2.0 SYNOPSIS

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission**	**(For National Authority Use only)**
Name of Finished Product: RHINOCORT® AQUA™	**Volume:**	
Name of Active Ingredient: Budesonide	**Page:**	

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of RHINOCORT® AQUA™ (budesonide) Nasal Spray on the Hypothalamic-Pituitary-Adrenal (HPA) Axis Function in Pediatric Patients with Allergic Rhinitis

Investigators:
See Table 1 of this report for a list of principal investigators.

Study Centers:
Multicenter study (11 centers) in the USA

Publication (reference):
N/A

Studied Period (years): Date of first patient enrollment: January 18, 2001 Date of last patient completed: October 8, 2001	**Phase of development:** IV

Objectives: The primary objective of this study was to evaluate the effect of RHINOCORT AQUA, administered intranasally once daily at a dose of 64 µg/day, compared with matching placebo, on the HPA axis function in pediatric patients aged 2 to 5 years, inclusive, with allergic rhinitis.

Methodology: A 6-week, multicenter, randomized, double-blind, placebo-controlled study.

Number of Patients (Planned and Analyzed):
Planned: 70
Randomized: 78
Analyzed for HPA Axis Function: 68 (intent to treatment [ITT]); 62 (per protocol)
Analyzed for Safety: 78
Analyzed for Efficacy: 68 (ITT)

Diagnosis and Main Criteria for Inclusion: Male and female patients ages 2 through 5 years, inclusive, who were candidates for treatment with nasal steroids based on a history of either inadequate control of symptoms or prior successful treatment with nasal steroids; a diagnosis of allergic rhinitis based on either a positive response to a skin prick test (wheal 3 mm greater than negative control or equal to positive control) for perennial or seasonal aeroallergens in the patient's environment *or* a documented history of at least 4 weeks of continuous chronic symptoms of allergic rhinitis prior to study entry *and* nasal secretions positive for eosinophils; and whose height and weight were within normal limits were considered eligible for this study.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
RHINOCORT AQUA (budesonide), 1 32 µg spray in each nostril once daily, bulk lot number 1070006602, packaging lot number AM-442.

Duration of Treatment:
6 weeks

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
Placebo, 1 spray in each nostril once daily, bulk lot number 8804909602, packaging lot number AM-442.

Criteria for Evaluation:

Safety: Changes in HPA axis function utilizing morning plasma cortisol levels and the results of a 1-hour intravenous (IV) low dose (10 µg) cosyntropin stimulation test performed at baseline and at the final visit. Safety was also assessed by incidence and severity of adverse events; clinical laboratory parameters (hematology, blood chemistry, urinalysis); vital signs (body weight, pulse rate, blood pressure); changes in physical and nasal examinations.

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Criteria for Evaluation (Continued):

Efficacy: Investigator and parent/legal guardian global assessment of efficacy and use of rescue medication.

Statistical Methods: For the primary study variable of HPA axis function, all data from pediatric patients who received at least 1 dose of study medication and who had values for both baseline and post-randomization plasma cortisol levels were included (ITT population). A per protocol (PP) population was also used to analyze the results of HPA axis function and included a subset of those pediatric patients from the ITT analysis who completed 6 weeks of double-blind therapy as well as all of the HPA axis function testing and who did not have any major protocol violations or deviations. Differences between the 2 treatment groups in HPA axis function were assessed using an analysis of covariance with terms for treatment, baseline plasma cortisol value, center, and age strata. The model considered the following separately as dependent variables: 1) change from baseline (Visit 2) to Visit 4 in the 0 (basal), 30, and 60 minutes post-cosyntropin stimulation plasma cortisol levels; and 2) change from baseline (Visit 2) to Visit 4 in change from 0 (basal) to 30 minutes and change from 0 (basal) to 60 minutes post-cosyntropin stimulation plasma cortisol levels. Split samples were taken for all plasma cortisol levels (one set was sent to the central laboratory and one was retained at the site). In cases in which the initial assay result was slightly above or below the normal/abnormal borderline level, the second set of samples was also sent to the central laboratory and assayed. All analyses were performed using each of the following: first value obtained, average of two values obtained, lowest of the two values, and highest of the two values.

Adverse events were tabulated by treatment group and preferred term using a modified World Health Organization adverse event dictionary (Astra Adverse Event Dictionary [AAED]).

Changes from baseline to the end of treatment in vital signs, body weight, and laboratory variables were examined by treatment group using descriptive statistics. Changes in physical and nasal examinations from baseline to the end of treatment were tabulated by treatment group.

