

ORIGINAL ARTICLE

A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma

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Summary

Background CRTH2 is a G-protein-coupled receptor that mediates the activation of Th2 lymphocytes, eosinophils and basophils in response to prostaglandin D₂ and may be involved in the pathogenesis of airway inflammation and dysfunction in asthma.

Objective To evaluate the effects of a potent and selective CRTH2 antagonist, OC000459, on the lung function, symptoms and eosinophilic airway inflammation in a double-blind, parallel group trial in steroid-free subjects with moderate persistent asthma.

Methods Adult subjects were randomized to oral OC000459 200 mg twice daily (*N* = 65) or a placebo (*N* = 67) for 28 days. The primary end-point was the change from baseline in pre-bronchodilator forced expiratory volume in 1 s (FEV₁); eosinophilic airway inflammation was assessed by induced sputum differential eosinophil count. The trial was registered on the clinicaltrials.gov database (Identifier NCT01057927).

Results Data were analysed for both the Full Analysis (FA) population and the Per Protocol (PP) population (55 treated with OC000459 and 52 with placebo), which excluded non-compliant subjects. In the FA population, the mean change in FEV₁ was 7.1% on OC000459 compared with 4.3% on placebo (not significant); in the PP population, the mean changes were 9.2% and 1.8%, respectively (*P* = 0.037). Improvement in quality of life was apparent in both FA and PP populations [difference from the placebo in AQLQ(S) total score of 0.29, *P* = 0.0113 and 0.37, *P* = 0.0022, respectively]. OC000459 also improved the night-time symptom scores (mean reduction of 0.36 vs. 0.11, *P* = 0.008, FA population; 0.37 vs. 0.12, *P* = 0.022, PP population). The geometric mean sputum eosinophil count reduced from 2.1% to 0.7% (*P* = 0.03) after OC000459, but this effect was not significant when compared with the change on placebo (*P* = 0.37). Adverse events on OC000459 were comparable to those on placebo; respiratory infections were notably less common during OC000459 than the placebo treatment.

Conclusion and Clinical Relevance This study provides the first clinical evidence that CRTH2 receptors contribute to airflow limitation, symptoms and eosinophilic airway inflammation in asthma. OC000459 shows promise as a novel oral treatment for asthma and related disorders.

Keywords asthma, CRTH2 antagonist, OC000459

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Introduction

Chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2, also known as DP₂) is a G-protein-coupled receptor expressed by Th2 lymphocytes, eosinophils and basophils, and mediates the activation of these cells in response to prostaglandin D₂ (PGD₂), a major

prostanoid product of activated mast cells [1, 2]. Mast cell-dependent activation of both Th2 lymphocytes and eosinophils is mediated by CRTH2 [3, 4] and PGD₂ stimulates Th2 cytokine production through an action on CRTH2 [5]. PGD₂ has been detected in the airways of allergic asthmatic subjects challenged with antigen [6] and may contribute to both the recruitment of Th2 lymphocytes to

asthmatic airways and their activation to elaborate Th2 cytokines. Studies in preclinical models of allergic disease support the view that CRTH2 plays a central role in leucocyte recruitment [7–11], airway hyperresponsiveness [11] and the production of cytokines [12, 13], mucus [8] and IgE [7, 12, 14].

OC000459 is an orally active CRTH2 antagonist that is under clinical investigation in asthma and allergic rhinitis. It has been shown to be highly potent and selective in inhibiting PGD₂-mediated activation of Th2 cells and eosinophils and is an ideal tool to explore the clinical utility of CRTH2 antagonism. It is also effective in inhibiting mast cell-dependent activation of Th2 cells and eosinophils and airway eosinophilia in rats. Here, we describe the results of a multi-centre study in subjects with moderate persistent asthma who were treated with oral OC000459 for 4 weeks. The primary objective of the study was to investigate the clinical effects of multiple twice-daily oral doses of OC000459 in comparison with placebo on clinic lung function [as assessed by forced expiratory volume in 1 s (FEV₁)]. Improvement in FEV₁ was selected as the primary end-point for this study because it is known that the anti-inflammatory action of inhaled corticosteroids, which act in part by inhibiting Th2-mediated eosinophilic inflammation, is associated with an improvement in lung function over a 4-week dosing period. In addition to assessing safety and tolerability, the secondary objectives were to investigate the effects on other clinic spirometry variables, diary-recorded peak expiratory flow (PEF), asthma symptoms, quality of life (QOL), salbutamol metered dose inhaler (MDI) usage, induced sputum differential eosinophil count and serum IgE levels.

Methods

Study design

The study was a randomized, double-blind parallel group comparison of OC000459 and placebo in an outpatient population with moderate persistent asthma. The study included steroid-free subjects allowed to use the short-acting β_2 agonist salbutamol.

One to 2 weeks after screening, subjects who met the eligibility criteria entered a 2-week, single-blind placebo run-in (Fig. 1). At the beginning of the placebo run-in period, subjects were trained to use a salbutamol MDI (100 μ g/actuation); this was the only permitted rescue therapy during the study. Baseline respiratory function and QOL were recorded at the final clinic visit of the placebo run-in and baseline diary data were taken from the last week of the run-in period.

Subjects meeting the randomization criteria continued into a 4-week, double-blind dosing period, at the conclusion of which there was a 2-week placebo washout. Subjects were seen weekly in the morning during run-in and double-blind treatment periods (Fig. 1).

Ethical permission for the study was obtained and all subjects gave written informed consent before participating. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines as issued by the International Conference on Harmonisation (ICH E6, 1996).

