AstraZeneca

Drug product:	RHINOCORT AQUA®	**SYNOPSIS**	
Drug substance(s):	Budesonide		
Edition No.:	Final		
Study code:	D5360C00703		
Date:	8 November 2005		

A Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel Group, Phase II Study to Assess the Efficacy and Safety of RHINOCORT AQUA® (budesonide) Nasal Spray, 16 μg, 32 μg and 64 μg per day versus Placebo in Pediatric Subjects, Ages 2-5 Years Old with Allergic Rhinitis

International co-ordinating investigator

Not applicable

Study center(s)

This study was conducted in the US (67 centers).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	27 April 2004	Therapeutic exploratory (II)
Last patient completed	23 May 2005	

Objectives

The primary objective of this study was to determine the efficacy of once daily administration of 16 μg, 32 μg and 64 μg of RHINOCORT AQUA® (budesonide) Nasal Spray [hereafter referred to as RAQ] compared with placebo in relieving the symptoms of allergic rhinitis (AR) in pediatric patients (2-5 years old inclusive), by assessment of the mean change from baseline in the [overall] reflective Total Nasal Symptom Score (TNSS), defined as the [average of the] sum of the morning (AM) and evening (PM) 12-hour reflective scores for rhinorrhea (runny nose), congestion (stuffy nose), nasal itching, and sneezing.

The null hypothesis was that there was no difference in the measurement of symptoms between RAQ and placebo as assessed by caregivers (parents or guardians) who completed the TNSS for patients since the children were too young to complete an assessment of efficacy. The primary alternative hypothesis was that patients receiving RAQ would have a greater reduction in symptom severity than the patients receiving placebo.

The secondary objectives were:

1. To determine if the doses of RAQ were effective at the end of the dosing interval through Instantaneous Total Nasal Symptom Scores (AM), measured at the end of the dosing interval. Instantaneous TNSS was defined as the sum of the instantaneous scores for rhinorrhea (runny nose), congestion (stuffy nose), nasal itching, and sneezing.

2. To assess the efficacy of the doses of RAQ through the caregiver's overall assessment of efficacy (COE), which provides a global assessment of the caregiver's perception of treatment efficacy. Caregivers (parents or guardians) completed the COE for the patients since the children were too young to complete an assessment of efficacy.

3. To assess the efficacy of the doses of RAQ through the physician's overall assessment of efficacy (POE), which provides a global assessment of the physician's perception of treatment efficacy.

4. To determine the safety of RAQ compared with placebo by assessment of adverse events and clinical measurements.

Study design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of once-daily 16 μg, 32 μg and 64 μg of RAQ versus placebo in children ages 2 to 5 years old, inclusive, with AR.

Target patient population and sample size

The target patient population was prepubescent males or females between the ages of 2 and 5 years (inclusive) who, in the opinion of the investigator, were candidates for treatment with nasal steroids based on a history of either (a) inadequate control of symptoms with antihistamines, decongestants and/or immunotherapy, or (b) prior successful treatment with nasal steroids. Patients had a documented history of AR (perennial allergic rhinitis [PAR] or seasonal allergic rhinitis [SAR] in season) and a positive response to a skin-prick test within 12 months of Visit 1 for perennial or seasonal allergens that must have been present in the patient's environment throughout the entire study.

The primary comparison in this study was the comparison of 64 μg of RAQ and the combined placebo group. For this comparison, 90% power was desired. The sample size was estimated for the primary variable (overall TNSS) assuming a 2-sided test with a 0.050 significance level. Assuming a common standard deviation of 2.1, a sample size of 94 in each group would have 90% power to detect a difference in means of 1.0 point in the overall TNSS. Allowing for a small number of randomized patients for whom data would be unavailable, a sample size of 100 patients per group was chosen. For the placebo group, the 100 patients were split among 3 different placebo groups: 2 groups of placebo patients received 1 spray per

nostril daily (placebo to RAQ 16 μg and 64 μg) and a third placebo group received 2 sprays per nostril daily (placebo to RAQ 32 μg).

