# 1 TITLE PAGE

**A dose-finding study of the effects of OC000459 on responses to allergen challenge in the Vienna chamber in subjects known to suffer from grass pollen induced allergic rhinitis: a randomised, double-blind placebo-controlled, parallel group evaluation of the dose response curve and minimum effective dose given orally for eight days**

| | |
|---|---|
| **Study code:** | OC000459/010/07 |
| **EudraCT Number:** | 2008-001659-24 |
| **Name of investigational product:** | OC000459 |
| **Indication:** | Allergic rhinitis |
| **Clinical phase:** | II |
| **Sponsor:** | Oxagen Ltd |
| **Sponsor address:** | 91 Milton Park<br>Abingdon<br>Oxfordshire<br>OX14 4RY<br>United Kingdom |
| **Sponsor representative:** | Dr C Mike Perkins |
| **Study dates:** | First subject screened: 26 May 2008<br>First subject dosed: 9 June 2008<br>Last follow-up assessment: 07 July 2008 |
| **Principal Investigator**: | Univ Professor Dr Friedrich Horak MD |
| **Study location**: | Allergie Zentrum Wien West<br>Abt. Vienna Challenge Chamber<br>Hütteldorferstrasse 44 / 2. Stock<br>Vienna 1150<br>Austria |
| **Report date:** | 24 June 2009 |

The study was performed in compliance with Good Clinical Practice Guidelines, including the archiving of essential documents

# 2 SYNOPSIS

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

| | | | |
|---|---|---|---|
| Title of study | A dose-finding study of the effects of OC000459 on responses to allergen challenge in the Vienna chamber in subjects known to suffer from grass pollen induced allergic rhinitis: a randomised, double-blind placebo-controlled, parallel group evaluation of the dose response curve and minimum effective dose given orally for eight days | | |
| Investigator(s) | Univ Prof Dr Friedrich Horak MD | | |
| Study centre(s) | Allergie Zentrum Wien West, Abt. Vienna Challenge Chamber, Hütteldorferstrasse 44 / 2. Stock, 1150-Vienna, Austria | | |
| Publication (reference) | None to date of CSR | | |
| Study period | First subject screened: 26 May 2008<br>Last follow-up assessment: 07 July 2008 | Clinical phase | II |
| Objectives | The primary objective of the study was to assess the efficacy of a range of doses of OC000459 given orally when subjects were challenged in the Vienna Challenge Chamber (VCC) for 6 hours.<br>Secondary objectives were: to assess the safety of this treatment schedule in male and female subjects with allergic rhinitis; and to assess plasma levels of OC000459 at the time of allergen challenge. | | |
| Methodology | Randomised, double-blind, placebo-controlled, parallel group evaluation of the effect of OC000459 given orally once daily (od) or twice daily (bd) for 8 days. A double-dummy technique was used to blind once and twice daily dosing schedules. Treatment groups consisted of 19-22 subjects and the study was conducted using six cohorts, a cohort being defined as a group of subjects who commenced treatment on the same day with 16-19 subjects being entered into the VCC at the same session.<br>After a screening period of up to 6 weeks, including an allergen challenge within 1-3 weeks of start of study treatment, subjects began treatment with OC000459 or placebo, the first day of treatment being Day 1. Treatment (OC000459 and/or placebo) was taken twice daily for 7 days with the final dose on the morning of Day 8. Subjects were exposed to grass pollen (up to 1500 grass pollen grains/$m^3$) for 6 hours starting in the morning of Day 8. They were assessed for nasal symptoms, eye symptoms, other symptoms, nasal secretion weight, $FEV_1$ (forced expiratory volume in one second) and anterior rhinomanometry over the 6-hour period. A follow-up visit was made 1-3 weeks after the last dose of study medication. | | |
| Number of subjects | Planned: up to 120 subjects were to be screened to enrol up to 105 subjects and yield at least 90 evaluable subjects (18 in each of five groups).<br>Studied: 105 subjects, 22 randomised to placebo, 21 to 50 mg bd, 22 to 100 mg od, 21 to 50 mg od and 19 to 25 mg od. | | |