The study was also conducted in compliance with applicable national and local regulations. The Independent Ethics Committee was The Ethics Committee within the Federal Department for Control over Quality of

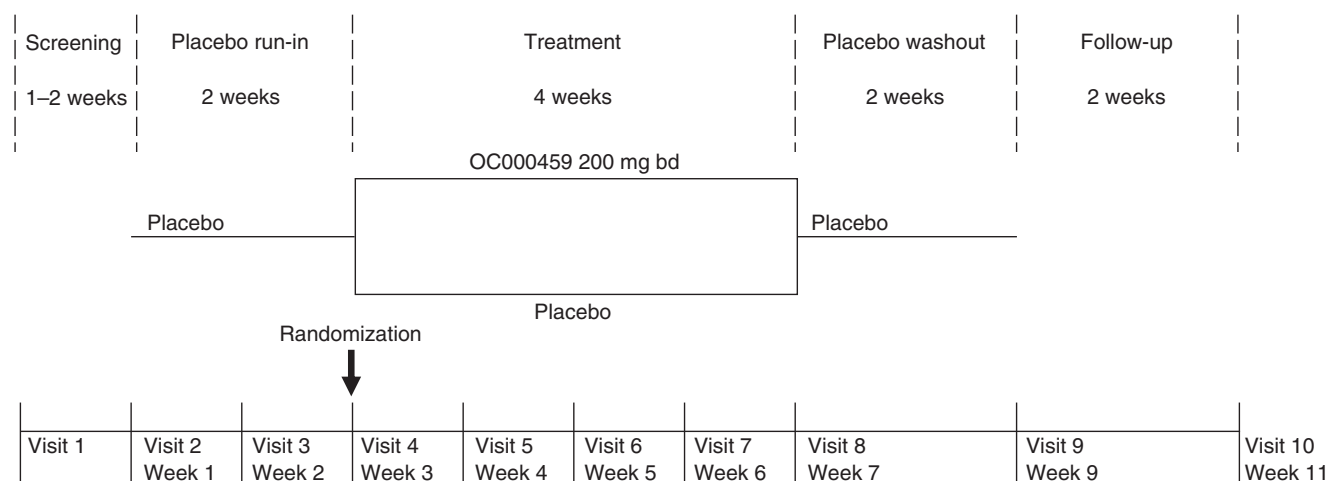


Fig. 1. Study design. A 2-week single-blind run-in on placebo was followed by a double-blind treatment (with OC000459 200 mg twice daily or placebo) for scheduled 4 weeks (28 days); double-blind treatment was followed by a 2-week single-blind washout on placebo. Subjects were assessed on a weekly basis during the placebo run-in and double-blind treatment. The end-point was visit 8 for clinic assessments (i.e. immediately after the end of the double-blind treatment) and the last week of double-blind treatment for diary data.

Pharmaceutical Products, 8 (3) Petrovsky Blvd, 127051, Moscow, chaired by Prof. F I Komarov. The trial was registered on the clinicaltrials.gov database (Identifier NCT01057927).

Subject selection

The planned enrolment was 140 (70/group), to yield approximately 120 subjects evaluable for efficacy. Male or female subjects aged 18–55 years with moderate persistent asthma, as defined by the Global Initiative for Asthma criteria, for at least 12 months were eligible [15]. Subjects had typical symptoms including, but not limited to, cough, wheezing and shortness of breath with a requirement for treatment with bronchodilators. They had a history of asthma symptoms in response to aero allergens and a positive skin prick test within 6 months of the screening visit; they could not have received steroid treatment for asthma within the 3 months before screening. Subjects were non-smokers for ≥ 12 months before screening with a smoking history ≤ 10 pack years.

Women of childbearing potential were required to have a negative pregnancy test at screening and before randomization and were required to practice two forms of contraception. Subjects who had a clinically significant medical condition or a clinically significant abnormality in laboratory tests, ECGs or chest X-ray were excluded.

To qualify for randomization, subjects were required to have FEV₁ 60–80% of the predicted value while abstaining from inhaled salbutamol for 6 h on at least two occasions during the placebo run-in and an increase in FEV₁ $\geq 12\%$ and/or an absolute increase of ≥ 200 mL between 20 and 30 min after inhaled salbutamol on at least two occasions during the run-in. Subjects were also required to average > 1 actuation/day of salbutamol over the last 7 days of the run-in.

Subjects were entered at 16 research centres in Russia.

Study treatment

A 2-week single-blind run-in on placebo was followed by double-blind dosing (with OC000459 200 mg twice daily or placebo) for a scheduled 4 weeks (28 days); there was then a 2-week single-blind washout on placebo (Fig. 1). Subjects were instructed to take study medication with water immediately after breakfast and the evening meal. On clinic days, they were told to take study capsules after breakfast and to refrain from using their usual bronchodilator (visit 2 only) or salbutamol MDI for 6 h before their appointment time and to avoid strong coffee for 2 h.

Subjects meeting the randomization criteria were allocated to a double-blind treatment according to a blocked randomization scheme generated by the Clinical Research Organisation PSI Co. Ltd, St Petersburg, Russia, to enable balanced allocation (1 : 1) of subjects to treatment groups;

they received the study medication supplies corresponding to the next free number on the randomization schedule for supplies at that centre. OC000459 (100 mg strength) and placebo were presented as gelatine capsules that were identical in appearance.

