# 1 TITLE PAGE

**A Phase II study of the efficacy (as assessed by bronchial allergen challenge) and safety of OC000459 dosed orally (200 mg BID with food) in subjects with allergic asthma; in a randomised, double-blind, two-way balanced crossover comparing OC000459 with placebo**

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| **Study code:** | OC000459/004/05 |
| **EudraCT Number:** | 2005-005838-12 |
| **Name of investigational product:** | OC000459 |
| **Indication:** | Allergic asthma |
| **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: 14 July 2006<br>First subject dosed: 9 August 2006<br>Last follow-up assessment: 31 October 2007 |
| **Chief Investigator**: | Dr Dave Singh |
| **Chief Investigator location**: | Medicines Evaluation Unit Ltd<br>The Langley Building<br>Wythenshawe Hospital<br>Southmoor Road<br>Manchester<br>M23 9QZ |
| **Report date:** | 09 May 2011 |

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

Document History
Version 1: 24 October 2008
Version 2: 09 May 2011

# 2 SYNOPSIS

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| **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)** |

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| Title of study | A Phase II study of the efficacy (as assessed by bronchial allergen challenge) and safety of OC000459 dosed orally (200 mg BID with food) in subjects with allergic asthma; in a randomised, double-blind, two-way balanced crossover comparing OC000459 with placebo. | | |
| Investigator(s) | Dr D Singh (MEU) and Dr B O'Connor (KCL). | | |
| Study centre(s) | Medicines Evaluation Unit Ltd (MEU), The Langley Building, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9QZ, UK and Department of Asthma, Allergy and Respiratory Science, King's College London School of Medicine (KCL), Bessemer Road, London, SE5 9PJ, UK. | | |
| Publication (reference) | None to date of CSR | | |
| Study period | First subject screened: 14 July 2006<br>Last follow-up assessment: 31 October 2007 | Clinical phase | II |
| Objectives | The primary objective of the study was to assess the effect of OC000459 in comparison with placebo on fall in $FEV_1$ during the late asthmatic response (LAR; 4-10 hours after allergen challenge) to inhaled allergen in subjects with allergic asthma.<br><br>Secondary objectives were: to assess the safety (including lung function) of OC000459 in comparison with placebo; to assess the effect of OC000459 in comparison to placebo on the early asthmatic response (EAR; $FEV_1$ 0-2 hours after allergen challenge) to inhaled allergen; to assess the effect of OC000459 on sputum eosinophilia following inhaled allergen; to assess the effect of OC000459 on exhaled NO pre- and post-allergen; to assess the effect of OC000459 on hyper-responsiveness to methacholine post-allergen challenge; and to assess the effect of OC000459 on eosinophil shape change in blood and to relate these changes to plasma drug concentrations. | | |
| Methodology | Randomised, double-blind, placebo-controlled, two-way crossover evaluation of the effect of the capsule formulation of OC000459 on the late and early asthmatic responses to bronchial allergen challenge in asthmatic subjects. Screening took place over a 3- to 7-day period and included baseline allergen and methacholine challenges and sputum eosinophil measurements. Dosing commenced 3 to 7 weeks after the screening allergen challenge and continued for 16 days. Respiratory function was monitored during the dosing period; an inhaled allergen challenge was performed on the fifteenth day of dosing (Day 14) and a methacholine challenge on the sixteenth day of dosing (Day 15). Challenges were administered 3 h after dosing. Standard allergens well known to the Regulatory Authorities were used: cat hair, pollen and house dust mite. There was then a 3- to 7-week washout period, after which the second arm, identical to the first, was conducted. A follow-up visit was conducted 4 to 5 weeks after the final dose of test article. | | |

