AstraZeneca

| **Clinical Study Report** | |
|---|---|
| Drug substance | Rhinocort Aqua™ (budesonide) |
| Edition No. | 1 |
| Study code | SD-005-0705 |
| Date | 20 December 2006 |

# A Double-Blind, Double-Dummy, Randomized, Placebo-controlled Cross-Over Exploratory Study to Assess the Efficacy of Rhinocort Aqua™ (budesonide) Nasal Spray in Combination with Intranasal OXIS TURBUHALER® in an Allergic Rhinitis Challenge Model – Test of Concept

**Study dates:** First subject enrolled: 14 October, 2002
Last subject completed: 11 April 2003

**Phase of development:** Phase 2

This study was performed in compliance with Good Clinical Practice.

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|---|---|---|---|
| Drug product | Rhinocort Aqua™ | **SYNOPSIS** | |
| Drug substance(s) | Budesonide | | |
| Edition No. | 1 | | |
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| Date | 20 December 2006 | | |

# A Double-Blind, Double-Dummy, Randomized, Placebo-controlled Cross-Over Exploratory Study to Assess the Efficacy of Rhinocort Aqua™P P(budesonide) Nasal Spray in Combination with Intranasal OXIS TURBUHALERP®P in an Allergic Rhinitis Challenge Model – Testoncept

**Objectives**

The primary objective of the study was:

To establish the absolute efficacy of once daily (od) administration of Rhinocort Aqua™ 64 μg plus OXIS 9 μg compared with placebo and to generate a relative efficacy of Rhinocort Aqua 64 μg plus OXIS 9 μg to an active comparator (Rhinocort Aqua 64 μg) in relieving the symptoms of allergic rhinitis in adults by assessment of reflective Total Nasal Symptom Scores (TNSS) in a nasal allergen challenge model.

The secondary objectives of the study were:

To compare the efficacy of once daily administration of OXIS 9 μg to that of placebo by assessment of reflective TNSS.

To assess the efficacy of the active treatments versus placebo in reducing instantaneous TNSS immediately prior to, and 10 and 20 minutes after allergen nasal challenge.

To assess the efficacy of the active treatments versus placebo in reducing the reflective and instantaneous individual nasal symptoms of rhinorrhea, nasal congestion, nasal itching, and sneezing.

To assess the efficacy of the active treatments versus placebo in improving Peak Nasal Inspiratory Flow (PNIF) measurements.

To assess the effect of the active treatments on reducing markers of inflammation, specifically eosinophilic cationic protein, tryptase, and $\alpha_2$-macroglobulin levels, in nasal lavage versus placebo.

To determine the safety of once daily administration of Rhinocort Aqua 64 μg plus Oxis 9 μg, Oxis 9 μg to placebo and Rhinocort Aqua 64 μg od by assessment of adverse events and clinical measurements.

**Study design**

This study was a single centre, double-blind, double dummy, randomised, crossover, placebo-controlled exploratory study to assess the efficacy and safety of Rhinocort Aqua 64 μg plus OXIS 9 μg versus placebo and an active comparator (Rhinocort Aqua 64 μg) in subjects with birch or timothy-grass pollen allergic rhinitis in a nasal challenge model performed outside the natural pollen season.

Target subject population and sample size

Forty males and females aged 18 to 65 years, with a history of seasonal allergic rhinitis due to birch or timothy pollen (to achieve 34 evaluable subjects).

**Investigational product and comparator(s): dosage, mode of administration.**
Investigational Product:
Rhinocort Aqua Nasal Spray, administered as 1 spray (32 μg per spray) in each nostril in the morning for a total daily dose of 64 μg plus OXIS TURBUHALER®(TBH), fitted with a nasal adaptor, administered a 1 inhalation (4.5 μg per inhalation) in each nostril for a total daily dose of 9 μg (combination therapy).
OXIS TBH 9 μg (delivered dose), fitted with a nasal adaptor, administered as 1 inhalation (4.5 μg per inhalation) in each nostril in the morning for a total daily dose of 9 μg.
Comparator:
Rhinocort Aqua Nasal Spray 64 μg administered as 1 spray (32 μg per spray) in each nostril in the morning for a total daily dose of 64 μg.
Placebo to Rhinocort Aqua Nasal Spray administered as 1 spray in each nostril in the morning.
Placebo to OXIS TBH, fitted with a nasal adaptor, administered as 1 inhalation in each nostril in the morning.

