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Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459

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Short title: Effect of OC000459 in eosinophilic asthma

Abstract

Background: The CRTH2 antagonist OC000459 has previously been demonstrated to reduce airway inflammation and improve lung function in moderate persistent asthma. A study was conducted to determine the effect of lower once daily doses of OC000459 and to define of the phenotype of subjects most responsive to treatment.

Methods: Adult subjects (%predicted forced expiratory volume in 1 second (FEV_1) 60-85%) were randomized to OC000459 at three dose levels (25 mg once daily, 200 mg once daily or 100 mg twice daily) or placebo for 12 weeks (n=117-125 per group, Full Analysis Set). The primary endpoint was the change from baseline in pre-bronchodilator FEV_1 and secondary endpoints included ACQ and AQLQ(S), and incidence of exacerbations and respiratory tract infections.

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Results: OC459 caused a significant improvement in FEV_1 compared with placebo at a dose of 25 mg once daily (p=0.028). A similar increase was observed in the other dose groups and the mean change in FEV_1 in the pooled dose groups at endpoint was 95 ml greater than placebo (p=0.024). In a post-hoc analysis of atopic eosinophilic subjects with uncontrolled asthma, a mean increase in FEV_1 of 220 ml was observed compared to placebo (p=0.005).The mean increase in FEV_1 was more marked in younger subjects in this group: for subjects aged ≤40 years, there was a mean increase of 355 ml compared with placebo (p=0.007). Improvements in ACQ and AQLQ(S) were observed in both the Full Analysis Set and the atopic eosinophilic subgroup. There was a lower incidence of exacerbations and respiratory infections in subjects treated with OC000459. There were no drug-related serious adverse events.
Conclusions: OC000459 is a safe and effective oral anti-inflammatory agent which achieved clinically meaningful improvements in lung function and asthma control in allergic asthmatics with an eosinophil-dominant form of the disease. A dose of 25 mg given once daily was as effective as the higher doses studied.

Key words
Asthma; eosinophil; OC000459; prostaglandin D_2

Introduction

CRTH2 is a G-protein-coupled receptor expressed by Th2 lymphocytes, eosinophils and basophils which mediates activation of these cell types in response to the mast cell product prostaglandin D_2 (1). CRTH2 plays a dominant role in mast cell-dependent activation of both Th2 lymphocytes and eosinophils (2-4), promoting both increased cell migration and elaboration of Th2 cytokines. Studies in CRTH2-deficient mice or in animals treated with small molecule antagonists have highlighted the involvement of this receptor in effector responses to allergen including leukocyte accumulation, Th2 cytokine production, tissue swelling, airway hyper-responsiveness and production of IgE (reviewed in (5)). Clinical studies have demonstrated that the CRTH2 antagonist OC000459 is effective in reducing airway inflammation and improving lung function and quality of life in steroid-naïve subjects with moderate persistent asthma (6) and to reduce both nasal and eye symptoms in allergic subjects exposed to grass pollen (7).

It is now recognized that asthma is a heterogeneous disease and considerable progress has been made in identifying distinct phenotypes that may respond differently to treatment (8,9). In subjects with active airway inflammation, the leukocytic infiltrate can be eosinophilic or neutrophilic or mixed. 40-50% of asthmatics have eosinophil-dominant airway inflammation as defined by sputum eosinophilia of ≥ 2 or 3% and these patients typically respond well to inhaled corticosteroids (ICS)(10-12). However, a small proportion of asthmatics have persistent sputum eosinophilia despite treatment with high dose ICS and this group have frequent exacerbations requiring hospitalization or treatment with oral steroids. The anti-IL-5 antibody mepolizumab is effective in reducing the rate of exacerbations (13,14) and steroid dependency (15) in this group of patients. Blood eosinophil count is a marker of Th2 dominant airway disease and has been shown to correlate with disease severity (16) and to identify the eosinophilic "Th2 high" phenotype responsive to both mepolizumab (13), lebrikizumab (17) and, more recently, dupilumab, an anti-IL-4 receptorα antibody that blocks both IL-4 and IL-13 signaling (18).