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

RAQ 16 μg per day administered as 1 spray (8 μg per spray) in each nostril; batch number DFB 8 and DFK 130

RAQ 32 μg per day administered as 2 sprays (8 μg per spray) in each nostril; batch number DFB 8 and DFK 136

RAQ 64 μg per day administered as 1 spray (32 μg per spray) in each nostril; batch number EF 360 and FB 416

RAQ 16 μg per day matched placebo administered as 1 spray in each nostril; batch number EI12-02/1

RAQ 32 μg per day matched placebo administered as 2 sprays in each nostril; batch number EI12-02/1

RAQ 64 μg per day matched placebo administered as 1 spray in each nostril; batch number EI12-02/1

Duration of treatment

At Visit 2 (following the screening period), eligible patients were randomized to receive 1 of the treatments described in the previous section each morning for a period of 2 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: overall (24-hour) TNSS (range, 0 to 12), defined as the average of the patient's morning (AM) and evening (PM) 12-hour reflective TNSS. A 12-hour reflective TNSS was calculated each morning and evening as the sum of the patient's scores for the symptoms of rhinorrhea, congestion, nasal itching, and sneezing over the previous 12 hours. The patient's average AM 12-hour reflective TNSS and PM 12-hour reflective TNSS were then calculated by averaging the daily sums over the 2-week treatment period. The patient's overall TNSS was the average of the AM and PM reflective TNSS.

- Secondary variables:

  – 12-hour reflective symptom scores (range, 0 to 12): the patient's rhinitis symptoms (rhinorrhea, congestion, nasal itching, and sneezing) over the previous 12 hours upon arising (prior to dosing) in the morning (AM 12-hour

reflective symptom scores) and again in the evening (PM 12-hour reflective symptom scores) over the 2-week treatment period

- Instantaneous symptom scores (range, 0 to 12): the patient's rhinitis symptoms (rhinorrhea, congestion, nasal itching, and sneezing) at the moment of recording upon arising (prior to dosing) in the morning over the 2-week treatment period

- COE (range, 0 to 4): the caregiver's overall assessment of efficacy (control of the patient's AR symptoms) at Visit 3

- POE (range, 0 to 4): the physician's overall assessment of efficacy (control of the patient's AR symptoms) at Visit 3.

In addition to the COE, all of the nasal symptom scores (reflective and instantaneous) were assessed by caregivers (parents or guardians) who completed the scoring for patients since the children were too young to complete an assessment of efficacy. When possible, the same caregiver was responsible for each assessment.

Safety

Standard safety assessments included any adverse events (AEs), serious adverse events (SAEs), discontinuations of study treatment due to adverse events (DAEs), other significant adverse events (OAEs), clinically significant findings on physical examination or visual examination of the nasal cavity, clinically significant abnormal vital sign findings not previously reported, and clinically significant abnormal laboratory values. 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) analysis set was the primary population analyzed for this study for both the primary and secondary efficacy variables. This population included all randomized patients who received at least 1 dose of study medication and contributed sufficient data for at least 1 efficacy variable to be calculated. In addition, for the primary efficacy endpoint (ie, the 2-week average overall [reflective] TNSS), an analysis was conducted on data from patients included in the per-protocol (PP) analysis set. This population excluded patients considered to be major protocol violators. The safety analysis set included all randomized patients who received at least 1 dose of study medication.

Patient population

The treatment groups were comparable in demographic and baseline characteristics. The patient population consisted of 40% females and 60% males. Patients' mean age (±SD) was 3.74 (±1.08) years. Caucasians comprised 72.0% of the patients, and 13.3% were Black, 2.5% were Oriental, and 12.3% were of other races. There was a relatively higher percentage of Black patients in the RAQ 64 μg and placebo groups compared to other 2 treatment groups.

Across treatment groups, the majority of patients (78%) had PAR. The treatment groups were comparable with respect to the other demographic variables.

The patient population was representative of the target pediatric patient population for RAQ. Disease severity, as demonstrated by the baseline reflective and instantaneous symptom scores, was comparable across treatment groups and was representative of a target population of patients with moderate to severe AR.

