CLINICAL STUDY REPORT

1 TITLE PAGE

Dose Finding Study in Patients with Mild to Moderate Persistent Asthma: a Parallel Group, Randomised, Placebo Controlled, Double Blind Assessment of Oral OC000459 Dosed at Three Dose Schedules for Twelve Weeks

Study code:	OC000459/012/08
EudraCT Number:	2008-006013-24
Name of investigational product:	(5-Fluoro-2-methyl-3-quinolin-2ylmethylindo-1-yl)-acetic acid (OC000459)
Indication:	Asthma
Clinical phase:	IIb
Sponsor:	Oxagen Ltd
Sponsor address:	91 Milton Park Abingdon Oxon OX14 4RY United Kingdom
Sponsor representative:	Dr C Mike Perkins
Study dates:	First subject provided informed consent: 12 May 2009 First subject dosed (placebo run-in): 20 May 2009 Last follow-up assessment: 07 April 2010
Study location:	94 research centres: 34 in Russia, 21 in Ukraine, 14 in Poland, 11 in Bulgaria, 10 in Romania and four in Hungary
Report date:	29 March 2011

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** None **NAME OF ACTIVE INGREDIENT** (5-Fluoro-2-methyl-3-quinolin-2ylmethylindo-1-yl)-acetic acid (OC000459)	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of study	Dose finding study in patients with mild to moderate persistent asthma: a parallel group, randomised, placebo controlled, double blind assessment of oral OC000459 dosed at three dose schedules for twelve weeks		
Investigators	A list of Investigators is provided in the body of the CSR.		
Study centres	The study was conducted in a total of 94 research centres: 34 in Russia, 21 in Ukraine, 14 in Poland, 11 in Bulgaria, 10 in Romania and four in Hungary		
Publication (reference)	None to date of CSR		
Study period	First subject screened: 12 May 2009 Last follow-up assessment: 07 Apr 2010	Clinical phase	IIb
Objectives	The primary objective was to establish the efficacy of three oral dose schedules of OC000459 (leading to $\geq$ 8% improvement in clinic FEV_1 over placebo) over a treatment period of 12 weeks. Secondary objectives were: • To assess the effects of three oral dose schedules of OC000459 in comparison to placebo on the Asthma Control Questionnaire (ACQ) and the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)). • To investigate the effects of three oral dose schedules of OC000459 in comparison to placebo on clinic PEF and FEV_1 and Vitalograph® 2110 spirometer/e-diary information on PEF, asthma symptoms and salbutamol metered dose inhaler (MDI) usage in this population. • To assess the safety and tolerability of three oral dose schedules of OC000459 • To assess the effects of OC000459 in comparison to placebo on serum IgE levels.		
Methodology	The study was a randomised, double-blind, parallel-group comparison of OC000459 tablets 200 mg once daily (OD) in the evening, 100 mg twice daily (BID) or 25 mg OD in the evening and placebo in an outpatient population with mild to moderate asthma. Subjects who met eligibility criteria entered a 3-week, single-blind, placebo run-in period. At the beginning of the placebo run-in period (Day 1, Week 1, Visit 2), subjects were instructed to use salbutamol MDI provided by the Sponsor (100 µg/actuation) as the only rescue therapy during the study. The use of all other bronchodilators was prohibited during the placebo run-in, dosing, and placebo washout periods. Subjects also were instructed in the use of the Vitalograph® 2110 spirometer/e-diary, which was used to record PEF, asthma symptom score, meals, salbutamol MDI use, and dosing of study medication twice daily throughout the study. Baseline respiratory function and ACQ and AQLQ(S) were recorded at the final clinic visit of the placebo run-in period (Day 1, Week 4, Visit 5). Subjects meeting randomisation criteria continued into a 12-week, double-blind dosing period and were randomly assigned to take OC000459 or matching placebo twice daily, after breakfast and the evening meal. At the conclusion of the double-blind dosing period, subjects continued into a 2-week, single-blind, placebo washout. The final evaluation was completed 2 weeks after the end of the placebo washout.		