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In the present study we investigated the effect of the CRTH2 antagonist OC000459 on lung function and asthma control in patients treated for a period of 12 weeks. A post hoc analysis was conducted to determine whether the degree of atopy and eosinophilia influenced the response of patients to OC000459.

Methods

Study Design

The study was a randomized, dose-finding, double-blind parallel group comparison of 3 dose levels of OC000459 and placebo in an outpatient population with mild-to-moderate persistent asthma. The study included steroid-free subjects allowed to use the short acting β_2 agonist salbutamol as a reliever therapy. One to 2 weeks after screening, subjects who met the eligibility criteria entered a 3-week, single-blind placebo run-in (Fig. 1). Baseline respiratory function was taken as the average of values recorded after 2 and 3 weeks of the placebo run-in period; and baseline Asthma Control Questionnaire (ACQ) and the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) were recorded at the final clinic visit of the placebo run-in period. Subjects meeting randomization criteria continued into a 12-week, double-blind dosing period and were randomly assigned to take OC000459 or matching placebo.

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 washout. Clinic visits were scheduled between 07.00 and 11.00 hours and occurred weekly during the placebo run-in and every 2 weeks thereafter. Clinic visits included in-clinic spirometry, vital signs, hematology and clinical chemistry tests, 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. On clinic visit days, study medication was taken after study assessments had been performed.

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 trial was registered on the clinicaltrials.gov database (Identifier NCT00890877).

Subject selection

Up to 900 subjects were to be screened to give at least 460 randomized subjects and approximately 440 subjects evaluable for efficacy in the Full Analysis Set. Male or female subjects aged 18-55 years with mild to moderate persistent asthma, as defined by the Global Initiative for Asthma criteria, were eligible. Subjects had typical symptoms including, but not limited to, cough, wheezing, and shortness of breath with a requirement for treatment with bronchodilators but had not received steroid treatment within the 3-month period before screening. Subjects were non-smokers for ≥12 months before screening with a smoking history ≤10 pack years.

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To be randomized, subjects were required to have FEV_1 60-85% of the predicted value while abstaining from inhaled salbutamol for 6 h averaged over the last two visits of the placebo run-in and an increase of ≥12% and/or an absolute increase of ≥200 ml between 20 and 30 min after inhaled salbutamol at both of the last two visits of the run-in. Subjects were also required to average >1 actuation/day of salbutamol over the last 7 days of the run-in.

The clinical trial was conducted at 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.

Study treatment

The placebo run-in was followed by a double blind dosing with placebo or OC000459 at 25 mg once a day, 100 mg twice a day and 200 mg once a day for 12 weeks. Double-blind treatment assignment was from a central schedule of permuted blocks in a 1:1:1:1 ratio for the various doses of OC000459 and placebo. Centers were allocated the next available complete block from this schedule as and when required. OC000459 was administered as an excipient-based tablet and placebo tablets were identical in appearance.

Efficacy and safety assessments

In-clinic spirometry was recorded using a centralized spirometry system (Vitalograph® Spirotrac, Maids Moreton, Buckinghamshire, UK). FEV_1, forced vital capacity (FVC), and peak expiratory flow (PEF) were performed as described previously (6). Subjects' use of the study drug, asthma symptoms and exacerbations were recorded in an electronic diary.

Quality of life 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. The AQLQ(S) comprises four domains: symptoms (12 items), activity limitation (11 items), emotional function (five items) and environmental stimuli (four items).

Subjects evaluated their asthma control by answering six questions of the ACQ. The seventh ACQ question related to the % of predicted FEV_1 of the subject at that visit and the score was calculated from the pre-bronchodilator spirometry data provided by Vitalograph®.

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Exacerbations were defined as a deterioration in asthma requiring other medical intervention and/or hospitalization and/or a fall in morning home PEF of >30% of the baseline value on two or more consecutive mornings (diary baseline = mean average PEF over the 7 days prior to randomization) with an associated increase in respiratory symptoms.

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.

Statistical analysis

The sample size was based on the average change from baseline in FEV_1 over the treatment period. Assuming a standard deviation of 0.450 L in the average change within each treatment group and a 1.67% significance level (Bonferroni adjustment) for 2-tailed testing, then 110 subjects per treatment group would enable an OC000459-placebo difference in means of 0.200 L (i.e. approximately 8% of the mean baseline FEV_1) to be detected with >80% power.