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

| | |
|---|---|
| Diagnosis and criteria for inclusion | The main inclusion criteria were healthy male and female subjects aged 18-50 years with a history of grass-pollen-related allergic rhinitis within the previous 2 years. Subjects had to be free of other significant illnesses and not to have smoked within the previous 3 months with a pack history of ≤ 1 pack years. $FEV_1$ within normal limits (≥ 90% of predicted). Asymptomatic at screening as characterised by a total nasal symptom score (TNSS) of < 4 at screening and on Day 1. A total nasal symptom score of at least 6 had to be recorded at screening after challenge with up to 1500 grass pollen grains/$m^3$ after 2 hours in the VCC and subjects had to have a positive Radio Allergen Sorbent Test (RAST) (≥ class 2) to grass pollen and a positive cutaneous response (wheal ≥ 3 mm compared to negative control) to mixed grass pollen within the last 12 months or at screening. |
| Test product, dose, mode of administration and batch number(s) | OC000459, taken orally, 50 mg twice daily, 100 mg once daily, 50 mg once daily or 25 mg once daily immediately after food for 8 days. (For once daily dosing regimens, the OC000459 dose was taken in the morning. Placebo tablets were also taken as necessary to maintain the blind.)<br>OC000459 provided as 25 mg and 100 mg tablets. Batches: 25 mg 0126D, expiry date 01 November 2008; 100 mg 0127D, expiry date 03 November 2008 |
| Duration of treatment | 8 days (with twice daily dosing on Days 1-7 plus dosing on the morning of Day 8) |
| Reference therapy, dose, mode of administration and batch number(s) | Placebo, two tablets orally twice daily immediately after food for 8 days.<br>Batch: 0453C, expiry date 19 December 2008 |
| Criteria for evaluation | Efficacy<br>Nasal symptom scores (for nasal obstruction, rhinorrhoea, nasal itch and sneezing, each scored on a scale from 0 to 3), eye symptom scores (for watery eyes, itchy eyes and red eyes, each scored on a scale of 0-3) and other symptom scores (for cough, itchy throat and itchy ears, each scored on a scale of 0-3) were rated by the subjects themselves pre-challenge and every 15 min from 0 to 6 hours after the start of the challenge on Day 8. The TNSS was derived by adding all the individual nasal symptom scores; similarly, the total eye symptom score and the total other symptom score were derived by adding the individual eye and other symptom scores.<br>Nasal secretion weight and active anterior rhinomanometry (nasal airflow resistance) every 30 min from 0 to 6 hours after the start of challenge on Day 8.<br>Plasma concentrations<br>Plasma levels of OC000459 pre-dose/pre-challenge and 6 hours after the start of the challenge on Day 8.<br>Safety<br>Adverse events, vital signs, electrocardiogram (ECG), physical examination and safety laboratory parameters.<br>$FEV_1$ pre-challenge and every hour from 0-6 hours after the start of challenge on Day 8. |

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

| | |
|---|---|
| Statistical methods | The TNSS was averaged over the 6-hour period on Day 8, as well as over the 0-2 hours, 2-4 hours and 4-6 hours periods. Individual components of TNSS, total eye symptom score, total other symptom score, secretion weight, and anterior rhinomanometry (nasal airflow resistance) on Day 8 were also averaged over the 6-hour allergen challenge period and over the time periods of 0-2 hours, 2-4 hour and 4-6 hours. The primary endpoint was the change from pre-challenge TNSS of the TNSS averaged over 0-6 hours on Day 8.<br>The primary endpoint was analysed using analysis of variance (ANOVA) with treatment and cohort as factors. Each of the OC000459 dose groups was compared with placebo. Least squares (LS)-means together with 95% confidence interval (CI) and 98.75% CI were calculated for the difference between each OC000459 dose group and placebo. In addition, a secondary pair of contrasts was considered to investigate the linear and quadratic components of dose response across the three once-a-day OC000459 dose groups.<br>If the assumptions underlying the parametric analysis did not hold, the Kruskal-Wallis test was used for testing the difference between treatment arms overall and the Wilcoxon rank sum test was used for pairwise comparisons between each of the OC000459 dose groups and placebo at the 1.25% level of significance as a consequence of the Bonferroni adjustment for multiple comparisons.<br>The primary analysis was based on the Full Analysis (FA) set of subjects (subjects who took at least one dose of study medication, complied with eligibility criteria and completed the study to Day 8) and was repeated excluding those subjects who had previously received OC000459.<br>Secondary efficacy endpoints were analysed in the same way as the primary efficacy endpoint. |

**SUMMARY - CONCLUSIONS**

SUBJECT DISPOSITION

In total, 105 subjects participated in the study; 17 had previously participated in a study of OC000459. Twenty-two (22) of the subjects were randomised to placebo, while 83 were randomised to OC000459: 21 to 50 mg bd, 22 to 100 mg od, 21 to 50 mg od and 19 to 25 mg od.