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	Clinic visits were scheduled between 07.00 and 11.00 hours and occurred weekly during the placebo run-in and every 2 weeks thereafter. Subjects were instructed to have a light breakfast at home, to refrain from taking study medication, and to avoid using their bronchodilator for at least 6 hours and avoid drinking strong coffee for 2 hours prior to their appointment time. Clinic visits included in-clinic spirometry, vital signs, haematology and clinical chemistry test, pregnancy test for women of child-bearing potential, plasma drug levels, study medication reconciliation, review of concomitant medication and adverse events, and download and review of electronic diary data. ACQ and AQLQ(S) were evaluated at baseline and every 4 weeks and serum IgE, at baseline and after 6 and 12 weeks of double-blind treatment. On clinic visit days, study medication was taken after study assessments had been performed.
Number of subjects	Planned: up to 900 screened subjects to yield 115 randomised subjects per treatment group and approximately 110 per group evaluable for efficacy. Studied: total of 519 randomised subjects of whom 134 subjects (46 male, 88 female, aged 18-55, median 41 years) were randomised to OC000459 200 mg OD, 132 (47 male, 85 female, aged 18-55, median 39.5 years) were randomised to OC000459 100 mg BID, 130 (56 male, 74 female, aged 18-55, median 43 years) to OC000459 25 mg OD and 123 (45 male, 78 female, aged 19 to 55, median 42 years) to placebo. All randomised subjects were included in the Safety Set, 482 in the Full Analysis Set and 427 in the Per Protocol Set.
Diagnosis and criteria for inclusion	The study population consisted of male and female subjects aged 18-55 years with mild to moderate asthma as defined by Global Initiative for Asthma (GINA) criteria. Subjects had typical symptoms including but not limited to cough, wheezing, and shortness of breath with periodic intervals requiring treatment with bronchodilators. Subjects were non-smokers for≥12 months prior to screening with a smoking history ≤10 pack years. Women of childbearing potential were required to have a negative pregnancy test at screening and prior to randomisation and were required to practise two forms of acceptable contraception. Subjects who had a clinically significant medical condition or clinically significant abnormality in laboratory tests, ECGs, or chest X-ray were excluded from the study. To qualify for randomisation, subjects were required to have stable FEV_1 while not taking salbutamol (at Weeks 3 and 4, difference in percent of predicted FEV_1 had to be within 15%) and the average of these readings had to be within 60-85% of predicted value. They also had to have an increase in FEV_1 ≥12% and/or absolute increase of≥200 mL between 20 and 30 minutes after inhaled salbutamol at both Weeks 3 and 4 (i.e., demonstrate reversibility). Subjects also were required to average >1 actuation/day of salbutamol over the last 7 days of the placebo run-in period, and to use the salbutamol MDI and to perform in-clinic spirometry and the home PEF test reliably.
Test product, dose, mode of administration and batch number(s)	Tablets containing 25 mg or 100 mg OC000459 for oral administration. Batch numbers: 0153D (25 mg), 0155 D (100 mg), 0381D (100 mg) and 0340D (100 mg). OC000459 was taken at 200 mg OD (in the evening) 100 mg BID or 25 mg OD (in the evening). Placebo (batch numbers provided under 'Reference therapy' below) was additionally taken in the morning for OD groups to maintain the blind.