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| Number of subjects | Planned: up to 30 subjects were to be randomised to yield 16 evaluable subjects who completed the study.<br>Studied: 51 subjects were screened of whom 21 (18 male, 3 female, aged 22-43 years) met selection criteria and were randomised; 16 subjects completed both arms of the study and constituted the Full Analysis population. |
| Diagnosis and criteria for inclusion | The main inclusion criteria were: male or female subjects, any racial group (females of childbearing potential had to practise two forms of contraception); aged 18-45 years inclusive; known history of asthma (intermittent wheezing, cough, dyspnoea responsive to inhaled short-acting beta agonists); $FEV_1$ >65% of predicted on at least two occasions at screening; at the screening allergen challenge, a decrease in $FEV_1$ of ≥20% in the EAR and of ≥15% in the LAR to allergen on three separate occasions between 4-10 hours post-allergen, two of which had to be consecutive; no steroid usage in the past 12 weeks; testing positive to skin prick challenge with at least one of the following allergens: house dust mite, pollen or cat hair within the previous 12 months; non-smokers for a minimum of 6 months and less than 10 pack year history. |
| Test product, dose, mode of administration and batch number(s) | Oral OC000459 200 mg (two 100-mg capsules) twice daily.<br>OC000459 (100 mg) gelatine capsules (size 0), batch 0022C, expiry date July 2008. |
| Duration of treatment | 16 days (Day 0 to Day 15) on each treatment arm. On Day 15, only the morning dose was taken. |
| Reference therapy, dose, mode of administration and batch number(s) | Matching placebo (two capsules) twice daily.<br>Batch: 0029C, expiry date July 2008. |
| Criteria for evaluation | Efficacy<br>$FEV_1$ was determined on Day 14 pre-bolus bronchial allergen challenge at 3 hours post-dose. $FEV_1$ was then recorded at 5, 10, 15, 20, 30, 45 and 60 minutes post-challenge and subsequently at half-hourly intervals until 10 hours following the challenge.<br>Methacholine $PC_{20}$ assessed 3 hours after dosing on Day 15.<br>Exhaled NO on Days 0, 7 and 14 pre-dose.<br>Sputum eosinophils after completion of the methacholine challenge on Day 15.<br>Eosinophil shape change (subset of subjects) in response to $PGD_2$ ($PGD_2$ eosinophil shift) measured pre-dose and at 2, 4, 6 and 8 hours after dosing on Day 7.<br>Plasma concentrations of OC000459.<br>Day 7 pre-dose (all subjects) and at 2, 4, 6 and 8 hours after dosing (subjects participating in eosinophil shape change testing) and on Day 14 pre-dose (all subjects).<br>Safety<br>Adverse events, vital signs (pre-dose and hourly for 6 hours post-dose on Day 0, pre-dose on Day 7, pre-dose and hourly for 10 hours post-challenge on Day 14 and |

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| | pre-dose on Day 15), laboratory tests (Days 0, 7 and 14 and at follow-up after a 10-hour fast), physical examination (follow-up). Also $FEV_1$ measurements on Day 0 pre-dose and then half hourly for 6 hours after dosing, and pre-dose on Day 7, Day 14 and Day 15 and exhaled NO on Day 0 post-dose hourly for 6 hours, Day 14 post-challenge hourly for 10 hours and pre-dose on Day 15 were considered as safety measures. |
| Statistical methods | The primary efficacy endpoint was the diminution in the LAR to bronchial allergen challenge as measured by the AUC (AUC(4-10)) and the maximum (Max(4-10)) of percentage changes in $FEV_1$ between 4 and 10 hours after allergen challenge.<br><br>Secondary biological activity endpoints included the diminution of the EAR to bronchial allergen challenge measured by the AUC (AUC(0-2)) and the maximum (Max(0-2)) of percentage changes in $FEV_1$ between 0 and 2 hours after allergen challenge, sputum eosinophilia after allergen challenge as measured by percentage of eosinophils and the number of cells/g sputum, the methacholine $PC_{20}$ after allergen challenge and change in exhaled NO pre-dose (and post-allergen on Day 14).<br><br>Data were analysed using a mixed model with period, sequence group, centre and treatment as fixed effects and subject as a random effect. If the treatment by centre interaction was not statistically significant, it was dropped from the final model and the mixed model was refitted.<br><br>Results were presented as adjusted values for placebo and OC000459 with the estimated treatment difference (with 95% confidence intervals (CI)) and p-value. Where log-transformation was required for analysis (for % eosinophils, exhaled NO, methacholine $PC_{20}$), the results were presented as adjusted geometric means for OC000459 and placebo, and the differences between placebo and OC000459 were presented as a ratio of geometric means (with 95% CI). A square root transformation was used for the number of eosinophils (and data were not back-transformed). |

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**SUMMARY - CONCLUSIONS**

SUBJECT DISPOSITION

In total, 51 subjects were screened, 24 at King's College London School of Medicine (KCL) and 27 at Medicines Evaluation Unit (MEU), of whom 21 complied with the inclusion and exclusion criteria and were randomised.

