AstraZeneca

Drug product	RHINOCORT AQUA®	**SYNOPSIS**	
Drug substance(s)	Budesonide		
Document No.	SD-005-0698		
Edition No.	1		
Study code	SD005-0698		
Date	20 February 2003		

A Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety, and Functionality of a New Nasal Device with Reformulated RHINOCORT AQUA® (budesonide) Versus the Current Product and Versus Placebo in Patients with Seasonal Allergic Rhinitis (SAR)

International Co-ordinating investigator

Shailen R. Shah, MD, Allergy & Asthma Consultants of NJ-PA, P.C., Collegeville Professional Center, 555 Second Avenue, Suite C-750, Collegeville, PA 19426

Study center(s)

This study was conducted in the USA (20 centers)

Publications

None at the time of writing this report

Study dates
First patient enrolled 12 April 2002
Last patient completed 07 August 2002

Phase of development
Therapeutic confirmatory (III)

Objectives

The primary objective of the study was to determine the efficacy of once daily administration of 64 μg and 128 μg of reformulated RHINOCORT AQUA® (budesonide; pH 4.0) delivered in the new nasal device (NND) versus placebo in relieving the symptoms of seasonal (grass) allergic rhinitis in children and adults by assessment of the overall Total Nasal Symptom Score (TNSS). The primary hypothesis was that patients receiving RHINOCORT AQUA (RAQ) NND would have a greater reduction in symptom severity than the patients receiving placebo.

The secondary objectives were:

- To determine comparability between the reformulated RAQ (pH 4.0) delivered in the NND and the current formulation of RAQ (pH 4.5) delivered in the current winged applicator (current product [CP]) by assessment of TNSS
- To assess the efficacy of the doses of the RAQ NND at the end of the once-daily dosing interval
- To assess efficacy through a patient's overall evaluation of treatment efficacy

- To assess the durability of the new nasal device during regular patient use through functionality testing
- To determine the safety of RAQ NND compared with placebo by assessment of adverse events and clinical measurements

Study design

This was a multi-center, double-blind, randomized, placebo-controlled, parallel group study to assess the efficacy, safety, and functionality of 2 doses of reformulated RAQ in a new nasal device versus placebo in patients with seasonal (grass) allergic rhinitis (SAR).

Target patient population and sample size

Males or nonpregnant, non-lactating females at least 6 years of age with at least a 1-year history of seasonal allergic rhinitis who, in the opinion of the investigator, were candidates for treatment with nasal steroids based on a history of either (1) inadequate control of symptoms with antihistamines, decongestants and/or immunotherapy or (2) prior successful treatment with nasal steroids. There were 592 patients recruited in this study, of which 49 patients were 6-11 years of age (inclusive).

For the primary comparison of efficacy of RAQ NND versus placebo, approximately 120 recruited patients were required in each treatment group for 90% power of detecting a difference in the mean 2-week overall TNSS of 1.0 point, based on a two-sided test with a 0.05 significance level and assuming a common standard deviation of 2.4.

For the secondary comparison of general comparability of RAQ NND and RAQ CP, approximately 120 recruited patients were required for the RAQ NND treatment group and 90 recruited patients were required for the RAQ CP treatment group to provide 80% power to detect a difference in the 95% confidence interval of the difference in the mean TNSS scores of approximately ±0.65 points. Approximately 90 recruited patients were required for the RAQ CP placebo treatment group to provide 80% power to compare RAQ CP and its placebo under the conditions stated above.

A total of 240 new nasal devices were returned after use, and 60 were randomly selected for spray characterization and dose analysis. The remaining 180 devices were tested for functionality. Additionally, 13 devices were not dispensed to patients because the site reported that the dose counter did not work. These devices were returned, and the dose counter functionality of 10 devices was evaluated separately from the functionality testing.

