AstraZeneca

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|---|---|---|---|
| Drug product: | budesonide | **SYNOPSIS** | |
| Drug substance(s): | RHINOCORT AQUA® | | |
| Document No.: | | | |
| Edition No.: | | | |
| Study code: | | | |
| Date: | 27 February 2004 | | |

# A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Phase IIIB Study to Assess the Efficacy, Safety and Product Attributes of RHINOCORT AQUA® (budesonide) Versus Placebo and Fluticasone Propionate as an Active Comparator in Patients 12 Years of Age and Older with Seasonal Allergic Rhinitis

**Co-ordinating investigator**

**Study center(s)**

Conducted in the USA (16 centers)

**Publications**

None at the time of this report

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 15 April 2003 | IIIB |
| **Last patient completed** | 11 July 2003 | |

**Objectives**

The primary objective of the study was to determine the efficacy of once-daily administration of 64 μg of RHINOCORT AQUA compared to its placebo in relieving the symptoms of seasonal (grass) allergic rhinitis in patients 12 years of age and older by assessment of Total Nasal Symptom Scores (TNSS). Once-daily fluticasone propionate 200 μg was included as an active comparator.

The secondary objectives of the study were:

1. To determine the efficacy of fluticasone propionate 200 μg once-daily compared to its placebo by assessment of the reflective TNSS

2. To determine the comparability of RHINOCORT AQUA 64 μg once-daily and fluticasone propionate 200 μg once-daily by assessment of reflective TNSS

3. To assess the impact of treatment on patients' Health Related Quality of Life (HRQL) by assessment of the Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S))

4. To assess efficacy through a patient's overall evaluation of treatment efficacy

5. To evaluate the safety of RHINOCORT AQUA by assessment of adverse events and clinical measurements. To evaluate the safety of fluticasone propionate by assessment of adverse events and clinical measurements

6. To evaluate components of patient satisfaction by assessment of Patient Use Questions

7. To assess patients' detection of product sensory attributes through an assessment of the Perception of Product Attribute Questions

**Study design**

This was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study.

**Target patient population and sample size**

Male and female patients 12 years of age and older with at least a 2-year history of seasonal (grass) allergic rhinitis. A sample size of 100 patients per group was chosen to provide 90% power to detect a difference of 1.00 in mean TNSS (the primary endpoint).

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

RHINOCORT AQUA 64 μg or fluticasone propionate 200 μg once-daily by intranasal inhalation, or their respective placebos. Batch numbers were: RHINOCORT AQUA 32 μg nasal spray, DM 316; RHINOCORT AQUA placebo, DDG 109; fluticasone propionate 50 μg nasal spray, C075423; fluticasone propionate placebo, DDM1

**Duration of treatment**

Two weeks

## Criteria for evaluation (main variables)

### Efficacy and pharmacokinetics

- Primary variable: Change from baseline to the average score during the two weeks of treatment in reflective Total Nasal Symptom Scores (TNSS)

- Secondary variables: AM and PM 12-hour reflective TNSS; Individual reflective symptom scores; Adult RQLQ(S); Patient's Overall Evaluation of Treatment Efficacy; Patient Use Questionnaire; Product Attribute Questions

### 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. 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 the overall reflective TNSS only.

### Patient population

The treatment groups were well balanced in demographic and baseline characteristics. The majority of the patients across all treatment groups were female (57.5%) and Caucasian (87.2%) with a mean age of 32.0±13.9 years. The treatment groups were comparable with respect to demographic variables and mean baseline reflective symptom scores. There was little variation in baseline mean values for TNSS, the primary variable, rhinorrhea, congestion, nasal itching, and sneezing. The overall medical history of the patients in this study was consistent with that expected of a typical population with seasonal allergic rhinitis with no differences between the 4 groups. In general, the patient population was representative of the target population. Patient disposition is summarized in Table S1.