Two subjects failed to complete the study; one was treated with 50 mg bd and withdrew because of severe adverse events (unrelated to study medication) while one was treated with 25 mg od and withdrew because of scheduling problems. Neither of these subjects was assessed on Day 8; the FA population thus excluded these two subjects.

EXPOSURE TO STUDY MEDICATION

Twenty-two (22) subjects were exposed to placebo for 8 days, while 21 were exposed to OC000459 50 mg bd (20 for 8 days and one for 7 days), 22 to 100 mg od (each for 8 days), 21 to 50 mg od (each for 8 days) and 19 to 25 mg od (18 for 8 days and one for 7 days). Within the FA set, all 103 subjects took placebo or OC000459 for 8 days.

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

EFFICACY

The pre-challenge TNSS and the changes (increases) from pre-challenge on Day 8 are summarised below. The increase was broadly similar in active and placebo groups; the greatest increases were seen at 50 mg od.

| TNSS Day 8 | OC000459 | | | | Placebo |
|---|---|---|---|---|---|
| | 50 mg bd N = 20 | 100 mg od N = 22 | 50 mg od N = 21 | 25 mg od N = 18 | N = 22 |
| Pre-challenge | | | | | |
| Mean (SD) | 0.6 (0.8) | 1.0 (1.2) | 0.8 (1.0) | 1.0 (1.0) | 0.6 (0.8) |
| Median | 0.0 | 0.5 | 1.0 | 1.0 | 0.0 |
| Average change 0-6 h | | | | | |
| Mean (SD) | 5.4 (2.5) | 5.9 (2.5) | 6.4 (3.0) | 5.4 (2.2) | 5.9 (2.5) |
| Median | 4.8 | 5.7 | 7.4 | 5.3 | 5.7 |
| Average change 0-2 h | | | | | |
| Mean (SD) | 4.7 (2.7) | 5.0 (2.3) | 5.9 (2.5) | 4.6 (2.1) | 5.3 (2.3) |
| Median | 4.8 | 4.6 | 6.1 | 4.6 | 5.3 |
| Average change 2-4 h | | | | | |
| Mean (SD) | 5.6 (2.5) | 6.3 (2.7) | 6.7 (3.3) | 5.6 (2.2) | 6.2 (2.8) |
| Median | 5.3 | 6.6 | 7.8 | 5.3 | 6.0 |
| Average change 4-6 h | | | | | |
| Mean (SD) | 6.0 (2.8) | 6.3 (3.0) | 6.7 (3.5) | 5.8 (2.5) | 6.2 (2.8) |
| Median | 4.8 | 6.6 | 7.8 | 6.0 | 6.0 |

The statistical analyses (see below) revealed no statistically significant results, indicating no difference between OC000459 and placebo and no dose-related effect of OC000459.

| | Overall p value | ANOVA contrast p value | Difference of LS means (98.75% CI) | Wilcoxon test p value |
|---|---|---|---|---|
| ANOVA model | | | | |
| Treatment effect | 0.742 | | | |
| Cohort effect | 0.849 | | | |
| Kruskal-Wallis test | 0.619 | | | |
| Pairwise comparisons | | | | |
| 50 mg bd vs placebo | | 0.513 | -0.531 (-2.375, 1.312) | 0.634 |
| 100 mg od vs placebo | | 0.497 | 0.530 (-1.239, 2.300) | 0.409 |
| 50 mg od vs placebo | | 0.568 | -0.451 (-2.243, 1.342) | 0.678 |
| 25 mg od vs placebo | | 0.984 | -0.015 (-1.764, 1.734) | 0.953 |
| Linear dose-response in OC000459 once daily dose groups | | | | |
| 25 mg vs 50 mg vs 100 mg | 0.532 | | | |
| Quadratic dose-response in OC000459 once daily dose groups | | | | |
| 25 mg vs 50 mg vs 100 mg | 0.820 | | | |

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

However, at screening the average TNSS over the 0-2 hour period was median 6.5 for placebo and 6.5, 6.3, 6.8 and 6.2 for those randomised to receive 50 mg bd, 100 mg od, 50 mg od, and 25 mg od OC000459, respectively, and were slightly higher than in the placebo group on Day 8 (median 5.6 over 0-2 hours). The response to the challenge thus seemed slightly diminished but there was no evidence that the actual stimulus was inadequate.