All 21 randomised subjects completed the first treatment period (TP 1); however, only 16 of them completed the second treatment period (TP 2). The Full Analysis set thus included 16 subjects. All 21 randomised subjects, 12 at KCL and 9 at MEU, were included in the Safety Analysis set; overall, 20 subjects took OC000459 and 19 took placebo.

EFFICACY

A fall in $FEV_1$ was apparent with both treatments by 5 minutes and was greatest over the period from 10 to 45 minutes inclusive. The reduction was progressively less from 60 minutes to 2 hours 30 minutes but increased from 3 hours, achieving approximately the same fall as had been seen at the earlier times. The data thus demonstrated the early and late asthmatic responses.

The results for LAR, represented by the primary efficacy endpoints of AUC(4-10) and Max(4-10) for the percentage changes in $FEV_1$, are provided below.

| Percentage changes in $FEV_1$ | OC000459 (N = 16) | Placebo (N = 16) | OC000459 (N = 16) | Placebo (N = 16) |
|---|---|---|---|---|
| | **AUC(4-10) (%*h)** | | **Max(4-10) (%)** | |
| Mean (SD) | -117.1 (71.90) | -139.1 (74.38) | -30.2 (12.05) | -33.5 (12.73) |
| Median | -105.4 | -123.8 | -30.4 | -31.0 |
| Adjusted mean | -111.6 | -136.9 | -29.4 | -33.3 |
| Estimate (95% CI) | 25.35 (5.1, 45.6) | | 3.90 (-0.3, 8.1) | |
| P-value | 0.0179 | | 0.0651 | |
| Period effect p-value | 0.0149 | | 0.0179 | |
| Treatment*centre p-value | 0.9295 | | 0.9075 | |

There was a statistically significant treatment effect for AUC(4-10) (p=0.0179); however, there was also a statistically significant period effect (p=0.0149). The apparent treatment effect (adjusted mean 25.35) was similar in size to the period effect (adjusted mean TP 1 – TP 2=-26.21, 95% CI -46.5, -5.9).

The magnitude of the adjusted means for Max(4-10) was less for OC000459 than for placebo, but the difference was not statistically significant (p=0.0651). As for AUC(4-10), a statistically significant period effect was found ( p=0.0179).

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Due to the presence of the statistically significant period effect, summary statistics for AUC(4-10) were also provided by sequence group (see next table).

| | Group A | | Group B | |
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| | OC000459<br>TP1 (N = 9) | Placebo<br>TP2 (N = 9) | Placebo<br>TP1 (N = 7) | OC000459<br>TP2 (N = 7) |
| AUC(4-10) (%*h) | | | | |
| Mean (SD) | -155.3 (72.85) | -154.4 (90.12) | -119.5 (46.92) | -67.9 (29.08) |
| Median | -152.5 | -147.4 | -116.9 | -68.1 |
| Max(4-10) (%) | | | | |
| Mean (SD) | -35.8 (12.10) | -34.4 (15.74) | -32.2 (8.46) | -23.1 (7.93) |
| Median | -38.7 | -33.6 | -28.5 | -21.6 |

AUC(4-10) was larger in magnitude for Group A subjects (randomised to OC000459 in TP 1 and placebo in TP 2) than for Group B subjects. There appeared to be a benefit of OC000459 amongst Group B but not Group A subjects, suggesting a possible carryover effect in Group A.

The data for Max(4-10) showed an advantage of OC000459 over placebo in Group B and a (lesser) benefit of placebo over OC000459 in Group A.

There were no significant treatment or period effects in the analysis of the EAR (AUC(0-2) and Max(0-2)).

Sputum eosinophil data were available for both treatment periods for 8 subjects from KCL and 3 from MEU. There was a statistically significant treatment effect for the overall analysis (i.e. combining data from both centres) of percentage of sputum eosinophils (p=0.0020) and for the KCL only analysis (p=0.0023). The period effect was not statistically significant (p=0.3857 overall, p=0.5153 for KCL only). The adjusted geometric mean percentage of eosinophils from the overall analysis was lower for OC000459 (5.2%) than for placebo (17.8%), with ratio of geometric means (OC000459/placebo) of 0.29 (95% CI 0.15 to 0.55).

There was also a statistically significant treatment effect for the overall analysis of the square root transformed number of eosinophils (p=0.0022) and for the KCL only analysis (p=0.0019). The square root transformation of the number of eosinophils was statistically significantly lower for OC000459 than for placebo. There was some evidence of a period effect although this was not statistically significant (p=0.1366 overall, p=0.0575 for KCL only).