Efficacy and safety assessments

In-clinic spirometry was recorded using a centralized spirometry system (Vitalograph[®] Spirotrac, Maids Moreton, Buckinghamshire, UK). FEV₁, forced vital capacity (FVC) and PEF were performed according to American Thoracic Society/European Respiratory Society guidelines [16, 17], with a full expiratory and inspiratory manoeuvre. Measurements were made during clinic visits and all readings were taken at the same time ± 1 h of the reading on visit 2 (start of run-in) by the same technician, if possible. The results were transmitted to the central monitoring over-readers who assessed the data and accepted or rejected the tests. If tests were rejected by the over-readers, the site was informed and suggestions for improvement were made. The subject was then requested to attend a repeat visit in order to obtain acceptable data. The FEV₁ and FVC came from the highest over-reader accepted tests, and PEF was selected from the manoeuvre with the largest sum of FVC + FEV₁.

A hand-held spirometer (Vitalograph[®]) and an electronic diary (Vitalograph[®] 2110 Diary) were given to the subjects who were trained in their use. The programme in the diary recorded the subject's use of the study drug and exacerbations defined as a decline in the morning PEF of $> 30\%$ from baseline on two consecutive days. The diary configuration allowed data to be recorded from 06:00 to 11:00 and 18:00 to 23:00 hours. On each day of the run-in, the randomized treatment and washout periods, the subject was required to record the answers to the diary questions concerning symptoms and then perform three PEF manoeuvres before a meal and the administration of asthma medication/study drug in the morning and in the evening.

Subjects evaluated their asthma symptoms separately for the night-time (questions answered in the morning) and the daytime (questions answered at the end of the day) using scales from 0 to 4, in which 0 represented no symptoms and 4 represented bad symptoms that kept the individual awake most of the night or prevented them from carrying out the usual daily activities. The questions used for daytime and night-time symptoms were as follows:

Daytime symptoms

0 = Very good, no symptoms

1 = One episode of wheezing, cough or breathlessness

2 = More than one episode of wheezing, cough or breathlessness without interfering with normal activities

3 = Wheezing, cough or short of breath most of the day which interfered to some extent with normal activities

4 = Asthma very bad. Unable to carry out daily activities as usual.

Night-time symptoms

- 0 = No symptoms, slept through the night
- 1 = Slept well but some complaints in the morning
- 2 = Woke up once because of asthma
- 3 = Woke up several times because of asthma
- 4 = Bad night, awake most of the night because of asthma

QOL was recorded using the Standardised Asthma quality-of-life questionnaire [AQLQ(S)], in which 32 questions (items) are answered on a 7-point scale (7 = no impairment, 1 = severe impairment), with the AQLQ(S) total score being calculated as the mean of all 32 items [18]. The AQLQ(S) comprises four domains: symptoms (12 items), activity limitation (11 items), emotional function (five items) and environmental stimuli (four items).

At selected centres, induced sputum was collected using an ultrasonic nebulizer and then processed to obtain Cytospin slides and cell-free supernatant [19, 20]. The Cytospin slides were stored in a clean and dry environment at room temperature until slide cell counts were performed by a central laboratory (Leicester Air, Leicester, UK).

The total serum IgE levels were determined in the entire study population at baseline, at the end of randomized treatment and at the end of placebo washout. These measurements were performed by a central laboratory (Quest International, Heathrow, UK).

Safety assessments included adverse events (AEs) and concomitant medications, blood pressure and heart rate, clinical laboratory tests, plasma drug levels and changes in physical examinations and ECGs. AEs were coded using Medical Dictionary for Regulatory Activities. Laboratory test data were graded using the parameters that are included in 'Common Terminology Criteria for Adverse Events version 3.0' [21].

The concentration of OC000459 in plasma samples taken at weekly visits during and at the end of the double-blind treatment was determined using a validated liquid chromatography-mass spectrometer bioanalytical method with a limit of quantification of 1 ng/mL. Analysis was performed by Quotient Bioresearch, Rushden, UK.

Statistical analysis

Sample sizing was carried out assuming a 5% significance level for two-sided testing. 60 subjects per group enabled an OC000459-placebo difference in means of 8% in the percentage change from baseline in FEV₁ to be detected with >80% power, assuming a standard deviation of 15% in the within-group percentage changes.

In order to detect 50% attenuation in sputum eosinophil levels on OC000459 compared with placebo, 21 subjects per group were required.

The Full Analysis (FA) population was defined as all subjects who received at least one dose of the double-blind study medication irrespective of compliance with eligibility and other protocol criteria. The statistical analysis plan for the study also pre-specified an analysis of the Per Protocol (PP) population as a secondary outcome measure. The PP population was defined as those subjects who complied with the major protocol criteria and the dosing regimen (at least 80% compliance with medication), refrained from use of any prohibited medication and completed the trial up to visit 8 (end of the double-blind treatment). Exclusions from the FA population to form the PP population were decided by reviewing protocol deviations and study termination records against the above criteria at a data-review meeting before the blind was broken. The main reasons for exclusion from the PP population were invalid spirometry data or e-diary data in the placebo run-in period and withdrawal from the study during the double-blind treatment period (see Fig. 2 for a detailed breakdown). All efficacy analyses were performed for both the FA and the PP populations.

The primary efficacy end-point was the percentage change from baseline in clinic FEV₁ at the end of the double-blind treatment period, which was analysed using a two-way analysis of covariance (ANCOVA) with treatment and centres as factors and baseline FEV₁ as a covariate (referred to as the primary model). Centres with <10 randomized subjects were grouped together for analysis purposes. Similar analyses were performed for secondary efficacy end-points of changes from baseline in clinic FEV₁, PEF, FVC, home PEF (morning and evening) and AQLQ(S), while percentage changes in salbutamol usage and changes in asthma symptoms (daytime and night-time) were analysed by analysis of variance (ANOVA), and serum IgE by Wilcoxon tests. Within- and between-group changes in log-transformed sputum eosinophil counts were analysed using Student's *t*-tests.