The change from baseline to endpoint (end of 12-week double-blind period) was analyzed using ANCOVA with treatment and country as factors and baseline FEV_1 as a covariate (primary analysis). In the cases of premature withdrawal, the last post-baseline measurement prior to withdrawal was set as endpoint (LOCF).Similar analyses were performed for ACQ and AQLQ(S) changes in total scores. The proportion of subjects showing an improvement in ACQ or AQLQ(S) total score at the end of double-blind treatment period of at least the minimal important difference (MID=0.5) was compared with placebo for each of OC000459 groups using the chi-square test.

Randomized treatment-emergent AEs were coded using MedDRA (version 11.1) preferred terms and system organ classes.

Results

Patient flow and characteristics

In total, 771 subjects were screened, of whom 708 entered the run-in period and 519 were randomized to double-blind treatment; 476 completed double-blind treatment and entered washout (Fig. 2). 134 subjects were randomized to OC000459 200 mg OD, 132 to OC000459 100 mg BID, 130 to OC000459 25 mg OD and 123 to placebo. All randomized subjects were included in the Safety Set; 482 were included in the Full Analysis Set, which consisted of all subjects who received at least one dose of double-blind study medication and who met the randomization criteria.

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Demographic data are shown in Table 1 for each analysis population, with baseline FEV_1 shown for the Full Analysis Set.

Effect of OC000459 on lung function

All doses of OC000459 caused a similar change in FEV_1 from baseline compared with placebo treatment in the Full Analysis population (Fig. 3). A significant improvement in FEV_1 compared to placebo was observed in the Full Analysis population with the 25 mg OD dose group (Table 2). Pooling of the dose arms showed a 149 ml mean change from baseline at endpoint, a change greater than that in the placebo group by 95 ml ($p = 0.024$, Table 2).

In order to investigate whether subjects with active eosinophilic airway inflammation responded preferentially to OC000459, a post hoc analysis was conducted in patients with blood eosinophil counts ≥250/µl. A significant change from baseline in FEV_1 was observed for the pooled doses in this group, whereas there was no benefit for subjects with blood eosinophil counts ≤250/µl (Figure 4). A significant improvement in PEF of 18.7L/min compared to placebo ($p=0.037$) was also observed in subjects with blood eosinophil counts ≥250/µl.

In skin-prick-test-positive subjects with ACQ≥1.5 and blood eosinophil count ≥250 per µl, a 220 ml benefit over placebo was observed in the mean change in FEV_1 (n= 104 on OC000459 and n=37 on placebo, $p=0.005$). Each of the individual groups caused a significant improvement in FEV_1 compared to placebo in the responder population (Table 3). Further benefit in lung function was also observed in younger patients with this atopic eosinophilic phenotype: there was a benefit over placebo in mean change in FEV_1 of 231 ml (n=87 on OC00459 and n=31 on placebo, $p=0.011$) and 355 ml (n=51 on OC000459 and n=16 on placebo, $p=0.007$) in subjects aged ≤50 and ≤40 years respectively. There was no apparent difference in response of patients with lower %predicted FEV_1 (data not shown).

Figure 5 illustrates the contribution of atopy, blood eosinophilia and age to the response of this phenotype.

For analysis of other endpoints the atopic eosinophilic subgroup was defined as skin-prick-test-positive subjects with ACQ≥1.5, blood eosinophilia ≥250/µl and age ≤50 years.

A significant improvement in PEF of 18.7L/min compared to placebo ($p=0.037$) was also observed in subjects with blood eosinophil counts ≥250/µl.

Effect of OC000459 on ACQ and AQLQ(S)

OC000459 improved ACQ and AQLQ (S) in both the Full Analysis Set and in the atopic eosinophilic subgroup. Significantly more patients taking OC 000459 than taking placebo had an improvement in ACQ and AQLQ(S) total score of ≥0.5 (the minimally important difference) (Table 4). Mean changes in both ACQ total score (-0.36 compared with -0.21) and AQLQ(S) total score (0.3 compared with 0.24) were numerically greater in the atopic eosinophilic subgroup than the Full Analysis Set.