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

Reformulated RAQ 64 μg/day administered as 1 spray (32 μg per spray) from a new nasal device (NND) in each nostril in the morning; batch number: DC 109-02/3

Reformulated RAQ 128 μg/day administered via an NND as 2 sprays (32 μg per spray) in each nostril in the morning; batch number: DC 109-02/3

Current formulation of RAQ 64 μg/day administered as 1 spray (32 μg per spray) via the current winged applicator (RAQ CP) in each nostril in the morning; batch number: 1070112026

RAQ NND 64 μg/day and 128 μg/day matching placebo; batch number: DC 11-02/1

RAQ CP 64 μg/day matching placebo; batch number: DB 11-02/1

Criteria for evaluation (main variables)

Efficacy

- Primary variable: TNSS (range, 0 to 12), defined as the average of the patient's AM TNSS and PM TNSS. Each morning and evening, the patient rated symptoms of rhinorrhea, congestion, nasal itching, and sneezing for the previous 12 hours (12-hour reflective scores; range, 0 to 3). The AM TNSS was the average daily sum of the morning 12-hour reflective symptom scores over the first 2 weeks of the

treatment period. The PM TNSS was the average daily sum of the evening 12-hour reflective symptom scores over the first 2 weeks of the treatment period.

- Secondary variables:
  - 12-hour reflective symptom scores: the patients' symptoms over the previous 12 hours upon arising (prior to dosing) in the morning (AM TNSS) and again in the evening (PM TNSS) over the first 2 weeks of the treatment period
  - Instantaneous symptom score: the patients' symptoms of SAR at the moment of recording upon arising (prior to dosing) in the morning over the first 2 weeks of the treatment period
  - Patient's overall evaluation of treatment efficacy: the patient's assessment of their allergic rhinitis symptoms at Visit 3 and at Visit 4.
  - New nasal device functionality testing: durability of the device and assessment of delivered dose, including droplet size distribution and spray pattern

Safety

Standard safety assessments included any adverse events, serious adverse events, discontinuations of study treatment due to adverse events, clinically significant findings on physical examination or visual examination of the nasal cavity, and clinically significant abnormal vital sign findings not previously reported. All randomized patients who received at least 1 dose of study medication were included in the safety analysis.

Statistical methods

The intention-to-treat (ITT) population was analyzed for all efficacy variables; the per-protocol (PP) population was analyzed for TNSS. The findings showed little difference in the results for the ITT and PP analysis populations, and there was no change in conclusions from the analysis of the PP population.

Patient population

The treatment groups were well balanced in demographic and baseline characteristics. The average age of patients in the study was 29.1 years. The patient population consisted of 56.8% females and 43.2% males. Caucasians comprised 91% of the patients, and 6% were Black, 1% were Oriental, and 2% were other races. The treatment groups were comparable with respect to demographic variables. The average TNSS at baseline was 9.2±1.7 for the reflective scores and 8.6±2.1 for the instantaneous scores. Mean baseline reflective and instantaneous symptom scores were comparable across treatment groups; the highest mean baseline scores were seen in the RAQ CP group (9.4 and 8.9, respectively) and the lowest mean baseline scores were seen in the RAQ NND 128 μg group (8.8 and 8.3, respectively).

The patient population was representative of the target patient population for RAQ NND. Disease severity, as demonstrated by baseline reflective and instantaneous symptom scores, indicates that the patient population was representative of the target population of patients with moderate to severe SAR. Patients in this study were predominantly female, Caucasian, and young; the mean age was due in part to the inclusion of forty-nine 6 to 11-year old (inclusive) patients.

Efficacy results

The results of this study indicate that once daily administration of 64 μg and 128 μg of reformulated RAQ delivered in the NND was statistically significantly more effective ($p<0.001$) than placebo in relieving the symptoms of seasonal (grass) allergic rhinitis in children and adults as assessed by the 2-week average overall TNSS. The changes from baseline in TNSS were –2.69 points and –2.94 points for patients who received RAQ NND 64 μg/day or RAQ NND 128 μg/day, respectively. The change from baseline was –1.55 for patients who received placebo. The differences in symptom relief between the active and placebo treatments were clinically relevant. Clinical relevance was defined as a difference of at least 1 point between the mean changes from baseline. The results from all secondary variables support the findings for the primary variable. The change

from baseline in TNSS was –2.58 points for patients who received RAQ CP 64 μg/day. This was not clinically or statistically different from the change from baseline in TNSS for either dose of RAQ NND.