With respect to exhaled NO, 15 subjects were evaluable for the Day 7 analysis of pre-dose values and 12 for the Day 14 analysis. There were no significant treatment effects at either Day 7 or Day 14 but the data were very variable. There were also no significant period effects.

There was no significant treatment effect and no significant period effect in the analysis of methacholine challenge results.

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Eosinophil shape change in response to $PGD_2$ was assessed in 7 subjects at Day 7. The adjusted mean for AUC of eosinophil shift for OC000459 (13.4) was lower than that for placebo (47.0) and this was a statistically significant effect (difference in means of -33.6, 95% CI -66.8 to -0.4, p=0.048). There was no evidence of a period effect (p=0.472). There was no apparent relationship between the shift and the plasma concentration of OC000459 at Day 7.

OC000459 was found in the plasma of all OC000459-treated subjects and was not detected after placebo treatment, indicating compliance with the treatment regimen.

SAFETY
Overall, 65% of those who received OC000459 and 74% of those who received placebo experienced one or more adverse events. Treatment-related adverse events were reported for 45% and 47%, respectively. There were no serious adverse events and no adverse events that led to withdrawal.

The most common adverse events (all causalities) were Respiratory, Thoracic and Mediastinal Disorders, which were reported for a higher proportion of subjects during OC000459 treatment than placebo treatment: 40% compared with 16%. Nervous System Disorders were also common and were more common during placebo than OC000459 treatment: 32% compared with 20%. The most common Nervous System Disorder was headache, which was reported for 20% of subjects during OC000459 treatment and 32% of subjects during placebo treatment.

Infections and Infestations affected twice as many subjects during placebo treatment than during OC000459 treatment: 21% compared with 10%. In contrast, General Disorders and Administration Site Conditions were more common during OC000459 treatment (20% versus 0%).

All but one of the treatment-related adverse events were described as possibly related to study treatment; the exception was a case of mild nasal congestion during placebo treatment that was described as probably related to treatment.

Treatment-related Respiratory, Thoracic and Mediastinal disorders were somewhat more common during OC000459 treatment than placebo treatment: 25% of subjects compared with 16% of subjects; however, no individual adverse event (preferred term) affected more than one subject during OC000459 treatment. Treatment-related General Disorders and Administration Site Conditions were also more common during OC000459 than placebo treatment, being recorded for 15% of subjects during OC000459 treatment but none during placebo treatment. Treatment-related Nervous System Disorders were recorded for 15% of subjects during OC000459 treatment and a higher proportion, 21%, during placebo treatment; headache was recorded for 10% and 16%, and dizziness for 5% (i.e. one subject) during each treatment. Treatment-related Infections and Infestations were also more common during placebo than OC000459 treatment, being reported for 16% and 5% of subjects, respectively.

The only apparent trend to a difference between OC000459 and placebo with regard to the laboratory test results was seen for uric acid: both groups showed a reduction in uric acid, but this was larger with OC000459 treatment than placebo at both Day 7 and Day 14. A number of out-of-range laboratory test results were seen but all were described as being without clinical relevance other than raised AST and ALT in one subject at follow-up. (These increases were reported as adverse events, unrelated to treatment.)

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Vital signs data revealed no apparent differences between OC000459 and placebo treatment and there were no changes of concern.

CONCLUSION
The LAR to inhaled allergen as measured by the AUC of percentage change in $FEV_1$ over 4 to 10 hours was reduced after OC000459 treatment compared with placebo, although there was evidence of a period effect. The summary of data by sequence groups indicated an effect of OC000459 when it was given after placebo, but not when it was administered before placebo, suggesting a carryover effect. The maximum percentage reduction in $FEV_1$ during the LAR showed a trend towards a reduction with OC000459 treatment compared with placebo.

There was no apparent effect of OC000459 compared with placebo with regard to exhaled NO or methacholine $PC_{20}$.

Both assessments of eosinophils showed an effect of OC000459 compared with placebo: the percentage of eosinophils in sputum and the number per gram of sputum was lower with OC000459 than placebo treatment. Furthermore, the AUC for eosinophil shape change in response to $PGD_2$ (eosinophil shift) was reduced by OC000459 treatment at Day 7 compared with placebo.

There were no findings of concern with regard to safety and tolerability as assessed by adverse events, laboratory tests, vital signs or physical examination.

DATE OF REPORT
09 May 2011