1 TITLE PAGE

A 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, two-way crossover evaluation of a dose schedule of 200 mg given twice daily orally for eight days in male subjects

Study code:	OC000459/007/06
EudraCT Number:	2007-000017-11
Name of investigational product:	OC000459
Indication:	Allergic rhinitis
Clinical phase:	II
Sponsor:	Oxagen Ltd
Sponsor address:	91 Milton Park Abingdon Oxfordshire OX14 4RY United Kingdom
Sponsor representative:	Dr C Mike Perkins
Study dates:	First subject screened: 12 March 2007 First subject dosed: 19 March 2007 Last follow-up assessment: 07 May 2007
Principal Investigator:	Univ Professor Dr Friedrich Horak MD
Study location:	Allergie Zentrum Wien West Abt. Vienna Challenge Chamber Hütteldorferstrasse 44 / 2. Stock Vienna 1150 Austria
Report date:	30 May 2008

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

2 SYNOPSIS

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

Title of study	A 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, two-way crossover evaluation of a dose schedule of 200 mg given twice daily orally for eight days in male subjects		
Investigator(s)	Univ Prof Dr Friedrich Horak MD		
Study centre(s)	Allergie Zentrum Wien West, Abt. Vienna Challenge Chamber, Hütteldorferstrasse 44 / 2. Stock, Vienna 1150, Austria		
Publication (reference)	None to date of CSR		
Study period	First subject screened: 12 March 2007 Last follow-up assessment: 07 May 2007	Clinical phase	II
Objectives	The primary objective of the study was to assess the efficacy of OC000459 200 mg twice daily orally in comparison to placebo when subjects were challenged in the Vienna Challenge Chamber for 6 hours Secondary objectives were: to assess the safety of this treatment schedule in male subjects with allergic rhinitis; and to assess plasma levels of OC000459 at the time of allergen challenge.		
Methodology	Randomised, double-blind, placebo-controlled, two-way crossover evaluation of the effect of OC000459. After a screening period of up to 3 weeks, subjects took OC000459 200 mg twice daily for 8 days or placebo twice daily for 8 days (Treatment Period 1). The first day of treatment was Day 1. After a washout period (scheduled to be at least one week and approx 3 weeks in practice), subjects switched to the alternative treatment for a further 8 days (Treatment Period 2). Subjects were exposed to grass pollen (≥1400 grass pollen grains/m^3) for 6 hours on the morning of Day 2 and Day 8 of each treatment period. They were assessed for nasal symptoms, eye symptoms, other symptoms, nasal secretion weight, FEV1 and rhinomanometry over the 6-hour period. A follow-up visit was made 1-3 weeks after the last dose of study medication in Treatment Period 2.		
Number of subjects	Planned: Up to 40 male subjects were to be randomised to achieve 32 subjects in the Full Analysis population. Studied: 36 male subjects (20-47 years, mean 29.6 years) were randomised of whom 35 (20-47 years, mean 29.7 years) completed the study and were in the Full Analysis population.		

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Diagnosis and criteria for inclusion	The main inclusion criteria were healthy male subjects aged 18-50 years with a history of allergic rhinitis within the previous 2 years. Subjects had to be free of other significant illnesses and not to have smoked within the previous 12 months with a pack history of ≤ 1 pack years. FEV1 within normal limits (≥ 90% of predicted). Asymptomatic at screening as characterised by a normal-appearing nasal mucosa with no active allergic rhinitis and a total nasal symptom score (TNSS) sheet on study entry so that subject produced a score of <2 at screening and on Day 1 of Treatment Periods 1 and 2. A total nasal symptom score (TNSS) of at least 6 had to be recorded at screening after challenge with ≥1400 grass pollen grains/m^3 after 2 hours in the Vienna Challenge Chamber (VCC) and subjects had to have a positive 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, 200 mg orally twice daily immediately after food for 8 days. OC000459 provided as 100 mg gelatine capsules containing unformulated active substance: Batch 0022C (expiry date July 2008)
Duration of treatment	Each treatment period lasted for 8 days, with a scheduled washout period of at least one week between the two treatment periods. (In practice, the washout was approximately 3 weeks.)
Reference therapy, dose, mode of administration and batch number(s)	Placebo, two capsules orally twice daily immediately after food for 8 days. Batch: 0029C (expiry date July 2008)
Criteria for evaluation	Efficacy 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 (15-60 min prior to dosing) and every 15 min from 0 to 6 h after the start of the challenge (which began 0-10 minutes after dosing) on Day 2 and 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. Nasal secretion weight and active anterior rhinomanometry (nasal airflow resistance) every 30 min from 0 to 6 hours on Day 2 and Day 8. Nasal endoscopy pre-challenge and at 6 hours on Day 2 and Day 8. Plasma concentrations Plasma levels of OC000459 pre-challenge and 4 h after the start of the challenge on Days 2 and 8. The pre-challenge sample was taken 15-60 min prior to dosing; the challenge began 0-10 minutes after dosing. Safety Adverse events, vital signs, ECG, physical examination and safety laboratory parameters. FEV_1 pre-challenge and every hour from 0-6 hours on Day 2 and Day 8.