There was little difference in the results for the ITT and PP analysis populations and no change in conclusions from the analysis of the PP population.

These results support the hypothesis that reformulated RAQ (pH 4.0) delivered in the NND was effective in reducing the symptoms of moderate to severe seasonal (grass) allergic rhinitis. The efficacy of RAQ NND was similar to that seen with the current formulation of RAQ (pH 4.5) delivered in the winged applicator (current product).

Safety results

RAQ delivered in the NND was well tolerated. The AEs reported were typical for SAR patients receiving intranasal corticosteroids. Two SAEs were reported for patients who received placebo; no SAEs were associated with RAQ NND use. DAEs occurred primarily among patients who received placebo. An overview of the number and type of adverse events reported by patients participating in this study is presented in Table S1.

Table S1 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety population), during double-blind treatment

	N (%) of patients who had an adverse event in each category[a]				
	RAQ NND			**RAQ CP**	
Category of adverse event	**64 μg/day (n=132)**	**128 μg/day (n=135)**	**Pbo (n=124)**	**64 μg/day (n=104)**	**Placebo (n=97)**
Any adverse events	29 (22.0%)	32 (23.7%)	36 (29.0%)	22 (21.2%)	19 (19.6%)
Serious adverse events	0	0	2 (1.06%)	0	0
SAEs leading to death	0	0	0	0	0
Discontinuations of study treatment due to AEs	0	3 (2.2%)	5 (4.0%)	1 (1.0%)	5 (5.2%)
Other significant AEs	0	0	0	0	0
	Total number of AEs[b]				
Adverse events	46	53	71	31	25
Serious adverse events	0	0	2	0	0
Adverse events leading to discontinuations of study treatment	0	7	7	1	6
Other significant adverse events	0	0	0	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.

Abbreviations: AE, adverse event; CP, current product; NND, new nasal device; Pbo, placebo; RAQ, RHINOCORT AQUA; SAE, serious adverse event.

Comparison of RAQ NND and placebo during double-blind treatment: Adverse events were reported by 22.8% (61/267) of patients on RAQ NND and 29.0% (36/124) of patients on matching placebo . The most common adverse events in patients receiving RAQ NND were similar to those patients who received placebo (headache NOS and pharyngitis). Serious adverse events were rare (1 case of calculus renal NOS reported by a patient who received RAQ NND placebo and 1 case of schizophrenia, paranoid type reported by another patient

who received RAQ NND placebo) and not considered treatment-related. Discontinuations of study treatment due to adverse events were more common among patients who had received RAQ NND placebo (4.0%, 5/124) or RAQ CP placebo (5.2%, 5/97) than among patients who received RAQ NND 64 μg/day (no DAEs), RAQ NND 128 μg/day (2.2%, 3/135), or RAQ CP 64 μg/day (1.0%, 1/104).

Comparison of RAQ NND and RAQ CP during double-blind treatment: The AE profile of RAQ NND was comparable to the AE profile of RAQ CP. The incidence of the most common adverse event (headache NOS) was slightly lower among patients who took RAQ NND than among patients who took RAQ CP. Slightly more patients receiving RAQ NND reported AEs of pharyngitis than patients who received RAQ CP. Myalgia was reported most frequently by patients who received RAQ NND 128 μg/day. No reports of myalgia were considered causally related to RAQ NND by the investigators, and all were mild to moderate in intensity and of short duration. No patients in active treatment groups reported serious adverse events, and discontinuations due to adverse events were rare in the active treatment groups, ranging from none to 2.2% of patients.

Date of the report

February 20, 2003