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Duration of treatment	3-week single-blind run-in on placebo followed by double-blind dosing (with OC000459 or placebo) scheduled for 12 weeks and then a 2-week single-blind washout on placebo.
Reference therapy, dose, mode of administration and batch number(s)	Matching placebo tablets for oral administration, BID. Batch numbers: 0380D and 0150D
Criteria for evaluation	Efficacy assessments included in-clinic spirometry (FEV_1, FVC, PEF, and $FEF_{25-75\%}$) performed according to ATS/ERS guidelines, with a full expiratory and inspiratory manoeuvre, home lung function tests (PEF), and diary-recorded asthma symptom scores and bronchodilator usage. The ACQ and AQLQ(S), and serum IgE levels also were evaluated. Safety assessments included adverse events (AEs) and concomitant medications, vital signs, clinical laboratory tests, and changes in physical examinations and ECGs. Plasma drug concentrations were also determined.
Statistical methods	The primary efficacy variable was FEV_1 measured during clinic visits. The average change from baseline over the 12-week double-blind period, the change from baseline to endpoint (end of double-blind period) and the percentage change from baseline to endpoint were analysed using ANCOVA with treatment and centres as factors and baseline FEV_1 as a covariate (primary analysis). The main analysis (Full Analysis Set) included all subjects who received at least one dose of double-blind treatment, who completed the trial at least until the end of Visit 5 (Day 1, Week 4), who complied with key randomisation criteria.. The LOCF principle was used to provide an endpoint value for analysis of change and percentage change. A Per Protocol analysis was also performed based on all subjects who complied with the major protocol criteria, were at least 80% compliant with double-blind treatment and completed the trial up to Visit 11 (Week 16). Comparisons between each of the OC000459 dose groups and placebo were tested at the 1.67% level of significance as a consequence of the Bonferroni adjustment. Similar analyses were performed for secondary efficacy endpoints other than IgE and the proportions of subjects with changes in ACQ and AQLQ(S) in relation to the minimal important difference (MID) of 0.5. The change from baseline to endpoint in IgE was analysed using the Kruskal-Wallis test for the comparison across all treatment groups and the Wilcoxon rank sum test for pairwise comparisons of active against placebo. The proportion of subjects showing an MID improvement in ACQ/AQLQ(S) total score at the end of double-blind treatment period was compared with placebo for each of active treatment groups using the chi-square test.

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Statistical methods	Subjects were also divided into 3 categories by MID (improved > MID, changed less than MID, and deteriorated > MID), with comparison for each active treatment with placebo being performed using the Cochran-Mantel-Haenszel (CMH) test for ordered categories. Baseline for clinical spirometry was the average of Visits 4 and 5 (after 2 and 3 weeks of placebo-run-in). For ACQ and AQLQ(S), the baseline was Visit 5. For diary data, baseline was the mean value of the data from the 7 days prior to randomisation (i.e., the third week of placebo run-in). For safety, the baseline was the last available value between Screening and Visit 5. Safety data were summarised using descriptive statistics, which included the number of observations, mean, standard deviation, median, minimum and maximum for continuous data and numbers and percentages for categorical data. Randomised-treatment-emergent AEs were summarised by treatment, MedDRA preferred term, and system organ class for all AE, as well as by severity and relationship to study medication.

SUMMARY - CONCLUSIONS

SUBJECT DISPOSITION

In total, 771 subjects were screened, of whom 708 entered the run-in period and 63 were screen failures; 519 were randomised to double-blind treatment, 476 completed double-blind treatment and entered washout. Follow-up was completed by 475 subjects.

Thirteen of the 134 subjects randomised to 200 mg OD OC000459, 12 of 132 randomised to 100 mg BID OC000459, 9 of 130 randomised to 25 mg OD OC000459 and 17 of 123 randomised to placebo failed to complete the double-blind treatment period. The most common primary reasons for withdrawal were adverse events (2, 1, 2 and 3 subjects, respectively), withdrawal of informed consent (3, 2, 3 and 2 subjects) and asthma deterioration (0, 2, 3 and 7 subjects).

EXPOSURE TO STUDY MEDICATION

For the Full Analysis Set, the exposure to treatment was similar across the four treatment groups and the median was 84 days in each. The majority of subjects (89% to 94% of the group) were treated for longer than 77 days, but in total 27 subjects were treated for 1-63 days and 10 for 64-77 days.

EFFICACY

An increase in FEV_1 with double-blind treatment was observed in all groups but was consistently greater in the OC000459 groups than the placebo group. The maximum effect of OC000459 was seen after about 2-4 weeks of treatment. The changes from baseline are summarised in the table.