Baseline was the last observation before the start of the double-blind treatment period for clinic assessments and the average of the last week of the placebo run-in for diary data. The end-point was visit 8 for clinic assessments (i.e. immediately after the end of the double-blind treatment) and the last week of double-blind treatment for diary data. The last observation carried forward (LOCF) approach was used in end-point analyses, taking forward the latest available data from visits 5, 6 and 7 for any subject who did not have an assessment at the end of the double-blind phase of the study. Change from baseline is defined as the LOCF minus the baseline value.

Sensitivity analyses were carried out to ensure that the findings from using the primary model were robust. These analyses included a comparison of the primary model findings with the unadjusted treatment effects, investigation of heterogeneity across centres and comparison with

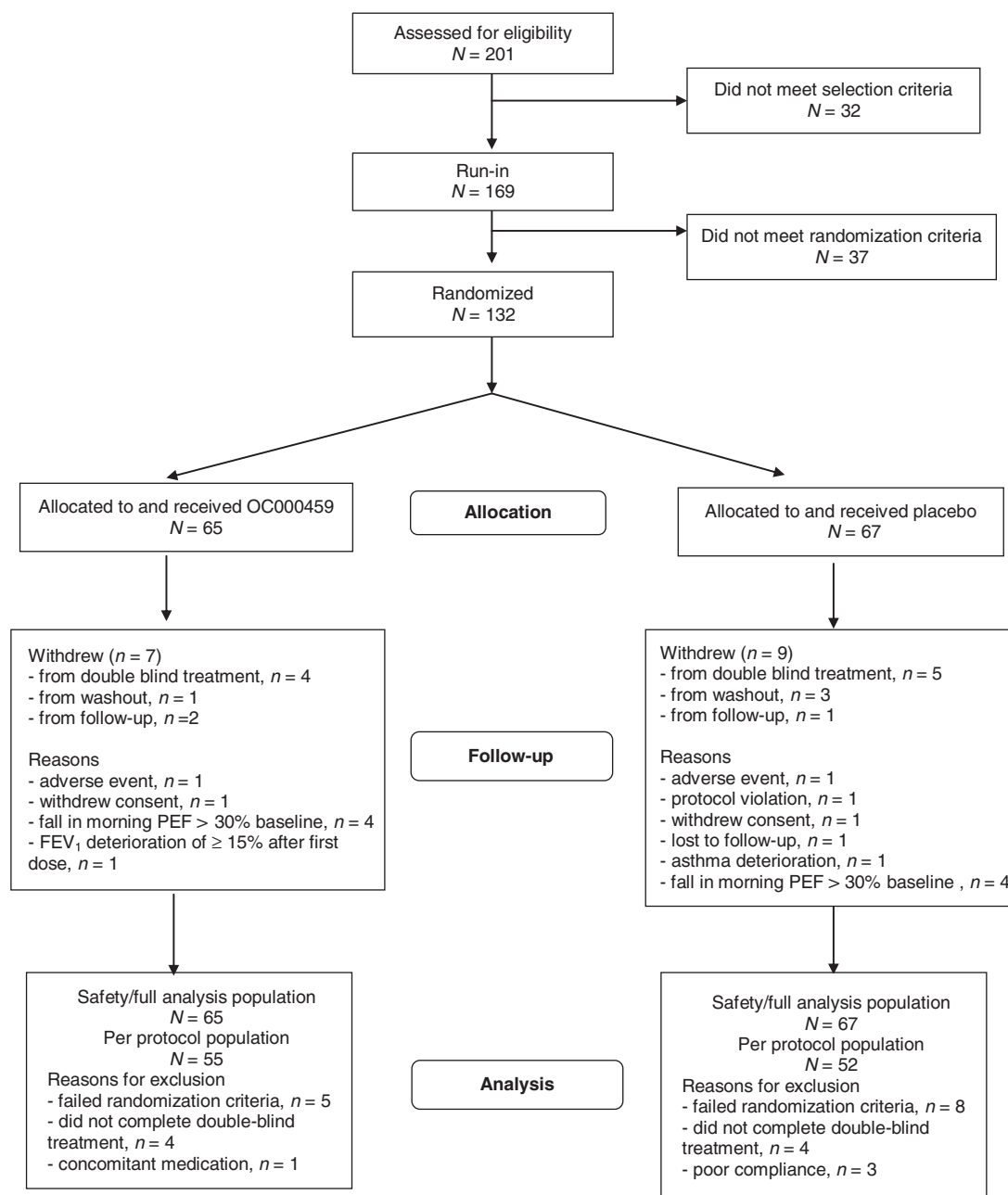


Fig. 2. Flow of participants through each stage of the study.

the findings from extended models including sex as an additional factor and interaction terms.

All analyses were conducted using SAS software v8.2. Significance was set at $P < 0.05$.

Results

Subjects

The study was conducted between 10 January and 22 November 2007. In total, 201 subjects were screened, of

whom 169 entered the run-in period; 132 subjects received double-blind treatment, 123 entered washout and 119 were included in follow-up. Sixty-five (65) subjects were randomized to OC000459 and 67 to placebo (Fig. 2). The most common reason for discontinuation was a decline in morning PEF of $> 30\%$ of baseline on two or more consecutive mornings (four/group). The other reasons for discontinuation were AE, withdrawal of consent, protocol violation, loss to follow-up and asthma deterioration. The FA population included all randomized subjects and the PP population included 107 subjects (55

treated with OC000459 and 52 with placebo). The numbers of subjects (OC000459+Placebo) in the FA population by centre were 6+6, 6+5, 5+8, 19+17, 7+6 and 5+6 and 17+19 for the grouped centre.