SUMMARY – CONCLUSIONS

HPA AXIS FUNCTION RESULTS:

A total of 78 pediatric patients were randomized into the study, 39 pediatric patients in each treatment group. The two treatment groups were well matched with respect to the age of the pediatric patients with approximately 50% of patients in both groups less than 4 years of age. Additionally, there were similar numbers of pediatric patients within each treatment group within each age strata; at least 6 subjects per treatment group per age strata completed the study. Plasma cortisol concentrations increased following cosyntropin stimulation in both treatment groups, and this was true for tests given at Visit 2 (baseline) and at the end of the 6-week treatment period (Visit 4). The adjusted mean changes from baseline in basal or post-cosyntropin plasma cortisol concentrations among young pediatric patients treated with RHINOCORT AQUA once daily were not statistically significantly different from the changes observed following treatment with placebo (see Table I). Three pediatric patients in the RHINOCORT AQUA group and six in the placebo group had subnormal HPA function at the end of the 6-week treatment period; one of these pediatric patients had subnormal function at baseline. An exception from the study team was granted allowing this patient to enter the study. There was no discernible age-related pattern with respect to the occurrence of subnormal HPA axis function.

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Table I: Changes in Plasma Cortisol Levels from Baseline: First Sample Analyzed
ITT Population

Variable	Adjusted Change from Baseline Mean (SE)	P-value	(95% CI on difference from placebo)
Change from BL to Visit 4: before cosyntropin			
Placebo (N=33)	-1.9 (14.6)	0.32	(-20.1to 61.1)
RHINOCORT AQUA (N=33)	-22.4 (16.0)		
Change from BL to Visit 4: 30 min post-cosyntropin			
Placebo (N=30)	-27.8 (19.7)	0.68	(-58.9 to 38.4)
RHINOCORT AQUA (N=35)	-17.6 (18.7)		
Change from BL to Visit 4: 60 min post-cosyntropin			
Placebo (N=32)	-48.9 (21.8)	0.54	(-70.0 to 37.3)
RHINOCORT AQUA (N=34)	-32.5 (21.6)		
Change from BL to Visit 4: difference from 0 min to 30 min post-cosyntropin			
Placebo (N=30)	-17.5 (20.3)	0.48	(-76.3 to 36.6)
RHINOCORT AQUA (N=33)	2.3 (21.1)		
Change from BL to Visit 4: difference from 0 min to 60 min post-cosyntropin			
Placebo (N=32)	-33.6 (21.4)	0.17	(-102.1 to 18.0)
RHINOCORT AQUA (N=32)	8.5 (23.6)		

SAFETY RESULTS:

The safety and tolerability profile of RHINOCORT AQUA nasal spray in pediatric patients aged 2 to 5 years with allergic rhinitis in this study was comparable to that of placebo. No pediatric patient was discontinued prematurely from study treatment as a result of an adverse event, and the only serious adverse event in this study occurred in a placebo-treated pediatric patient (thrombocytopenia). Most of the adverse events reported in this study reflected medical conditions and symptoms common to children, with the most common adverse events in the RHINOCORT AQUA and placebo groups being accident and/or injury (10% vs. 0%), fever (8% vs. 3%), otitis media (8% vs. 5%), and respiratory infection (5% vs. 8%) (Table II). Although the overall incidence of adverse events was higher among pediatric patients receiving RHINOCORT AQUA (59%) compared with those receiving placebo (31%), three adverse events, nasal irritation (Patient 307), nervousness and increased appetite (both in Patient 209) treated with RHINOCORT AQUA, were considered by the investigator to be treatment-related. Mean changes from baseline in hematology and clinical chemistry parameters, as well as mean changes in vital sign measurements and body weight, were small and comparable in the RHINOCORT AQUA and placebo groups. With the exception of thrombocytopenia in a placebo-treated pediatric patient, there were no clinically significant clinical laboratory changes. All visual examinations of the nasal cavity were normal following study treatment, and the relatively infrequent abnormalities found on post-treatment physical examination were mainly related to the pediatric patients' underlying allergic rhinitis and occurred with a similar frequency in the two treatment groups.

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Table II: Frequency of Most Common Adverse Events (≥5% in Either Treatment Group) Reported during Treatment Period (Safety Population)

Adverse Event (AAED Preferred Term)	RHINOCORT AQUA (N=39)	Placebo (N=39)	Total (N=78)
No. (%) Patients with AEs	23 (59%)	12 (31%)	35 (45%)
Accident and/or Injury	4 (10%)	0 (0%)	4 (5%)
Otitis Media	3 (8%)	2 (5%)	5 (6%)
Fever	3 (8%)	1 (3%)	4 (5%)
Respiratory Infection	2 (5%)	3 (8%)	5 (6%)
Gastroenteritis	2 (5%)	2 (5%)	4 (5%)
Parasitosis	2 (5%)	1 (3%)	3 (4%)
Coughing	2 (5%)	0 (0%)	2 (3%)
Headache	1 (3%)	2 (5%)	3 (4%)

EFFICACY RESULTS:
Global assessments of symptom control at the end of the study treatment period were made by the investigator and parent/guardian. Data from both the investigator and parent/guardian assessments indicated that approximately one-half of pediatric patients had substantial or total symptom control with either RHINOCORT AQUA or placebo, and there was no statistically significant difference in global assessments between the two treatment groups (p=0.214 and p=0.774).

Date of the Report: March 6, 2002

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