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Summary of change from baseline in clinic FEV_1: FAS

FEV_1 in L		OC000459 200 mg OD N = 123	OC000459 100 mg BID N = 117	OC000459 25 mg OD N = 125	Placebo N = 117
Average change from baseline over the double-blind period	n Mean (SD) Median Min to Max	122 0.15 (0.295) 0.12 -0.36 to 1.33	117 0.14 (0.417) 0.08 -0.53 to 2.29	122 0.16 (0.323) 0.12 -0.43 to 1.45	116 0.08 (0.298) 0.01 -0.65 to 1.33
Change from baseline to endpoint	n Mean (SD) Median Min to Max	122 0.14 (0.357) 0.10 -0.71 to 1.30	117 0.15 (0.484) 0.08 -1.27 to 2.25	122 0.16 (0.377) 0.08 -0.50 to 1.44	116 0.06 (0.369) -0.01 -0.82 to 1.47
Percentage change from baseline to endpoint	n Mean (SD) Median Min to Max	122 6.40 (16.111) 3.91 -35.7 to 65.60	117 6.17 (19.543) 3.41 -48.7 to 85.66	122 6.76 (16.110) 3.14 -22.5 to 54.44	116 3.00 (15.784) -0.20 -29.7 to 58.78

The results of the statistical analysis showed no significant difference between OC000459 and placebo groups at the 1.67% level of significance.

Statistical analysis of change in FEV_1: FAS

FEV_1 in L	Average change from baseline over the double-blind period			Change from baseline to endpoint			Percentage change from baseline to endpoint		
	LS Mean	Active – placebo	P value	LS Mean	Active – placebo	P value	LS Mean	Active – placebo	P value
200 mg OD	0.14	0.07	0.109	0.14	0.08	0.128	6.69	3.41	0.116
100 mg BID	0.14	0.06	0.155	0.16	0.09	0.068	6.60	3.32	0.130
25 mg OD	0.16	0.09	0.042	0.18	0.11	0.028	7.49	4.21	0.053
Placebo	0.08			0.06			3.28		

The results from the PPS for FEV_1 were similar to those of the FAS; the changes were greater with 25 mg OD than the other dose groups on average, but no significant differences between OC000459 and placebo were seen.

In the light of the lack of difference between the three OC000459 groups, the results were pooled across groups in an unplanned analysis. This showed an appreciably greater improvement in FEV_1 with OC000459 than placebo.

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Analysis of change from baseline of clinic FEV_1 for pooled OC000459 groups: FAS

FEV_1 in L	Average change from baseline over the double-blind period			Change from baseline to endpoint			Percentage change from baseline to endpoint		
	LS Mean	95% CI	P-value	LS Mean	95% CI	P-value	LS Mean	95% CI	P-value
Pooled OC000459	0.15	0.11 to 0.19	0.039	0.16	0.11 to 0.21	0.024	6.93	4.86 to 8.99	0.041
Placebo	0.07	0.01 to 0.14		0.06	-0.01 to 0.14		3.28	0.05 to 6.50	

Some planned and several post-hoc subgroup summaries and analyses were performed to determine whether certain subgroups of subjects responded to a greater extent than others to OC000459 with regard to change in FEV_1.

When the analysis of change from baseline to endpoint in clinic FEV_1 was restricted to those with a percent predicted FEV_1 of ≥60 to ≤80 who were also skin prick positive, the LS mean change in FEV_1 was 0.22 L for pooled OC000459 groups and 0.10 L for placebo with a treatment effect from the ANCOVA of 0.009.

The response to OC000459 was also related to the subject's eosinophil status at baseline, with the effect being greater in those with a high eosinophil count (≥ 250/µL) than in those with a low eosinophil count (<250/µL). In the former subpopulation, the LS mean change in FEV_1 from baseline was 0.13 L in the pooled OC000459 groups compared with -0.03 L in placebo-treated subjects (p = 0.010), while there was little difference between treatments on average in those of low eosinophil count (LS mean 0.16 versus 0.13 L). It should be noted that subjects with eosinophil counts at baseline ≥ 250/µL had a greater deterioration on placebo than those with <250/µL.