Demographic data and baseline FEV₁ are shown in Table 1 for each analysis population. Other baseline characteristics are shown in Table 2. OC000459 and placebo groups were generally well matched.

Efficacy

Lung function. There was an increase in FEV₁ during treatment with both OC000459 and placebo, but the change and percentage change from baseline was greater with OC000459 than with placebo. Furthermore, when OC000459 treatment was stopped, there was a decline in FEV₁ towards the baseline value. Figure 3 displays the treatment mean ($\pm$ SEM) percentage changes in FEV₁ and the changes in FEV₁ over the duration of the study for the PP population.

At the end-point, the observed mean percentage change in FEV₁ from baseline was 7.1% for OC000459 and 4.3% for placebo (FA population) (Table 3). For the FA population, the treatment effect was not significant, but a trend towards greater improvement in the OC000459-treated group was observed [difference in least squares (LS) means of 2.4%, $P=0.482$].

The results from the planned analysis of the PP population for FEV₁ were in agreement with those of the FA population, but the difference between treatments with regard to percentage change from baseline was more marked. At the end-point, the percentage change from baseline was mean 9.2% for OC000459 and 1.8% for placebo. ANCOVA showed a significant treatment effect ($P=0.037$), with the difference between treatments from the model being 7.7% (95% CI 0.49%, 14.82%). The change from baseline was mean 0.21 L for OC000459 and 0.03 L for placebo. ANCOVA again showed a significant treatment effect ($P=0.027$), with the difference between

treatments from the model being 0.20 L (95% CI 0.02, 0.37). The sensitivity analyses (as described in 'Statistical analysis') confirmed that these findings were robust.

No significant centre effect was observed for either the FA population ($P=0.738$) or the PP population ($P=0.658$).

The change in clinic PEF was in favour of OC000459 but the difference between treatments did not achieve statistical significance in the FA population (Table 3). However, in the analysis of the PP population, there was a significant treatment effect [$P=0.009$, treatment difference LS mean 31.41 L/min, (95% CI 7.99, 54.83)]. There

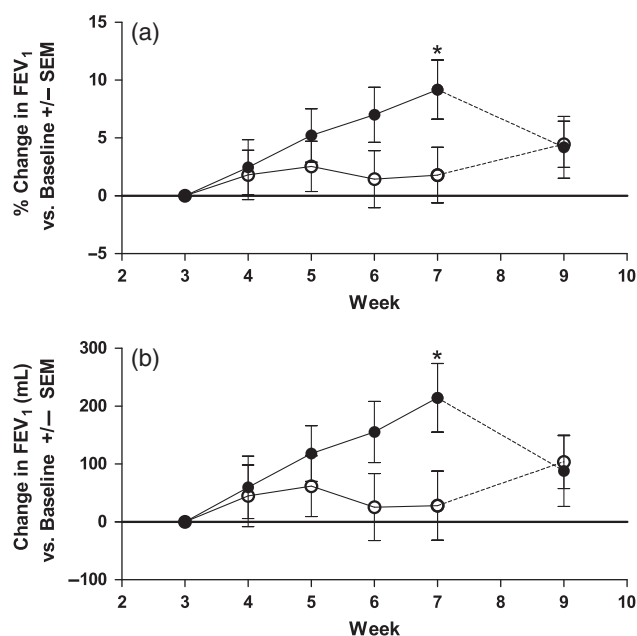


Fig. 3. Percentage change (a) and change (b) in forced expiratory volume in 1 s (FEV₁) during the study for Per Protocol subjects treated with OC000459 at 200 mg twice daily (●) or placebo (○). Data are presented as mean $\pm$ SEM. *Statistically significant ($P<0.05$) difference between OC000459 and placebo at the end-point [two-way analysis of covariance (ANCOVA) with treatment and centres as factors and baseline FEV₁ as a covariate].

Table 1. Demographic data and baseline FEV₁ for the study subjects

	Full Analysis population		Per Protocol population	
	OC000459 (N = 65)	Placebo (N = 67)	OC000459 (N = 55)	Placebo (N = 52)
Sex: male/female	38/27	38/29	30/25	28/24
Age (years)				
Mean (range)	43.4 (18–55)	40.0 (18–55)	43.5 (18–55)	40.9 (18–55)
FEV ₁ (L) at baseline				
Mean (SD)	2.42 (0.67)	2.53 (0.69)	2.37 (0.69)	2.47 (0.67)
Range	1.24–4.00	1.38–4.30	1.24–4.00	1.42–4.02
Number of observations	65	67	55	50

Baseline is the pre-dose on Day 1 of Week 3 (end of run-in/start of the double-blind treatment).

In the Per Protocol population, two subjects in the placebo group did not have a valid baseline for FEV₁ although they did have post-baseline data. FEV₁, forced expiratory volume in 1 s.

Table 2. Subject characteristics (Full Analysis population)

	OC000459 (N = 65)	Placebo (N = 67)
Time since asthma diagnosis (years)		
Mean (SD)	6.5 (6.29)	8.1 (8.66)
Median	4.0	5.0
Range	1.0–28.9	1.1–45.7
Skin prick test positive	65	67
Relevant conditions at baseline (n)		
Allergic rhinitis	6	11
Atopic rhinitis	0	1
Chronic rhinitis	1	0
Vasomotor rhinitis	1	0
Vasomotor allergic rhinitis	0	1
Atopic dermatitis	3	1
Allergic dermatitis	0	1
Allergic conjunctivitis	2	1
Allergic rhinoconjunctivitis	0	1
Pollinosis	1	0
Chronic preatrophic rhinopharyngitis	0	1
Drug allergy	1	1
Food allergy	1	0
Pollen allergy	0	1
Nasal polyposis	0	1
Quincke's oedema	0	1
Domestic allergic reaction	0	1
Polyvalent allergy	0	1
Never smoked	54 (83.1%)	64 (95.5%)
Former smoker	11 (16.9%)	3 (4.5%)
Salbutamol usage (MDI) at baseline		
Mean (SD)	3.4 (2.00)	3.8 (4.07)
n	65	66
AQLQ(S) at baseline		
Mean (SD)	4.76 (0.820)	4.63 (0.716)
n	54	58
Day asthma symptom score at baseline		
Mean (SD)	1.22 (0.55)	1.21 (0.55)
Night asthma symptom score at baseline		
Mean (SD)	1.15 (0.57)	1.09 (0.62)