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Effect of OC000459 on exacerbations and respiratory infections

The percentage of subjects with exacerbations in the placebo group was 7.7%. The number of exacerbations was lower in all OC000459 dose groups (Table 5) but these effects did not reach statistical significance even when the dose groups were pooled (3.8% incidence of exacerbations, p=0.107).

The percentage of subjects with respiratory infections in the placebo group was 23.1%, which was significantly higher than each of the OC000459 dose groups (Table 4), including the pooled dose group (12.3%, p=0.003).

Safety, tolerability and drug exposure

The overall incidence of treatment-emergent adverse advents was low and fewer adverse events were observed in the drug-treated groups than the placebo group (Table 6). The difference between treatments was accounted for by a reduction in respiratory infections. The mean plasma concentrations of OC000459 in samples collected 12 hours after the preceding dose on each 2-weekly visit are shown in Table 5. The levels in each dose group were similar at each time point and well in excess of the whole blood K_B level of 10 ng/ml (4) for each of the 3 dose levels.

Discussion

A modest effect of OC000459 in improving lung function and asthma symptoms was observed in a non-stratified asthma population that included both atopic and non-atopic subjects with varying degrees of blood eosinophilia. All dose levels of OC000459 were similarly equally active suggesting that 25 mg (or less) administered once daily is sufficient to provide maximal efficacy, a view supported by the high plasma concentrations of drug detected at this dose. The concentration of OC000459 at 12 hours after dosing at each 2 weekly visit was consistently detected at around 90 ng/ml which is approximately 9 times higher than the K_B for inhibition of PGD_2-mediated eosinophil activation in whole blood (4). In healthy subjects, the Cmin level of OC000459 (at 24 hours after dosing) at a dose of 25 mg is ~30 ng/ml suggesting that a trough level of approximately 3 times whole blood K_B is sufficient for maximal efficacy. Further studies are required to determine if lower doses of OC000459 are also effective and the precise pharmacokinetic/pharmacodynamic relationship associated with maximal efficacy.

In order to increase the power to identify potential responder populations, the data in the 3 dose groups were pooled since the effect of each dose was similar. Using this approach, it became apparent that atopic subjects with active disease (ACQ≥1.5) and blood eosinophil counts ≥250/µl had a heightened improvement in lung function, with eosinophilia having the greatest effect. No improvements relative to placebo in lung function were observed in subjects with blood eosinophil counts <250/µl. The level of eosinophilia of ≥250/µl selected to stratify responses represents approximately 45% of the total study population which is similar to the proportion of the asthmatic patients with eosinophilic disease most often defined as having sputum eosinophilia ≥ 2% or 3% (10-12). A similar pattern of response was observed when data from an earlier Phase 2a trial (6) were re-

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analysed, suggesting that blood eosinophil count is a reliable method to identify eosinophilic asthmatics responsive to this class of drug (unpublished data). Interestingly, the response of subjects to OC000459 was increased dramatically in younger patients which may reflect greater Th2 dominance in these patients. The responder population can therefore being defined as being young (aged ≤40 or ≤50) with active eosinophilic airway inflammation, most likely driven by an allergic process. In this subset of patients, the effects on lung function are clinically meaningful and the proportion of patients showing at least a minimally important improvement in asthma control (ACQ) was also increased.

It is becoming increasingly apparent that Th2-dominant eosinophilic disease represents a subset of asthma that responds preferentially to ICS and anti-Th2 therapies. The anti-IL-5 antibody mepolizumab does not have efficacy in all patients but is effective in reducing exacerbations (13,14) and steroid dependency (15) in patients with persistent sputum eosinophilia despite high dose ICS/LABA treatment. Blood eosinophilia can also be used to predict response to mepolizumab but, unlike omalizumab and OC000459, response is apparently independent of atopy (14). Responses to anti-IL-5 therapy may be further enhanced by refinement of the target population since although mepolizumab does not improve asthma symptoms or quality of life in subjects with severe eosinophilic asthma (13,14), another anti-IL-5 antibody, reslizumab, improved ACQ in eosinophilic patients with co-morbid nasal polyps (20). Responders to the anti-IL-13 antibody lebrikizumab were identified by high circulating levels of periostin or a combination of blood eosinophilia and total serum IgE (18) and response to the anti-IL-13 antibody tralokinumab were enhanced in patients with high levels of sputum IL-13 (21). These studies highlight the need to stratify the asthma patients to identify those patients likely to derive benefit from anti-Th2 therapies and may explain why some trials with CRTH2 antagonists in non-stratified asthma populations have not yielded positive results (22).