Table S1 Patient population and disposition

		Treatment				
		RAQ 16 µg	**RAQ 32 µg**	**RAQ 64 µg**	**Placebo**	**Total**
Population						
N randomized (N planned)		93 (100)	97 (100)	107 (100)	103 (100)	400 (400)
Demographic characteristics						
Sex (n and % of patients)	Female	35 (37.6)	44 (45.4)	43 (40.2)	38 (36.9)	160 (40.0)
	Male	58 (62.4)	53 (54.6)	64 (59.8)	65 (63.1)	240 (60.0)
Age (years)	Mean (SD)	3.60 (1.12)	3.89 (1.09)	3.67 (1.04)	3.78 (1.08)	3.74 (1.08)
	Range	2.0 to 5.0	2.0 to 5.0	2.0 to 5.0	2.0 to 5.0	2.0 to 5.0
Race (n and % of patients)	Black	10 (10.8)	9 (9.3)	19 (17.8)	15 (14.6)	53 (13.3)
	Caucasian	67 (72.0)	75 (77.3)	74 (69.2)	72 (69.9)	288 (72.0)
	Oriental	3 (3.2)	3 (3.1)	2 (1.9)	2 (1.9)	10 (2.5)
	Other	13 (14.0)	10 (10.3)	12 (11.2)	14 (13.6)	49 (12.3)
Type of AR (n and % of patients)	PAR	70 (75.3)	76 (78.4)	86 (80.4)	81 (78.6)	313 (78.3)
	SAR	23 (24.7)	21 (21.6)	21 (19.6)	22 (21.4)	87 (21.8)
Baseline characteristics						
Overall reflective symptom scores[a]		(n=93)	(n=96)	(n=107)	(n=102)	(n=398)
TNSS	Mean (SE)	8.00 (0.20)	7.75 (0.18)	7.89 (0.20)	7.76 (0.19)	7.85 (0.10)
Rhinorrhea	Mean (SE)	2.06 (0.06)	1.99 (0.06)	2.01 (0.06)	2.07 (0.06)	2.03 (0.03)
Nasal congestion	Mean (SE)	2.23 (0.06)	2.20 (0.06)	2.23 (0.06)	2.26 (0.06)	2.23 (0.03)
Nasal itching	Mean (SE)	1.99 (0.07)	1.91 (0.06)	1.90 (0.06)	1.83 (0.07)	1.90 (0.03)
Sneezing	Mean (SE)	1.73 (0.07)	1.65 (0.07)	1.75 (0.07)	1.60 (0.08)	1.68 (0.04)

Table S1 Patient population and disposition

		Treatment				
		RAQ 16 μg	RAQ 32 μg	RAQ 64 μg	Placebo	Total
AM instantaneous symptom scores		(n=93)	(n=97)	(n=106)	(n=103)	(n=399)
TNSS	Mean (SE)	7.51 (0.25)	7.25 (0.22)	7.31 (0.25)	7.35 (0.22)	7.35 (0.12)
Rhinorrhea	Mean (SE)	1.98 (0.08)	1.93 (0.07)	1.89 (0.07)	1.94 (0.07)	1.93 (0.04)
Nasal congestion	Mean (SE)	2.21 (0.06)	2.14 (0.07)	2.19 (0.06)	2.25 (0.06)	2.20 (0.03)
Nasal itching	Mean (SE)	1.83 (0.08)	1.73 (0.07)	1.75 (0.07)	1.77 (0.08)	1.77 (0.04)
Sneezing	Mean (SE)	1.50 (0.09)	1.45 (0.09)	1.48 (0.09)	1.40 (0.09)	1.46 (0.04)
Disposition						
N (%) of patients who:	Completed	91 (97.8)	95 (97.9)	102 (95.3)	97 (94.2)	385 (96.3)
	Discontinued	2 (2.2)	2 (2.1)	5 (4.7)	6 (5.8)	15 (3.8)
N analyzed for safety[b]		93	97	107	103	400
N analyzed for efficacy (ITT)		91	95	106	103	395
N analyzed for efficacy (PP)		73	78	87	80	318

[a] Overall scores were calculated as the average of the reflective AM and PM scores.
[b] Number of randomized patients who received at least 1 dose of study medication.
RAQ=RHINOCORT AQUA (budesonide) Nasal Spray; N=Number; SD=standard deviation; SE=standard error of the mean; ITT=intention-to-treat; PP=per-protocol

Overall, 673 pediatric AR patients were screened and 400 were randomized. All 400 patients randomized to treatment were analyzed for safety. The ITT analysis set was composed of 395 patients, and 318 patients comprised the PP analysis set. The overall number of discontinuations was low and consistent across treatment groups. There were no differences among treatment groups in the number of patients who had protocol deviations that were considered serious enough to warrant exclusion of data from the PP analysis.