N = 65 for OC000459 and n = 67 for the placebo group, unless otherwise shown.

Baseline is the pre-dose on Day 1 of Week 3 (end of the run-in/start of the double-blind treatment) or the average of the last week of the placebo run-in for diary data (symptoms and salbutamol usage).

was no significant treatment effect for FVC in either population.

There were no significant differences between treatments with regard to home assessments of PEF (Table 3). The daytime asthma symptom scores improved with both the treatments, with a non-significant trend towards improvement with OC000459 compared with placebo (Table 3). Improvements were also observed in night-time asthma symptoms: the difference (LS mean) between treatments of -0.26 (95% CI -0.45 , -0.07) was

significant ($P = 0.008$). This finding was supported by the analysis of the PP population: the ANOVA of change from the baseline to the end-point yielded a treatment difference of -0.25 (LS mean), 95% CI -0.47 , -0.04 , with a P -value for the treatment effect of 0.022.

The use of salbutamol decreased with both treatments, the percentage reduction being greater with placebo for the FA population (observed reduction mean 26.1% compared with 16.1% at end-point), and being greater with OC000459 than placebo for the PP population (mean 31.8% compared with 23.9% at end-point), but there were no significant treatment effects in the ANOVA models.

Immunoglobulin E. OC000459 treatment was also associated with a numerically greater reduction in IgE than was observed with placebo. The median reduction in IgE at the end-point was 13.0 IU/mL compared with 3.0 IU/mL ($P = 0.100$ FA population; $P = 0.084$ PP population; Wilcoxon test).

Eosinophils. Induced sputum was available for differential cell counting in 13 subjects treated with OC000459 and 14 treated with placebo (patients from the subset of centres who were selected to participate in sputum induction). The geometric mean sputum eosinophil count reduced significantly from 2.1% to 0.7% (mean reduction 3.1-fold; 95% CI 1.1, 8.8; $P = 0.03$) after treatment with OC000459 (Fig. 4). However, this did not differ significantly from the change seen with placebo ($P = 0.34$). For subjects treated with placebo, the geometric mean sputum eosinophil count reduced from 1.8% to 1.2% (mean reduction 1.5-fold; 95% CI 0.4, 5.3; $P = 0.50$).

Quality of life. An increase in the AQLQ(S) total score (improvement) was seen in both groups, with the increase being statistically significantly greater with OC000459 than placebo: at the end-point, the observed increase from baseline was 0.64 for OC000459 and 0.42 for placebo, the difference (LS mean) being 0.29 (95% CI 0.07, 0.52; $P = 0.0113$) (Table 4). The results for the PP population were very similar, with the increase from baseline at the end-point being 0.70 for the OC000459 group and 0.39 for the placebo group, a difference (LS mean) of 0.37 (95% CI 0.14, 0.61; $P = 0.0022$). Differences between OC000459 and placebo were also observed by domain (Table 3): the difference between OC000459 was significant for symptoms ($P = 0.0113$, FA population; $P = 0.0059$, PP population), activity limitation ($P = 0.0197$, PP population) and emotional function ($P = 0.0179$, PP population). For the FA population, 55.8% of those treated with OC000459 showed an improvement in the total score equal to or greater than the minimal important difference (0.5) compared with 35.7% on placebo ($P = 0.036$).

Table 3. Comparison of change from baseline to end-point for clinic and home assessments

	Full Analysis population			Per Protocol population		
	OC000459 mean (SD)	Placebo mean (SD)	Treatment difference LS mean (95% CI)	OC000459 mean (SD)	Placebo mean (SD)	Treatment difference LS mean (95% CI)
Clinic measurements						
<i>n</i>	64	67		55	50	
FEV ₁ (L)	0.17 (0.49)	0.09 (0.46)	0.08 (−0.09,0.25)	0.21 (0.44)	0.03 (0.42)	0.20 (0.02, 0.37)*
FEV ₁ (%)	7.10 (20.63)	4.32 (18.52)	2.44 (−4.42,9.31)	9.18 (19.03)	1.80 (16.97)	7.66 (0.49, 14.82)*
PEF (L/min)	24.53 (71.31)	7.70 (66.21)	13.37 (−10.55,37.29)	32.55 (61.75)	−0.20 (55.47)	31.41 (7.99, 54.83)*
FVC (L)	0.14(0.57)	0.09 (0.52)	0.05 (−0.14,0.24)	0.17 (0.51)	−0.01 (0.47)	0.18 (−0.01, 0.38)
Home assessments						
<i>n</i>	64	67		55	52	
PEF: morning (L/min)	12.8 (55.66)	8.3 (56.31)	3.61 (−16.00,23.22)	11.0 (49.33)	2.9 (46.96)	7.03 (−11.65, 25.71)
PEF: evening (L/min)	15.8 (59.61)	5.1 (55.11)	8.88 (−10.34,28.11)	15.7 (49.76)	−1.7 (40.33)	14.83 (−2.54, 32.19)
Symptoms: day	−0.32 (0.64)	−0.18 (0.46)	−0.14 (−0.33,0.05)	−0.33 (0.63)	−0.17 (0.47)	−0.16 (−0.38, 0.05)
Symptoms: night	−0.36 (0.59)	−0.11 (0.51)	−0.26 (−0.45,−0.07)*	−0.37 (0.57)	−0.12 (0.55)	−0.25 (−0.47, −0.04)*

Treatment difference is OC000459 minus placebo.