**Duration of treatment**
Subjects were treated over approximately an 18-week period. Each treatment period was 15 days with allergen challenges on the last 7 days followed by a histamine provocation on the 15$^{th}$ day. Each treatment period was followed by a 2-week washout period. Each subject participated in 4 treatment periods, and had 38 clinic visits.
Criteria for evaluation (main variables)

**Efficacy**
Primary variable: Assessment of overall TNSS was the criteria used to evaluate the efficacy of Rhinocort Aqua 64 μg plus OXIS 9 μg (combination therapy) compared with placebo and to generate a relative efficacy of combination therapy compared with Rhinocort Aqua 64 μg (active comparator) in relieving the symptoms of seasonal allergic rhinitis.
Secondary variables: Individual Reflective Symptom Scores, TNSS (instantaneous) and PNIF measurements were the criteria used to evaluate the efficacy of Rhinocort Aqua 64 μg plus OXIS 9 μg (combination therapy) compared with placebo and to generate a relative efficacy of combination therapy compared with Rhinocort Aqua 64 μg (active comparator) in relieving the symptoms of seasonal allergic rhinitis.

**Safety**
Safety was assessed on the basis of subjects reporting AEs, serious adverse events (SAEs), discontinuations of study treatment due to AEs, clinically significant physical examination results, nasal examination results, and vital signs. All randomised subjects who received at least 1 dose of study medication were included in the safety analysis.

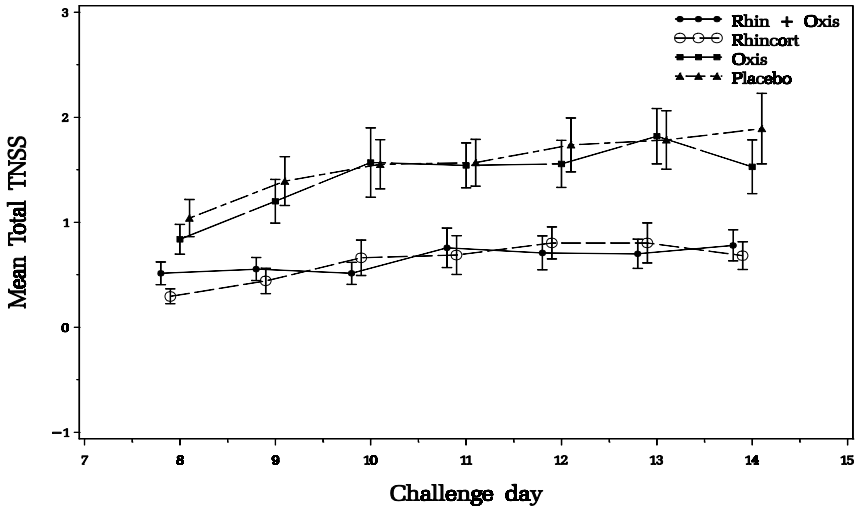
**Statistical methods**
All statistical comparisons were based on a 2-sided test. Statistical significance was declared if the p-value was less than or equal to 0.050. The Intention-to-treat (ITT) population was the primary population analysed for all efficacy variables.

**Subject population**
In total, 40 subjects were enrolled in this study, all of which were included in the safety analysis. Thirty-three subjects completed this study. One subject discontinued the study during treatment with placebo because of an AE during the treatment period. The average age of the subjects in the study was 25.2 years. The subject population was 62.5% male and 37.5% female, and 100% of the population was Caucasian.

**Efficacy results**
Primary:

Rhinocort Aqua 64 μg administered alone or in combination with OXIS 9 μg was significantly more effective (p<0.001) than placebo in relieving the symptoms of allergic rhinitis in the allergen challenge model.
Rhinocort Aqua 64 μg plus OXIS 9 μg did not statistically significantly reduce TNSS compared to Rhinocort Aqua 64 μg administered alone (p=0.7387) (See Figure S1).

**Figure S1 Mean Total Nasal Symptom Score (TNSS) over time, by treatment**




Rhin + Oxis free combination of Rhinocort Aqua 64 μg plus OXIS 9 μg; Rhincort Rhinocort Aqua 64 μg; Oxis OXIS 9 μg.