Efficacy results

The primary efficacy endpoint was the overall TNSS (reflective). There was a marked reduction from baseline in the overall TNSS in all treatment groups, including placebo. The difference between the RAQ 64 μg group and placebo was not statistically significant. No additional formal hypothesis testing was conducted. The magnitude of the difference between the RAQ 32 μg group and placebo in the change in the overall TNSS from baseline was 0.84 points (unadjusted p-value=0.008). Similar effects of RAQ 32 μg compared to placebo were also demonstrated in the AM and PM 12-hour reflective TNSS, the instantaneous TNSS, the POE, and each of the individual reflective symptom scores. No notable differences between the RAQ 16 μg group and placebo were observed.

Table S2 Summary of efficacy variables by treatment group (ITT analysis set)

Variable Treatment	n	Baseline mean (SE)	Adjusted change from baseline, mean (SE)	Difference from placebo in adjusted change from baseline, mean (SE)	Unadjusted p-value vs placebo	95% CI for difference from placebo
Primary variable						
Overall TNSS						
RAQ 16 µg	91	8.02 (0.21)	-2.92 (0.23)	0.19 (0.32)	0.552	-0.43 to 0.81
RAQ 32 µg	93	7.76 (0.19)	-3.57 (0.23)	0.84 (0.32)	0.008[a]	0.22 to 1.46
RAQ 64 µg	105	7.90 (0.20)	-2.72 (0.21)	-0.01 (0.31)	0.973	-0.61 to 0.59
Placebo	99	7.80 (0.19)	-2.73 (0.22)			
Secondary variables						
TNSS: AM 12-hour reflective						
RAQ 16 µg	91	7.84 (0.22)	-2.78 (0.23)	0.10 (0.32)	0.743	-0.52 to 0.73
RAQ 32 µg	95	7.55 (0.20)	-3.32 (0.23)	0.64 (0.31)	0.042[a]	0.02 to 1.26
RAQ 64 µg	106	7.64 (0.22)	-2.49 (0.21)	-0.18 (0.31)	0.554	-0.78 to 0.42
Placebo	102	7.71 (0.21)	-2.68 (0.22)			
TNSS: PM 12-hour reflective						
RAQ 16 µg	91	8.16 (0.20)	-3.15 (0.24)	0.26 (0.33)	0.429	-0.39 to 0.91
RAQ 32 µg	94	7.99 (0.19)	-3.78 (0.24)	0.89 (0.33)	0.007[a]	0.25 to 1.54
RAQ 64 µg	105	8.10 (0.20)	-2.90 (0.22)	0.01 (0.32)	0.970	-0.61 to 0.64
Placebo	101	7.92 (0.19)	-2.89 (0.23)			
TNSS: Instantaneous (AM)						
RAQ 16 µg	91	7.54 (0.25)	-2.83 (0.23)	0.14 (0.31)	0.646	-0.47 to 0.76
RAQ 32 µg	95	7.26 (0.22)	-3.31 (0.22)	0.63 (0.31)	0.043[a]	0.02 to 1.24
RAQ 64 µg	105	7.31 (0.25)	-2.57 (0.21)	-0.12 (0.30)	0.699	-0.71 to 0.48
Placebo	102	7.35 (0.22)	-2.69 (0.21)			

[a] Unadjusted p-value ≤0.05.

ITT=intention-to-treat; RAQ=RHINOCORT AQUA (budesonide) Nasal Spray; SE=standard error of the mean; CI=confidence interval