*Statistically significant ($P < 0.05$) treatment effect in the ANOVA/ANCOVA comparison of changes from baseline to end-point.

One subject in the OC000459 group was excluded from the LOCF (end-point) summaries for the Full Analysis population owing to no available on-treatment data due to withdrawal in the 6 h after the first dose.

Two subjects in the placebo group were excluded from the clinic measurements for the Per Protocol population as they had no valid baseline data.

LS means are from the primary model and so are adjusted for centre and baseline value.

FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; FVC, forced vital capacity.

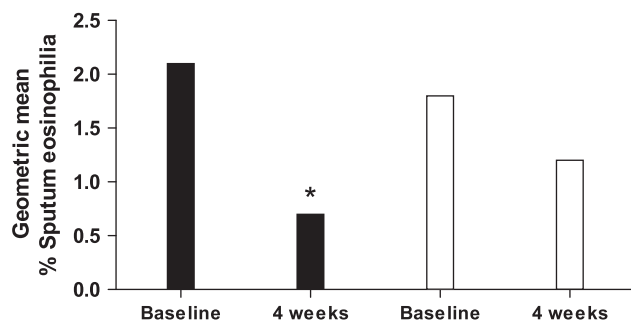


Fig. 4. % sputum eosinophilia at baseline and after 4 weeks of treatment with OC000459 200 mg twice daily (closed bars, $n = 13$ subjects) or placebo (open bars, $n = 14$ subjects). Results are shown as geometric mean. *Statistically significant ($P < 0.05$) change within the OC000459 group (Student's t -test after log-transformation). The change within the placebo group was not statistically significant.

Safety and tolerability. The overall incidence of treatment-emergent AEs was similar – and low – for both OC000459 and placebo treatment: 21.5% and 22.4%, respectively. The most commonly reported AEs were Infections and Infestations and these were notably more common in the placebo than in the OC000459 group (13.4% compared with 4.6%); the difference between groups was mainly accounted for by influenza [five subjects (7.5%) compared with one (1.5%)]. Transient increases in ALT and AST (to CTCAE grade 3) were observed in an OC000459-treated subject who had a history of fatty hepatosis. There were no findings of note

in other laboratory test results or vital signs, physical examinations and ECGs. AEs that were considered related to study treatment are shown in Table 5.

OC000459 in the plasma was measured at weekly intervals during the double-blind treatment period and was detected in at least one sample for all but three subjects in the OC000459 group. Subjects were instructed to take their capsules at home with food before the study visit. Therefore, the exact timing of the pharmacokinetic samples relative to the dose is not known but it is expected to be 1–3 h after dosing as the subjects were to attend the clinic between 7:00 and 11:00 hours. The mean concentration detected after 4 weeks of dosing was 600.3 ng/mL (SD 431.8 ng/mL). This is 172 times higher than the receptor binding K_i value and 17.2 times higher than the whole-blood IC_{50} value of 35 ng/mL.

Discussion

This study indicated that OC000459 treatment at 200 mg twice daily for 4 weeks was associated with greater improvement in several measures of asthma than was seen with placebo treatment. The results from the different assessments were consistent, but did not always achieve statistical significance at the end-point (end of double-blind treatment). Analyses of the data were planned based on two populations: the FA population and the subset of the population that complied with the protocol (the PP population). Of the 65 subjects randomized to OC000459 and 67 to placebo, 10 and 15, respectively, were excluded

Table 4. Quality of life: changes from baseline to end-point in the total score and the four domains of the AQLQ(S)

	Full Analysis population			Per Protocol population		
	OC000459	Placebo	Treatment difference LS mean (95% CI)	OC000459	Placebo	Treatment difference LS mean (95% CI)
Total score						
Mean (SD)	0.64 (0.66)	0.42 (0.61)	0.29 (0.07, 0.52)*	0.70 (0.66)	0.39 (0.58)	0.37 (0.14, 0.61)*
<i>n</i>	52	56		46	47	
Symptoms						
Mean (SD)	0.79 (0.85)	0.51 (0.74)	0.36 (0.08, 0.63)*	0.84 (0.86)	0.49 (0.71)	0.41 (0.12, 0.70)*
<i>n</i>	58	57		52	48	
Activity limitation						
Mean (SD)	0.50 (0.62)	0.36 (0.57)	0.20 (−0.01, 0.41)	0.55 (0.63)	0.37 (0.56)	0.27 (0.04, 0.49)*
<i>n</i>	55	57		49	48	
Emotional function						
Mean (SD)	0.61 (0.99)	0.38 (0.76)	0.27 (−0.01, 0.54)	0.67 (1.00)	0.31 (0.69)	0.35 (0.06, 0.64)*
<i>n</i>	59	58		53	49	
Environmental stimuli						
Mean (SD)	0.44 (1.02)	0.37 (0.73)	0.12 (−0.18, 0.42)	0.49 (1.06)	0.31 (0.72)	0.21 (−0.12, 0.55)
<i>n</i>	59	58		53	49	

*Statistically significant ($P < 0.05$) treatment effect in ANCOVA comparison of changes from baseline to end-point.