Blood eosinophil counts are accessible and preliminary studies suggest that it has utility in identifying responders to anti-IL-5, anti-IL-13 and anti-CRTH2 therapies. However, blood eosinophilia and the other Th2 markers so far described (e.g. periostin, exhaled nitric oxide) are likely to vary with disease severity and response to drug therapy. Genetic markers of Th2 high phenotype which are fixed may therefore have some advantage in identifying responders reproducibly. The PGD_2/CRTH2 pathway is up-regulated in severe eosinophilic asthma (23) and genetic polymorphisms in CRTH2 are associated with increased receptor expression, blood eosinophilia and the development of severe asthma (24,25). Further research is therefore required to determine if measurement of polymorphisms in CRTH2 represents a reliable way to identify asthma patients with CRTH2-mediated eosinophilic disease.

OC000459 was also effective in reducing respiratory infections confirming the effects observed in a previous 1-month asthma study and most likely related to dampening down Th2-mediated immune responses and so leaving Th1-dependent and innate immune responses unopposed (6). There was also a trend to reduce exacerbations over the 3-month trial period and further longer-term studies are required to confirm these observations.

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In summary, the CRTH2 antagonist OC000459 was safe and effective in the treatment of eosinophilic asthma when administered orally once daily. Further research is warranted to define the minimally effective dose of OC000459 and to optimize methods to identify the Th2 high responder phenotype.

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	Placebo	OC000459		
		25 mg OD	100 mg BD	200 mg OD
Safety Set				
N	123	130	132	134
Male/female	45/78	56/74	47/85	46/88
Age (years)				
Mean (SD)	40.3 (10.89)	40.1 (11.3)	38.7 (11.4)	39.5(10.3)
Min to max	19 to 55	18 to 55	18 to 55	18-55
Full Analysis Set				
N	117	125	117	123
Male/female	43/74	55/70	41/76	42/81
Age (years)				
Mean (SD)	40.4 (11.03)	40.4 (11.4)	38.9 (11.4)	39.7(10.2)
Min to max	19 to 55	18 to 55	18 to 55	18-55
Baseline FEV_1 (l)				
Mean (SD)	2.35 (0.58)	2.43 (0.57)	2.37 (0.54)	2.34(0.55)
Min to max	1.25 to 4.37	1.32 to 3.87	1.34 to 3.61	1.33 to 3.74
% Predicted FEV_1				
Mean (SD)	70.6 (6.1)	71.5 (6.1)	71.5 (6.9)	71.0 (6.2)
Min to max	60.2 to 84.8	60.1 to 84.9	60.4 to 84.7	60.6 to 84.7

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% Change in FEV_1 after salbutamol Mean (SD) Min to max	24.3 (11.8) 9.4 to 68.5	25.9 (14.7) 7.1 to 85.1	27.0 (14.9) 9.6 to 123.3	24.2 (12.1) 6.3 to 67.7
Peak expiratory flow Mean (SD) Min to max	372.4 (81.8) 165 to 660.0	384.6 (90.9) 200.5 to 628.5	366.6 (74.8) 205.5 to 560.5	374.2 (87.1) 188.5 to 714.5
Number of puffs of salbutamol per day Mean (SD) Min to Max	3.6(2.3) 1.1 to 14.4	3.5 (2.4) 1.1 to 14.7	3.4 (2.4) 1.1 to 20.4	3.6 (3.1) 1.1 to 30.5
ACQ Mean (SD) Min to max	2.1 (0.7) 0.7 to 4.7	2.1(0.7) 0.6 to 3.7	2.1 (0.6) 0.6 to 3.6	2.1 (0.7) 0.6 to 3.9
AQLQ(S) Mean (SD) Min to max	4.9 (0.8) 2.3 to 6.9	4.9(0.8) 2.8 to 6.8	4.8(0.8) 2.5 to 6.6	4.9(0.8) 2.5 to 6.7