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Statistical methods	The TNSS was averaged over the 6-hour period on Day 2 and Day 8, as well as over the 0-2 h, 2-4 h and 4-6 h periods on each of the days. Individual components of TNSS, total eye symptom score, total other symptom score, secretion weight, and rhinomanometry (nasal airflow resistance) on Day 2 and 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, where possible. Nasal endoscopy scores were summarised at pre-challenge and 6 hours. The primary endpoint was the TNSS averaged over 0-6 h on Day 8. Crossover analysis was performed using a general linear model approach to examine treatment, sequence and period effects. Comparable non-parametric analysis of treatment and sequence effects was performed using the Wilcoxon rank test. In the light of statistically significant sequence/period effects, the data were analysed for Treatment Period 1 only, using both ANOVA and Wilcoxon tests. This approach was pre-planned and described in the Statistical Analysis Plan. Analysis of covariance (ANCOVA) was also performed for the primary endpoint, with the 2-h post-challenge TNSS at screening as covariate.

SUMMARY - CONCLUSIONS

SUBJECT DISPOSITION

A total of 36 subjects were randomised, 18 to each treatment sequence; 35 subjects completed the study receiving both OC000459 and placebo while the remaining subject withdrew from placebo treatment during Treatment Period 1 for personal reasons.

EXPOSURE TO STUDY MEDICATION

Overall, 36 subjects received placebo and 35 received OC000459. Placebo was taken for the scheduled 8 days by 35 subjects and for 2 days by one subject; OC000459 was taken for the scheduled 8 days by 35 subjects.

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EFFICACY

The TNSS on Day 8 are summarised by treatment and period below. While there was evidence that the TNSS was reduced by OC000459 treatment compared with placebo, there were sequence and period differences, which were statistically significant in the crossover analysis.

TNSS Day 8	OC000459/Placebo		Placebo/OC000459	
	OC000459 Period 1 N = 18	Placebo Period 2 N = 18	Placebo Period 1 N = 17	OC000459 Period 2 N = 17
Average score 0-2 hours Mean (SD) Median	 4.6 (2.30) 4.2	 4.4 (1.57) 4.6	 7.7 (1.78) 8.1	 5.2 (2.75) 4.9
Average score 2-4 hours Mean (SD) Median	 5.9 (2.76) 6.0	 5.5 (1.88) 5.9	 9.0 (2.13) 9.5	 7.2 (2.77) 6.4
Average score 4-6 hours Mean (SD) Median	 5.9 (3.01) 6.1	 6.2 (1.70) 6.3	 8.8 (2.29) 9.4	 7.4 (2.79) 8.0
Average score 0-6 hours Mean (SD) Median	 5.5 (2.56) 5.7	 5.4 (1.50) 5.8	 8.5 (1.96) 9.2	 6.6 (2.64) 5.8

The table below shows the crossover analysis using data from both treatment periods as well as the analysis of Treatment Period 1 data only (in the light of the period and sequence effects). The crossover analysis showed a consistently lower score for OC000459 than placebo treatment, but this comparison is affected by the other significant effects. The analysis of Treatment Period 1 data only shows an increased and statistically significant difference, with lower average scores on OC000459 than placebo.

TNSS Day 8	Combined Treatment Periods		Treatment Period 1		
	Median difference (95% CI)	p values[a]	Median		p values[a]
			OC000459	Placebo	
Average score 0-2 h	-0.9 (-2.00, -0.13)	0.005	4.2	8.1	0.001
Average score 2-4 h	-0.5 (-1.50, 0.50)	0.207	6.0	9.5	0.004
Average score 4-6 h	-0.9 (-1.89, -0.25)	0.092	6.1	9.4	0.010
Average score 0-6 h	-0.7 (-1.79, -0.17)	0.038	5.7	9.2	0.003
	LS mean for difference (95% CI)	p values[b]	LS mean for difference (95% CI)		p values[b]
Average score 0-2 h	-1.17 (-1.87, -0.48)	0.002	-3.1 (-4.55, -1.71)		< 0.001
Average score 2-4 h	-0.72 (-1.70, 0.26)	0.142	-3.1 (-4.80, -1.40)		< 0.001
Average score 4-6 h	-0.89 (-1.93, 0.14)	0.088	-3.0 (-4.83, -1.14)		0.002
Average score 0-6 h	-0.92 (-1.78, -0.07)	0.035	-3.1 (-4.63, -1.48)		< 0.001

LS = least squares
Difference for OC000459 minus placebo; p values for treatment effect
[a] non-parametric analysis [b] parametric analysis

A post-hoc ANCOVA in which the screening TNSS at 2 hours was introduced as a covariate indicated that the benefit in favour of OC000459 in the Treatment Period 1 analysis was not due to any screening imbalance, but was a genuine treatment effect.

Analysis of the data from Day 2 showed a benefit of OC000459 over placebo even at this early stage; as for Day 8, there were period/sequence effects and analysis of data from Treatment Period 1 only showed an increased difference (in favour of OC000459) between treatments. The treatment difference increased with duration of treatment from 2 to 8 days.