Planned analyses of other endpoints were also in favour of OC000459 treatment. The table shows the change from baseline to endpoint for clinic PEF and FVC. There were no statistically significant differences between OC000459 and placebo groups for FVC, but the difference between 25 mg OD and placebo achieved significance with regard to the average change from baseline for PEF (active – placebo difference of 15.00 L/min, p = 0.014).

Change from baseline to endpoint in PEF and FVC: FAS

		OC000459			Placebo
		200 mg OD	100 mg BID	25 mg OD	
	n	122	117	122	116
PEF (L/min)	Mean (SD) Median	18.7 (50.06) 16.3	19.4 (71.50) 6.0	25.6 (65.55) 12.8	13.0 (55.43) 2.8
FVC (L)	Mean (SD) Median	0.17 (0.454) 0.08	0.19 (0.587) 0.04	0.20 (0.504) 0.08	0.12 (0.490) 0.03

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Diary data did not reveal any statistically significant difference between any of the three OC000459 groups and placebo other than for daytime asthma symptom score which showed a greater reduction from baseline to endpoint with OC000459 200 mg OD than placebo treatment (active – placebo difference was -0.18, p = 0.015, FAS). Other diary results were numerically in favour of OC000459 treatment.

ACQ decreased to a greater extent with OC000459 treatment than placebo treatment. (Note that a decrease in ACQ equates to an improvement in asthma control.) For the FAS, the active – placebo differences for 200 mg OD, 100 mg BID and 25 mg OD were -0.16 (p = 0.082), -0.20 (p = 0.032) and -0.28 (p = 0.003), respectively. The proportion of subjects showing an improvement of at least the MID was 32.5% for placebo and 46.3% (p = 0.024), 48.7% (p = 0.011) and 52.8% (p <0.001) for 200 mg OD, 100 mg BID and 25 mg OD respectively.

AQLQ(S) increased to a greater extent with OC000459 treatment than placebo treatment. (Note that an increase in AQLQ(S) equates to an improvement in quality of life.) For the FAS, the active – placebo differences for 200 mg OD, 100 mg BID and 25 mg OD were 0.24 (p = 0.014), 0.24 (p = 0.016) and 0.25 (p = 0.011), respectively. The proportion of subjects showing an improvement of at least the MID was 36.8% for placebo and 54.5% (p = 0.005), 52.1% (p = 0.017) and 52.0% (p 0.012) for 200 mg OD, 100 mg BID and 25 mg OD respectively.

There were no effects of OC000459 compared with placebo on serum IgE.

SAFETY

The overall incidence of treatment-emergent adverse events (TEAEs) was similar for the three OC000459 groups and was lower than during placebo treatment (see table below). Treatment-related TEAEts were also less common on OC000459 than placebo treatment. Similarly, the proportion of subjects discontinuing treatment because of adverse events was lower with active treatment (1.5% to 3.7% of OC000459 groups) than placebo (6.5%).

Overview of adverse events

	OC000459			Placebo N = 123
	200 mg OD N = 134	100 mg BID N = 132	25 mg OD N = 130	
Number of subjects:	n (%)	n (%)	n (%)	n (%)
With any TEAE	37 (27.6%)	38 (28.8%)	31 (23.8%)	53 (43.1%)
With treatment-related TEAE	12 (9.0%)	12 (9.1%)	9 (6.9%)	18 (14.6%)
With treatment discontinued owing to TEAE	5 (3.7%)	2 (1.5%)	4 (3.1%)	8 (6.5%)
With treatment discontinued owing to treatment-related TEAE	4 (3.0%)	1 (0.8%)	3 (2.3%)	2 (1.6%)
With SAE	0	0	0	2 (1.6%)
With treatment-related SAE	0	0	0	0

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The most common System Organ Class (SOC) of TEAEs was Infections and infestations, under which TEAEs were recorded for a lower percentage of OC000459-treated subjects (10.4% to 15.2% of each group) than placebo-treated subjects (25.2%). Adverse events under the SOC of Respiratory, thoracic and mediastinal disorders were also less common in OC000459 groups (6.0% to 7.7%) than the placebo group (10.6%). Events classified as Nervous system disorders were reported for a lower percentage of OC000459 groups (2.3% to 5.3%) than the placebo group (7.3%) while Gastrointestinal disorders were recorded for 2.3% to 5.2% of OC000459 groups and 4.1% of the placebo group. The most commonly reported individual adverse events were nasopharyngitis (4.5% to 6.2% of OC000459 groups compared with 9.8% of the placebo group), asthma (3.0% to 5.4% compared with 8.1%) and headache (2.2% to 5.3% compared with 4.9%).