**Table S1 Patient Disposition**

| Disposition | | RAQ 64 μg | RAQ placebo | FP 200 μg | FP placebo |
|---|---|---|---|---|---|
| N (%) of patients who | Completed | 101 (95.3) | 102 (99.0) | 104 (96.3) | 99 (95.2) |
| | Discontinued | 5 (4.7) | 1 (1.0) | 4 (3.7) | 5 (4.8) |
| N analyzed for safety | | 106 (100.0) | 103 (100.0) | 108 (100.0) | 104 (100.0) |
| N analyzed for efficacy (ITT) [a] | | 106 (100.0) | 103 (100.0) | 108 (100.0) | 104 (100.0) |
| N analyzed for efficacy (PP) | | 94 (88.7) | 93 (90.3) | 97 (89.8) | 98 (94.2) |

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

FP=Fluticasone propionate; ITT=Intention to treat; N=Number; PP=Per-protocol; RAQ=RHINOCORT AQUA

Data derived from Table 11.1.1.1 and 11.1.1.2, Section 11.1.

## Efficacy results

Once-daily administration of RHINOCORT AQUA RAQ 64 μg during the two-week study period was significantly better than placebo in relieving the symptoms of seasonal allergic rhinitis (SAR) based on overall TNSS, the primary study variable (Table S2). This significant difference between RHINOCORT AQUA 64 μg and its placebo was clinically relevant (indicated by a difference in mean change from baseline of ≥1 point). There was also a statistically significant difference between RHINOCORT AQUA 64 μg and its placebo in the individual components of TNSS (AM TNSS, PM TNSS, individual reflective nasal symptom scores). Once-daily fluticasone propionate 200 μg also demonstrated significantly better efficacy than its placebo and achieved a greater reduction in overall TNSS than RHINOCORT AQUA 64 μg. Both RHINOCORT AQUA 64 μg and fluticasone propionate 200 μg were significantly better than their respective placebos in the reduction of Adult RQLQ(S) scores and the patients' overall evaluation of treatment efficacy. Patients in both RHINOCORT AQUA 64 μg and fluticasone propionate 200 μg treatment groups were also significantly more satisfied and more likely to take their medications again if prescribed than their respective placebos. Patients in the RHINOCORT AQUA 64 μg group had significantly less perception of their product sensory attributes including smell, taste, throat and nose runoff, force of spray, moistness in the nose, and aftertaste than patients in the fluticasone propionate 200 μg group.

**Table S2** **Summary of statistical change from baseline in overall TNSS in the ITT population**

| Treatment | N | Baseline mean (SE) | Adjusted change from baseline mean (SE) | p Value versus placebo | 95% CI on difference from placebo |
| --- | --- | --- | --- | --- | --- |
| RAQ 64 μg | 106 | 9.20 (0.18) | -2.91 (0.20) | <0.001 | 0.45 to 1.59 |
| RAQ placebo | 103 | 9.25 (0.17) | -1.90 (0.21) | | |
| FP 200 μg | 108 | 9.22 (0.17) | -3.85 (0.20) | <0.001 | 1.47 to 2.60 |
| FP placebo | 104 | 9.17 (0.16) | -1.81 (0.21) | | |

Data derived from Table 11.2.1.7, Section 11.2.

## Safety results

Overall, RHINOCORT AQUA 64 μg and fluticasone propionate 200 μg were well tolerated. The overall frequency of adverse events in patients who received either RHINOCORT AQUA 64 μg or fluticasone propionate 200 μg once-daily was similar to that in patients receiving their respective placebos. The most frequently reported adverse events were epistaxis (4.6% fluticasone propionate 200 μg; 0% RHINOCORT AQUA 64 μg) and pharyngolaryngeal pain (4.7% RHINOCORT AQUA 64 μg; 0% fluticasone propionate 200 μg). Serious adverse events (SAEs) were rare: only 2 (0.5%) patients reported SAEs (one in each active drug treatment group) and these occurred after the treatment period. Discontinuations of

investigational product due to adverse events (DAEs) were reported in 8 patients: 2(1.9%) RHINOCORT AQUA 64 μg, 1(1.0%) RHINOCORT AQUA placebo, 2(1.9%) fluticasone propionate 200 μg, and 3(2.9%) fluticasone propionate placebo. There were no other significant adverse events and no deaths in the study.

**Date of the report**

23 January 2004