Safety results

Overall, RAQ was safe and well-tolerated. The incidence of AEs was about 30% and similarly distributed across all 4 treatment groups. No deaths occurred. The only SAE was a case of periorbital cellulitis that occurred in a patient in the RAQ 64 μg group; the event was not considered by the investigator to be causally related to study treatment. Although the incidence of DAEs appeared to be dose-ordered across the RAQ groups, the incidence of DAEs was similar to that of the placebo group (RAQ 16 μg [1.1%; 1/93]; RAQ 32 μg [2.1%; 2/97]; RAQ 64 μg [4.7%; 5/107]; placebo [3.9%; 4/103]). Most of the DAEs were related to infections or respiratory tract conditions. None of the DAEs were considered by the investigators to be causally related to study treatment except for 2 cases of epistaxis (1 patient in the RAQ 64 μg group and 1 patient who received placebo). Two cases of benign transient hyperphosphatasemia, which occurred in 2 twin brothers at 1 study center (1 in the RAQ 64 μg group and 1 in the placebo group), were classified as OAEs. Neither event was considered by the investigator to be causally related to study treatment.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events, during double-blind treatment[a] (safety analysis set)

Category of adverse event	Number (%) of patients who had an adverse event in each category[b]			
	RAQ 16 μg (n=93)	RAQ 32 μg (n=97)	RAQ 64 μg (n=107)	Placebo (n=103)
Any adverse events	28 (30.1)	29 (29.9)	36 (33.6)	33 (32.0)
Serious adverse events	0	0	1 (0.9)	0
SAEs leading to death	0	0	0	0
SAEs not leading to death	0	0	1 (0.9)	0
Discontinuations of study treatment due to adverse events	1 (1.1)	2 (2.1)	5 (4.7)	4 (3.9)
Other significant adverse event	0	0	1 (0.9)	1 (1.0)
	Total number of adverse events[c]			
Any adverse events	46	55	60	52
Serious adverse events	0	0	1	0
Discontinuations of study treatment due to adverse events	1	3	6	4
Other significant adverse events	0	0	1	1

[a] From Visit 2 through Visit 3; excludes screening and follow-up periods.
[b] 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.
[c] An adverse event may be counted more than once if a patient had multiple occurrences of the event.
RAQ=RHINOCORT AQUA (budesonide) Nasal Spray; SAEs=serious adverse events

Table S4 **Number (%) of patients with the most commonly reported[a] adverse events during double-blind treatment, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)**

MedDRA Preferred term[b]	Treatment			
	RAQ 16 µg (n=93)	RAQ 32 µg (n=97)	RAQ 64 µg (n=107)	Placebo (n=103)
Cough	5 (5.4)	3 (3.1)	6 (5.6)	5 (4.9)
Epistaxis	7 (7.5)	2 (2.1)	5 (4.7)	4 (3.9)
Pyrexia	3 (3.2)	9 (9.3)	4 (3.7)	0
Headache	1 (1.1)	4 (4.1)	2 (1.9)	2 (1.9)
Otitis media	0	3 (3.1)	1 (0.9)	5 (4.9)
Nasopharyngitis	1 (1.1)	3 (3.1)	2 (1.9)	2 (1.9)
Upper respiratory tract infection	2 (2.2)	0	5 (4.7)	1 (1.0)
Diarrhoea	0	3 (3.1)	0	4 (3.9)
Vomiting	2 (2.2)	3 (3.1)	0	1 (1.0)
Pharyngolaryngeal pain	1 (1.1)	2 (2.1)	0	2 (1.9)
Sinusitis	1 (1.1)	1 (1.0)	2 (1.9)	1 (1.0)
Arthropod bite	1 (1.1)	0	2 (1.9)	1 (1.0)
Pain in extremity	0	4 (4.1)	0	0
Rhinorrhea	2 (2.2)	0	2 (1.9)	0
Viral infection	1 (1.1)	0	2 (1.9)	1 (1.0)
Wheezing	1 (1.1)	0	1 (0.9)	1 (1.0)
Asthma	0	0	2 (1.9)	0
Excoriation	1 (1.1)	0	1 (0.9)	0
Skin laceration	1 (1.1)	0	1 (0.9)	0
Contusion	1 (1.1)	0	0	0

[a] Sorted by decreasing frequency as summarized over all treatment groups (safety analysis set). Adverse events for which the highest frequency in any treatment arm was ≤1.0% are excluded.

[b] Patients with multiple events with the same MedDRA preferred term are counted only once for that term.

RAQ=RHINOCORT AQUA (budesonide) Nasal Spray

There were no clinically important findings in clinical laboratory results, vital signs, physical examination, or examination of the nasal cavity from the baseline period to the end of treatment among any of the treatment groups.