LS means are from the primary model and so are adjusted for centre and baseline value.

from the PP population primarily due to unreliable baseline spirometry and diary data and this, in part, may explain the differences between the sets of analyses.

Repeated dosing with OC000459 led to high plasma levels of drug (measured approximately 1–3 h post-dosing), whose mean values were 125–172 times the K_i (3.5 ng/mL) and 17 times higher than the whole-blood IC_{50} , suggesting that this dosing regimen achieved substantial receptor blockade.

The primary end-point was the percentage change in FEV_1 at the end-point and the results showed an improvement in the OC000459 group, which was numerically greater than that with placebo; the difference was statistically significant in the PP analysis, but not the Full Analysis population. In the FA population, there was no statistically significant difference between OC000459 and placebo groups with regard to PEF and FVC; in the PP analyses, there was a statistically significant difference in favour of OC000459 for PEF. The degree of improvement in lung function at the 4-week time-point is similar to that for montelukast in similar patient populations [22, 23]. However, the gradual increase in FEV_1 seen in this study is in contrast to the profile of treatment with montelukast, which has a rapid effect on lung function; hence, longer treatment may have further increased the response. Furthermore, preliminary data on sputum eosinophilia and circulating IgE suggest that further improvement in lung function and improved asthma control may become apparent over a longer treatment period. Future studies will focus on asthma control, particularly in patients not well controlled by corticosteroids or combinations of corticosteroids and long-acting β -agonists.

Several measures of efficacy that were assessed by the subjects themselves indicated the superiority of OC000459 over placebo in the FA population. There was greater improvement in day-time asthma symptoms; this difference was not statistically significant, but the greater improvement in night-time symptoms did achieve statistical significance. The result for night-time symptoms was backed up by a statistically significant difference in the planned PP population. Sleep disturbances are common in asthmatic individuals, and nocturnal asthma appears to be promising as a marker for poorly controlled asthma [24].

We also found statistically significantly greater improvement in QOL [as shown by the AQLQ(S) total score] with OC000459 than placebo in both analysis populations; improvement over such a short treatment period (4 weeks) was somewhat unexpected and was again very encouraging.

The clinical efficacy findings with OC000459 are consistent with the results of preclinical studies in CRTH2-deficient mice and with small-molecule antagonists where reduction in eosinophil accumulation [8–11] and lower levels of IgE [7, 12] have been observed. These data are consistent with *in vitro* studies that demonstrate an important role for CRTH2 in mast cell-dependent activation of Th2 lymphocytes and eosinophils and likely to be related to the reduced production of Th2 cytokines. These effects lead to a significant improvement in clinical asthma, albeit with a slow onset of action.

The tolerability of OC000459 was generally comparable to that of placebo. One notable difference between the groups was the incidence of infections, which were more common in the placebo group than in the OC000459

Table 5. Treatment emergent adverse events

MedDRA system order class and preferred term	OC000459 (N = 65)	Placebo (N = 67)
Any treatment emergent adverse event	14 (21.5%)	15 (22.4%)
Cardiac disorders	1 (1.5%)	0
Sinus bradycardia	1 (1.5%)	0
Gastrointestinal disorders	0	1 (1.5%)
Nausea	0	1 (1.5%)
General disorders and administration site conditions	0	1 (1.5%)
Asthenia	0	1 (1.5%)
Infections and infestations	3 (4.6%)	9 (13.4%)
Influenza	1 (1.5%)	5 (7.5%)
Nasopharyngitis	0	2 (3.0%)
Pharyngitis	1 (1.5%)	0
Pneumonia	1 (1.5%)	0
Respiratory tract infection	0	1 (1.5%)
Rhinitis	0	1 (1.5%)
Musculoskeletal and connective tissue disorders	1 (1.5%)	0
Arthritis reactive	1 (1.5%)	0
Nervous system disorders	1 (1.5%)	0
Dizziness	0	1 (1.5%)
Headache	2 (3.1%)	1 (1.5%)
Somnolence	1 (1.5%)	0
Reproductive system and breast disorders	0	1 (1.5%)
Menorrhagia	0	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	3 (4.6%)	2 (3.0%)
Asthma	0	2 (3.0%)
Cough	1 (1.5%)	0
Dyspnoea	1 (1.5%)	0
Pharyngolaryngeal pain	1 (1.5%)	0
Productive cough	1 (1.5%)	0
Skin and subcutaneous tissue disorders	1 (1.5%)	2 (3.0%)
Hyperhidrosis	1 (1.5%)	2 (3.0%)
Pruritus	1 (1.5%)	0
Pruritus allergic	0	1 (1.5%)
Rash	1 (1.5%)	1 (1.5%)
Skin fissures	1 (1.5%)	0
Vascular disorders	2 (3.1%)	0
Hypertension	2 (3.1%)	0

Number (%) of subjects.

group. It is possible that the lower rate of infections was associated with a greater control of airway function, particularly Th2 cell activity, as Th2 bias is associated with more severe cold symptoms and delayed viral clearance in human subjects infected with rhinovirus [25]. Th2 cytokines induce the expression of inter-cellular adhesion molecule 1 (ICAM-1), the receptor for rhinovirus, by bronchial epithelial cells [26] and conversely, Th1 cytokine IFN- γ promotes shedding of ICAM-1 by these cells [27]. These findings, combined with the observation that exacerbation of allergic airway inflammation and decline in lung function induced by dsRNA is reduced in CRTH2-deficient mice [28], suggest that the CRTH2 antagonist may find utility in the prevention or the treatment of viral exacerbations in asthmatic subjects.

It is concluded that OC000459 shows promise in the treatment of asthma and warrants further investigation in this indication.

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