There were no significant results when the analysis was repeated excluding those who had previously received OC000459.

The results for total eye symptoms and total other symptoms over the 0-6 hour period are shown below: the table presents the pre-challenge scores and the average change (an increase) from pre-challenge over 0-6 hours.

| | OC000459 | | | | Placebo |
|---|---|---|---|---|---|
| | 50 mg bd N = 20 | 100 mg od N = 22 | 50 mg od N = 21 | 25 mg od N = 18 | N = 22 |
| **Total eye symptoms** | | | | | |
| Pre-challenge | | | | | |
| Mean (SD) | 0.2 (0.4) | 0.2 (0.7) | 0.3 (0.6) | 0.1 (0.5) | 0.2 (0.5) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Average change 0-6 h | | | | | |
| Mean (SD) | 1.4 (1.6) | 2.0 (1.9) | 1.9 (1.7) | 1.6 (2.0) | 1.8 (2.1) |
| Median | 0.8 | 1.5 | 1.3 | 1.6 | 1.2 |
| **Total other symptoms** | | | | | |
| Pre-challenge | | | | | |
| Mean (SD) | 0.2 (0.4) | 0.5 (1.0) | 0.2 (0.5) | 0.1 (0.5) | 0.1 (0.3) |
| Median | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Average change 0-6 h | | | | | |
| Mean (SD) | 0.9 (1.1) | 0.9 (1.3) | 1.1 (1.2) | 0.9 (1.0) | 0.6 (1.2) |
| Median change | 0.3 | 0.8 | 0.9 | 0.3 | 0.1 |

There were no significant differences or effects. There were also no significant results in the analyses of anterior rhinomanometry and nasal secretion weight.

PLASMA CONCENTRATIONS

Plasma levels of OC000459 were determined before breakfast (and thus pre-dose/pre-challenge) and at 6 hours post-challenge on Day 8. The data are summarised in the next table.

OC000459 was detected in all subjects in OC000459 groups. The mean concentrations at 0 hours were similar in those who took 25 mg od and 50 mg od, were higher in those taking 100 mg od and markedly higher in those taking 50 mg bd. Large differences were seen between subjects. In all four OC000459 groups, the mean plasma concentration was higher at 6 hours than 0 hours, but the increase was less marked in the 50 mg bd group as the 0 hour concentration was much higher in this group. The mean concentration at 6 hours increased with dose from 25 mg od, to 50 mg od to 100 mg od. The mean concentration in the 50 mg bd group was very similar to that in the 100 mg od group. OC000459 was not detected in the plasma of any subject in the placebo group.

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

| ng/mL OC000459 | 0 h | 6 h |
|---|---|---|
| 50 mg bd (N = 20) | | |
| Mean (SD) | 333.2 (249.0) | 485.8 (176.1) |
| Min – max | 8.3 – 873.7 | 277.5 – 868.6 |
| 100 mg od (N = 22) | | |
| Mean (SD) | 73.9 (51.9) | 484.3 (201.8) |
| Min - max | 8.4 – 172.3 | 205.7 – 872.7 |
| 50 mg od (N = 21) | | |
| Mean (SD) | 49.9 (30.6) | 371.2 (130.5) |
| Min - max | 16.9 – 114.8 | 170.7 – 635.3 |
| 25 mg od (N = 18) | | |
| Mean (SD) | 43.4 (38.0) | 291.3 (64.9) |
| Min - max | 16.8 – 175.7 | 187.5 – 394.4 |

SAFETY

Treatment-emergent adverse events (TEAEs) were reported for 10 of the 83 subjects (12.0%) who received OC000459 and 5 of the 22 subjects (22.7%) who received placebo. The most common adverse event was headache, recorded for six subjects after OC000459 and for none after placebo treatment. Other than for headache, there were no clear differences between active and placebo treatment. There was also no apparent relationship between dose of OC000459 and adverse event profile.

