patients who did not have a height measurement at 1 year of treatment but did have at least 3 valid recorded height measurements during treatment.
Treatment period growth velocity was analyzed using the primary analysis model of an analysis of covariance with the treatment period growth velocity as the dependent variable, treatment, gender, and site as study factors and baseline age and baseline growth velocity as covariates.

Patient population

The treatment groups were well balanced in demographic and baseline characteristics. Growth at baseline was similar between treatment groups. In total, 407 patients were screened and 229 patients were randomized from 28 centers. The size and distribution of the primary analysis population between treatment groups provided sufficient statistical power to evaluate the effects of long-term (12 months) treatment with RAQ 64 μg/day on growth velocity. The patients in both treatment groups were primarily male and Caucasian, with a mean age of 5.9 years. The reasons for discontinuations from study were similar between treatment groups. Protocol deviations, rescue medication use, and compliance in both treatment groups were also similar between treatment groups. Concomitant medication use and medical history were similar between the treatment groups and typical of the pediatric population with PAR. The mean age of the patient population was slightly younger than the target patient population of prepubescent children with allergic rhinitis (at least 6 years of age) due to the inclusion of patients 4 years of age or older. Patients 4 to 6 years of age were included because their growth velocities are slightly higher than those for older patients.

Table S1 Patient population and disposition

		RAQ 64 μg/day		Placebo		Total	
Population							
N randomized (N planned)		155	(160)	74	(80)	229	(240)
Demographic characteristics							
Sex (n and % of patients)	Male	98	(63.2%)	54	(73.0%)	152	(66.4%)
	Female	57	(36.8)	20	(27.0%)	77	(33.6%)
Age (years)	Mean (SD)	5.9	(1.34)	5.9	(1.30)	5.9	(1.32)
	Range	4 to 8		4 to 8		4 to 8	
Race (n and % of patients)	Caucasian	116	(74.8%)	56	(75.7%)	172	(75.1%)
	Black	17	(11.0%)	9	(12.2%)	26	(11.4%)
	Hispanic	13	(8.4%)	4	(5.4%)	17	(7.4%)
	Oriental	3	(1.9%)	4	(5.4%)	7	(3.1%)
	Other	6	(3.9%)	1	(1.4%)	7	(3.1%)
Baseline characteristics							
Growth velocity (cm/year)	Mean (SD)	6.7	(2.4)	6.6	(2.0)	6.7	(2.3)
Height (cm)	Mean (SD)	121.8	(8.9)	121.2	(8.5)	121.6	(8.7)
Disposition							
N (%) of patients who	Completed	110	(71.0%)	58	(78.4%)	168	(73.4%)
	Discontinued	45	(29.0%)	16	(21.6%)	61	(26.6%)
N analyzed for safety [a]		155		74		229	
N analyzed for primary and secondary variables (primary analysis population)		130		61		191	
N analyzed for primary and secondary variables (sensitivity analysis No. 1)		123		60		183	

[a] Number of patients who took at least 1 dose of study medication.
Abbreviations: RAQ, RHINOCORT AQUA; SD, standard deviation.

Efficacy and pharmacokinetic results

The findings from both the global assessments of efficacy and the PRQLQ indicate that the use of RAQ 64 μg/day to treat perennial allergic rhinitis in prepubertal children results in a trend toward improved symptom control from baseline to the end of 12 months of treatment when compared with placebo. The study was not designed specifically to assess efficacy, and patients were allowed to use allergic rhinitis rescue medications at any time during the study. Pharmacokinetics was not assessed in this study.

Safety results

RHINOCORT AQUA 64 μg/day was well tolerated for the treatment of perennial allergic rhinitis in the pediatric population (ages 4 years to <9 years). Growth velocity was similar between RAQ and placebo treatment groups after 12 months of therapy: mean (SE) placebo–RAQ difference in growth velocity after 12 months was 0.27±0.18 cm/year (95% confidence interval [CI] -0.07 to 0.62). A sensitivity analysis of the results eliminating questionable data provided the same findings as the primary analysis. This analysis and 3 other analyses were suggested in US FDA draft Guidance for Industry. The incidences and types of AEs reported were typical for a pediatric population with PAR and similar between treatment groups. There were 5 patients who reported SAEs during the study; no patients reported SAEs while receiving RAQ treatment. Two patients randomized to receive RAQ reported 1 SAE each pre-treatment and 1 patient who received RAQ reported 2 SAEs post-treatment. Two patients randomized to receive placebo reported 3 SAEs during treatment. There were no deaths.

Table S2 **Number (%) of patients who had at least 1 adverse event in any category and total numbers of adverse events during the treatment period (safety analysis population)**

Category of adverse event	RAQ 64 μg [a] (n=155) n (%)		Placebo [a] (n=74) n (%)	
Any adverse events	121	(78.1%)	63	(85.1%)
Serious adverse events	0		2	(2.7%)
Serious adverse events leading to death	0		0	
Serious adverse events not leading to death (overall)	3	(1.9%)	2	(2.7%)
Serious adverse events not leading to death (on-treatment)	0		2	(2.7%)
Discontinuations of study treatment due to adverse events (overall)	7	(4.5%)	1	(1.4%)
Other significant adverse events	0		0	
	Total number of adverse events [b]			
Any adverse events	604		281	
Serious adverse events (overall)	4		3	
Other significant adverse events	0		0	

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Adverse events may have been counted more than once if the patient had multiple occurrences of the event.

Note: One patient reported SAEs of lobar pneumonia NOS and asthma exacerbation prior to randomization and was excluded from study.

The most commonly occurring AE, upper respiratory tract infection NOS, had a higher incidence in the placebo treatment group (25.7%) than in the RAQ treatment group (14.2%). Other commonly occurring AEs included pyrexia, cough, and nasopharyngitis, and the incidences of these AEs were similar between treatment groups. The investigators in this study rated the majority of AEs as mild or moderate in intensity; none of the AEs rated as severe were judged to be causally related to the study drug by the investigators.

There were no clinically important changes in vital signs, physical exams, nasal exams, and laboratory values, including 24-hour urinary cortisol/creatinine ratios, for patients in either treatment group. The change in 24-hour urinary cortisol/creatinine ratios from baseline to the end of treatment was similar between treatment groups.

Date of the report

28 August 2003