As was the case of all TEAEs, treatment-related Infections and infestations were more common in the placebo group (5.7%) than the OC000459 groups (1.5% to 4.5%). The most common individual treatment-related adverse events were nasopharyngitis (1.5% of OC000459 subjects in each group compared with 3.3% of placebo-treated subjects) and asthma (0.7% to 1.5% of OC000459 groups compared with 2.4% of the placebo group).

Treatment-emergent SAEs reported were uterine haemorrhage, endometrial hyperplasia and ovarian cyst in one placebo-treated subject and sinusitis in another placebo-treated subject. Two other subjects who were not randomised experienced SAEs: limb injury in one and asthma (exacerbation) in another.

The number of subjects (in the Safety Set) with asthma exacerbations reported from Week 5 to Week 20 was 4 (3.0%) for OC000459 200 mg OD, 4 (3.0%) for OC000459 100 mg BID, 7 (5.4%) for OC000459 25 mg OD and 10 (8.1%) for placebo. Asthma exacerbations were also analysed for the FAS by Kaplan-Meier plots and the log-rank test, but the differences between OC000459 and placebo did not achieve statistical significance.

There were no apparent differences between OC000459 and placebo groups with regard to haematology and clinical chemistry test results: changes from baseline were observed in all groups for all laboratory tests, but the 95% confidence limits of the difference between groups almost always encompassed zero. The pattern of shifts (above/within/below the reference range) from baseline to Week 16 was very similar in the three OC000459 groups and the placebo group. There were no differences between groups with respect to vital signs, physical examination or ECG.

PLASMA CONCENTRATIONS
Plasma levels of OC000459 in subjects randomised to OC000459 are summarised in the next table. Mean concentrations were comparable in those randomised to 100 mg BID or 200 mg OD and lower in those randomised to 25 mg OD.

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	Mean (SD) OC000459 ng/mL		
	200 mg OD	25 mg OD	100 mg BID
Visit 6	228 (220) n = 132	94 (95) n = 126	238 (219) n = 129
Visit 7	229 (233) n = 129	93 (85) n = 124	236 (202) n = 125
Visit 8	243 (229) n = 125	102 (92) n = 122	244 (240) n = 123
Visit 9	232 (228) n = 123	94 (83) n = 122	233 (201) n = 123
Visit 10	216 (201) n = 122	87 (80) n = 123	215 (177) n = 121
Visit 11	224 (222) n = 120	85 (82) n = 122	212 (215) n = 122

CONCLUSION

Treatment with OC000459 was associated with an improvement in lung function. The improvement was broadly comparable with 200 mg OD, 100 mg BID and 25 mg OD. Additional analysis indicated that inflammatory status, as signalled by eosinophilia, affected the response, as those with high eosinophil counts showed a greater improvement on OC000459 when compared with placebo.

The improvement in lung function was accompanied by a beneficial decrease in ACQ and a beneficial increase in AQLQ(S) scores in OC000459-treated subjects.

The data suggest that a similar response to treatment was seen for the once daily and twice daily dosing regimens; therefore once daily dosing with OC000459 may be appropriate.

OC000459 was generally very well tolerated, with the incidence of adverse events being comparable to that on placebo. A difference between groups was noted with regard to infections, which were notably less common during OC000459 than placebo treatment. Asthma exacerbations were also less frequent with OC000459 than placebo treatment but the differences between OC000459 and placebo did not achieve statistical significance.

There were no clinically important findings in haematology and clinical chemistry tests, physical examination and ECG assessments.

DATE OF REPORT: 29 March 2011