The proportion of subjects experiencing one or more treatment-related treatment-emergent adverse events was also no higher after OC000459 than placebo treatment: treatment-related adverse events were reported for 4 subjects on OC000459 (4.8%) and 2 subjects on placebo (9.1%). The table displays the treatment-related adverse events.

| | OC000459 | | | | Placebo |
|---|---|---|---|---|---|
| | 50 mg bd<br>N = 21 | 100 mg od<br>N = 22 | 50 mg od<br>N = 21 | 25 mg od<br>N = 19 | <br>N = 22 |
| n (%) with TEAEs | 2 (9.5%) | 2 (9.1%) | 4 (19.0%) | 2 (10.5%) | 5 (22.7%) |
| n (%) with treatment-related TEAEs | 1 (4.8%) | 0 | 2 (9.5%) | 1 (5.3%) | 2 (9.1%) |
| Gastrointestinal disorders | 1 (4.8%) | 0 | 1 (4.8%) | 0 | 1 (4.5%) |
| Abdominal pain upper | 0 | 0 | 1 (4.8%) | 0 | 1 (4.5%) |
| Nausea | 1 (4.8%) | 0 | 0 | 0 | 0 |
| Nervous system disorders | 1 (4.8%) | 0 | 0 | 1 (5.3%) | 0 |
| Headache | 1 (4.8%) | 0 | 0 | 1 (5.3%) | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (4.8%) | 0 | 1 (4.5%) |
| Nasal discomfort | 0 | 0 | 0 | 0 | 1 (4.5%) |
| Sneezing | 0 | 0 | 1 (4.8%) | 0 | 0 |

No subject reported a serious adverse event.

| **NAME OF COMPANY**<br>Oxagen Ltd<br><br>**NAME OF FINISHED PRODUCT**<br><br>**NAME OF ACTIVE INGREDIENT(S)**<br>OC000459 | **INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD**<br><br>Volume:<br><br>Page: | **(FOR NATIONAL AUTHORITY USE ONLY)** |
|---|---|---|

There was one withdrawal because of adverse events: a subject in the 50 mg bd group withdrew after 7 days of treatment because of severe pyrexia and pharyngolaryngeal pain (unrelated to study treatment).

There were no apparent trends or differences between OC000459 and placebo treatment with regard to the changes in laboratory test results other than for uric acid: there was a trend towards a reduction in uric acid with OC000459 treatment compared with placebo treatment. The change from baseline to Day 8 was mean/median -0.5/-0.5 mg/dL with 50 mg bd, -0.4/-0.4 mg/dL with 100 mg od, -0.1/-0.2 mg/dL with 50 mg od and -0.4/0.7 mg/dL with 25 mg od compared with 0.2/-0.1 mg/dL with placebo.

The majority of laboratory test results showed no change from baseline to Day 8 with respect to shifts to/from within to/from outside the reference ranges. Some shifts from within to outside the reference ranges were observed, but these occurred with both OC000459 and placebo treatment and there was generally no apparent difference between OC000459 and placebo or any dose-related effect within the OC000459 groups. However, there did seem to be a trend towards lower uric acid concentrations with OC000459 than with placebo: while the majority of results in the 50 mg bd, 100 mg od, 50 mg od and 25 mg od groups showed no change (80.0%), 81.8%, 81.0% and 77.8% compared with 90.9% for placebo), there were several subjects showing a shift from normal to below the reference range (10.0%, 13.6%, 4.8% and 11.1% compared with 0% for placebo).

On average, systolic blood pressure tended to increase on placebo and to decrease with OC000459; a similar pattern was seen for diastolic blood pressure. The observed mean/median changes were modest and not of clinical concern.

There were no statistically significant changes in $FEV_1$. The median change from pre-challenge to the average over 0-6 hours was a small increase or decrease: +0.017 L for placebo and -0.045, +0.010, -0.023 and -0.007 L for 50 mg bd, 100 mg od, 50 mg od, and 25 mg od OC000459 groups, respectively.

CONCLUSION
It is concluded that this study failed to demonstrate any statistically or clinically significant benefit of OC000459 over placebo treatment in subjects with allergic rhinitis exposed to a grass pollen challenge. OC000459 was safe and well tolerated at doses of 50 mg bd, 100 mg od, 50 mg od and 25 mg od for 8 days.

DATE OF REPORT
24 June 2009