The mean change from baseline in TNSS was 0.12 points and 0.06 points for subjects who received Rhinocort Aqua 64 μg plus OXIS 9 μg or Rhinocort Aqua 64 μg, respectively. The mean change from baseline in TNNS was 0.98 points and 1.11 points for subjects who received OXIS 9 μg or placebo, respectively.
Comparisons change from baseline to challenge period in the TNSS revealed that the Rhinocort Aqua 64 μg plus OXIS 9 μg treatment group was statistically significant (p<0.0001) from the placebo group. However, TNSS changes in the Rhinocort Aqua 64 μg plus OXIS 9 μg group was not statistically significant (p=0.7387) from Rhinocort Aqua 64 μg.

Secondary:
TNSS, adjusted for baseline, in the OXIS 9 μg treatment was not statistically (p=0.4126) different from that in placebo group.
Instantaneous TNSS immediately prior to and 10 and 20 minutes after allergen nasal challenge in the Rhinocort Aqua 64 μg plus OXIS 9 μg or Rhinocort Aqua 64 μg alone groups were significantly reduced compared to placebo and OXIS treatments.
The reflective and instantaneous individual nasal symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) in the active treatment groups (Rhinocort Aqua 64 μg plus OXIS 9 μg or Rhinocort Aqua 64 μg alone) were reduced compared to placebo and OXIS treatments.

Peak Nasal Inspiratory Flow measurements were improved in the active treatment groups (Rhinocort Aqua 64 μg plus OXIS 9 μg or Rhinocort Aqua 64 μg alone) compared to placebo and OXIS treatments.

The inflammatory markers, eosinophilic cationic protein, tryptase and $\alpha_2$-macroglobulin were reduced following active treatments compared to placebo, however, these reductions were not statistically significant. Combination treatment (Rhinocort Aqua 64 μg plus OXIS 9 μg) was not more effective at reducing inflammatory markers compared to Rhinocort Aqua 64 μg treatment alone.

There were negligible difference in the results for the ITT and per protocol (PP) analyses and therefore the same conclusions could be drawn from both analyses.

**Safety results**

Rhinocort Aqua 64 μg and OXIS 9 μg administered alone or in combination were well tolerated by all subjects. The frequency of AEs was similar across treatment arms. There were no AEs or SAEs associated with the active treatment groups. The number of AEs reported by subjects participating in this study is presented in Table S1.

**Table S1 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety population), during treatment period**

| Category of adverse event | N (%) of subjects who had an adverse event in each category[a] | | | |
|---|---|---|---|---|
| | Rhinocort Aqua 64 μg + OXIS 9 μg (N=38) | Rhinocort Aqua 64 μg + Placebo OXIS (N=39) | Placebo Rhinocort Aqua + OXIS 9 μg (N=38) | Placebo Rhinocort Aqua + Placebo OXIS (N=39) |
| Any adverse events | 13 (34.2%) | 24 (61.5%) | 15 (39.5) | 19(48.7) |
| Serious adverse events | 0 | 0 | 0 | 0 |
| Serious adverse events leading to death | 0 | 0 | 0 | 0 |
| Serious adverse events not leading to death | 0 | 0 | 0 | 0 |
| Discontinuations of study treatment due to adverse events | 0 | 0 | 0 | 1(0.6%) |
| Other significant adverse events | 0 | 0 | 0 | 0 |
| | **Total number of adverse events** | | | |
| Adverse events | 22 | 45 | 35 | 41 |
| Serious adverse events | 0 | 0 | 0 | 0 |
| Adverse events leading to discontinuation of study treatment | 0 | 0 | 0 | 1 |
| Other significant adverse events | 0 | 0 | 0 | 0 |

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

Adverse events were reported by 46.1% (71/154) of the total study population. The most common AEs (nasopharyngitis, headache, pyrexia) in subjects receiving active treatment were similar across treatment groups. No subjects in any of the treatment groups reported SAEs. One subject discontinued the study due to an AE (pyrexia) during treatment with placebo; this subject had also stopped treatment during placebo+Oxis due to common cold. Five other subjects stopped 1 or 2 of the treatments due to AEs (including common cold, mononucleosis, tonsillitis and cough) but continued subsequent treatment periods as allowed by the protocol.

Date of the report
20 December 2006