Analysis of the individual nasal symptom scores of itchy nose, nasal obstruction, rhinorrhoea and sneeze showed a reduction in symptoms with OC000459 compared with placebo treatment, with a benefit being observed at Day 2 as well as Day 8. In each case, sequence/period effects were present and analysis of Treatment Period 1 only increased the treatment difference in favour of OC000459.

The total eye symptom scores over 0-6 hours on Day 8 are summarised by treatment and period below. There was evidence of a reduction in eye symptoms with OC000459 treatment but, as for nasal symptom scores, there were period/sequence effects.

Total Eye Symptoms Day 8	OC000459/Placebo		Placebo/OC000459	
	OC000459 Period 1 N = 18	Placebo Period 2 N = 18	Placebo Period 1 N = 17	OC000459 Period 2 N = 17
Average score 0-6 hours				
Mean (SD)	1.1 (1.00)	1.1 (1.01)	2.7 (2.10)	1.2 (1.75)
Median	0.9	0.9	2.7	0.4

The next table shows the crossover analysis using data from both treatment periods as well as the analysis of Treatment Period 1 data only (in the light of the period and sequence effects). The crossover analysis showed a lower score for OC000459 than placebo treatment, but this analysis is influenced by the other significant effects. The analysis of Treatment Period 1 only shows an increased difference, with lower average scores on OC000459 than placebo.

Total Eye Symptoms Day 8: Average score 0-6 h				
Combined Treatment Periods		Treatment Period 1		
Median difference (95% CI)	p values[a]	Median		p values[a]
		OC000459	Placebo	
-0.4 (-1.17, -0.04)	0.003	0.9	2.7	0.060
LS mean for difference (95% CI)	p values[b]	LS mean for difference (95% CI)		p values[b]
-0.74 (-1.17, -0.32)	0.001	-1.6 (-2.70, -0.45)		0.007
LS = least squares Difference for OC000459 minus placebo; p values for treatment difference [a] non-parametric analysis [b] parametric analysis				

Analysis of the data from Day 2 showed a benefit of OC000459 over placebo: as for Day 8, there were period/sequence effects and analysis of data from Treatment Period 1 only showed an increased difference (in favour of OC000459) between treatments.

Analysis of total other symptoms showed some benefit of OC000459 over placebo at Day 8 but not Day 2. Analysis of nasal secretion weight gave results that were in line with those of TNSS: a reduction in secretion weight on both Day 2 and Day 8 that was greater when data from Treatment Period 1 only were analysed. However, the reduction in secretion weight on OC000459 compared with placebo did not typically achieve statistical significance. There was also no consistent reduction in secretion weight from Day 2 to Day 8 with OC000459 treatment.

There was no evidence of any effect of OC000459 on rhinomanometry or nasal endoscopy scores.

PLASMA CONCENTRATIONS

Plasma levels of OC000459 were determined pre-challenge and at 4 hours post-challenge on Days 2 and 8. The data are summarised in the next table.

With the exception of one subject at one time point (4 hours post-challenge, despite a concentration of 492.6 ng/mL pre-challenge), all subjects who took active compound had detectable levels of drug in blood, thus confirming compliance with the dosing schedule.

Time	Group A Treatment Period 1 (N = 18)	Group B Treatment Period 2 (N = 17)
	Mean (SD) ng/mL	
Pre-challenge on Day 2	484.2 (198.5)	443.1 (304.4)
4 h post-challenge on Day 2	851.3 (314.3)	784.6 (336.7)
Pre-challenge on Day 8	611.4 (283.0)	569.5 (248.2)
4 h post-challenge on Day 8	878.5 (349.7)	789.5 (228.0)

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SAFETY

Treatment-emergent adverse events were reported for 4 of the 35 subjects (11.4%) who received OC000459 and 2 of the 36 subjects (5.6%) who received placebo. Treatment-related adverse events were reported for 3 subjects on OC000459 (8.6%) and 1 subject on placebo (2.8%).

The most common adverse event was fatigue which was reported for 3 subjects (8.6%) after OC000459 and one subject (2.8%) after placebo, and was described as treatment-related in all of these subjects.

No subject reported a serious adverse event and no withdrawals or deaths were reported while on study medication.

There were no clinically important differences between OC000459 and placebo treatment with regard to changes in vital signs, physical examination and laboratory test results; there were no clinically significant laboratory test abnormalities and no abnormal ECG results. There was no evidence of any effect of OC000459 on FEV_1.

CONCLUSION

There was strong and statistically significant evidence that OC000459 given as 200 mg capsules twice daily alleviated nasal and eye symptoms associated with exposure of subjects with allergic rhinitis to grass pollen. Determination of the extent of the alleviation was confounded by sequence and period effects in the crossover analysis and analysis of data from Treatment Period 1 only showed an increased benefit of OC000459 over placebo. The data suggest that exposure to OC000459 has an effect that persisted beyond its presence in plasma.

OC000459 was safe and well tolerated, with a safety profile comparable to that of placebo. The most common adverse event was fatigue, which was recorded for 3 subjects after OC000459 and one subject after placebo.

DATE OF REPORT

30 May 2008