Table 1. Subject Demographics

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		Placebo	OC000459			
			25 mg OD	100 mg BID	200 mg OD	Pooled
	N	116	122	117	122	361
FEV_1 change from baseline to endpoint (ml)	Mean	57	162	149	136	149
	(SD)	(369)	(377)	(484)	(357)	(408)
	LSmeanP-value *		176	158	141	158
	Mean (SD)		0.028	0.068	0.128	0.024
PEF change from baseline to endpoint (ml/min)	LS Mean	13.0	25.6	19.4	18.7	
		(55,4)	(65.6)	(71.5)	(50.1)	
	P-value*		14.7	6.2	5.9	
			0.060	0.433	0.45	

* P-value for the mean change comparison with placebo from the ANCOVA.

Table 2. Summary of Change from Baseline of Clinic FEV_1: Full Analysis Set

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		Placebo	OC000459			
			25 mg OD	100 mg BID	200 mg OD	Pooled
FEV_1 change from baseline to endpoint (ml)	N	37	32	33	39	104
	Mean (SD)	-5 (434)	197 (462)	182 (491)	207 (391)	196 (442)
	LSmean		199	221	244	223
	P-value *		0.047	0.026	0.011	0.005
* P-value for the mean change comparison with placebo from the ANCOVA.						

Table 3: Summary of change from baseline FEV_1: Eosinophilic responder population

	% Subjects with improvement in ACQ total score ≥MID			**% Subjects with improvement in AQLQ(S) total score ≥MID**		
Full Analysis Set	Placebo N = 115	Pooled OC000459 N = 356	p value	Placebo N = 115	Pooled OC000459 N = 356	p value
	33.0	50.6	0.001	37.4	54.2	0.002
Atopic eosinophilic subgroup	Placebo N = 31	Pooled OC000459 N = 85	p value	Placebo N = 31	Pooled OC000459 N = 85	p value
	38.7	65.9	0.009	45.2	63.5	0.076

Table 4. % Subjects with improvements in ACQ and AQLQ total scores greater or equal to the minimal important difference (MID=0.5). Pooled OC000459 vs placebo data were compared using a chi-square test.

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	Placebo (N=117)	OC000459 25 mg OD (N=125)	OC000459 100 mg BD (N=117)	OC000459 200 mg OD (N=123)	OC000459 Pooled (N=365)
Exacerbations (%)	7.7	4.8	3.4	3.3	3.8
Respiration tract infections (%)	23.1	12.8*	13.7*	10.6*	12.3*

Table 5. Percentage of subjects in the Full Analysis Set with asthma exacerbations and respiratory tract infections. (* indicates statistically significantly reduced compared with placebo, $p<0.05$ using the log-rank test).

	Placebo (N=123)	OC000459 25 mg OD (N=130)	OC000459 100 mg BD (N=132)	OC000459 200 mg OD (N=134)
Adverse events (%)	43.1	23.8	28.8	27.6
Treatment-related adverse events (%)	14.6	6.9	9.1	9.0
Serious adverse events (%)	1.6	0	0	0

Table 6. Percentage of subjects with treatment-emergent adverse events (in the Safety Set)

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Week of double-blind period	Mean (±SD) plasma concentrations of OC000459 (ng/ml)		
	25 mg OD	100 mg BD	200 mg OD
2	94±95	238±219	228±220
4	93±85	236±202	229±233
6	102±92	244±240	243±229
8	94±83	233±201	232±228
10	87±80	215±177	216±201
12	85±82	212±215	224±222

Table 7. Plasma concentrations of OC000459 at various times during the study. Blood was collected at approximately 12 hours after the previous dose. Results are expressed as the mean ± SD from N = 120-132 subjects per group.

Figure Legends

Figure 1. Study Design

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

Figure 3. Effect of OC000459 on FEV_1 compared with placebo in the Full Analysis Set. Mean changes from Baseline (+/- SEM). Results are shown for individual (A) and pooled (B) doses (see Table 2 for p values and number of patients per group).

Figure 4. Effect of OC000459 on FEV_1 compared with placebo in subjects with blood eosinophil counts ≥250/µl (A) and in subjects with blood eosinophil counts <250/µl (B). Mean changes from Baseline (+/- SEM).

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Figure 5. Mean change (+/- SEM) in FEV_1 in response to OC000459 (pooled doses, closed circles) compared with placebo (open circles) in the uncontrolled asthma population (ACQ≥1.5) (A), uncontrolled skin prick test positive subjects (B), uncontrolled skin prick test positive subjects with blood eosinophil counts ≥250/µl (C) and skin prick test positive subjects with blood eosinophil counts ≥250/µl aged ≤50 years (D).

Authors Contributions

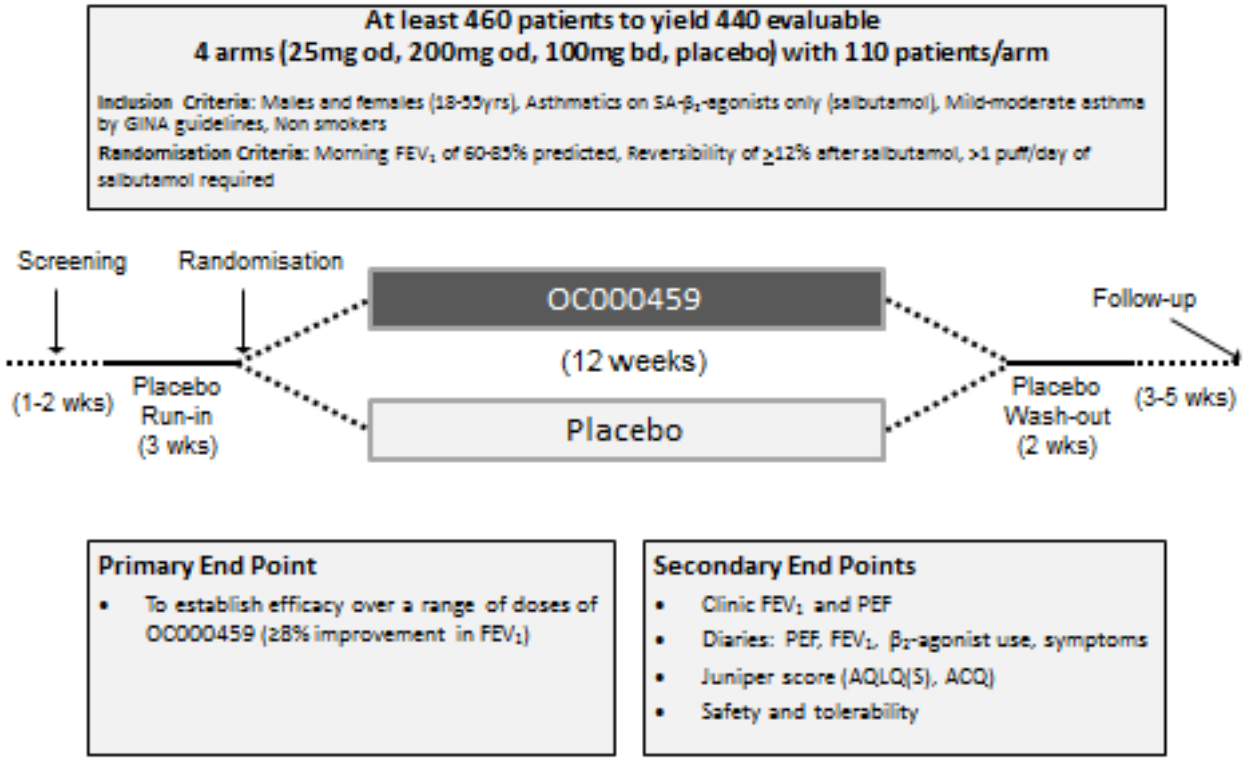
RP, MGH, CMP, TL, JS, JB and MAP contributed to the conception and design of the study and interpretation of the data

LPC, TL, MB were involved in the acquisition of data and its analysis

RP and TL wrote the manuscript which was revised by MGH, CMP, JS, JB and MAP

Conflict of Interest Statement

RP, MGH, JB and MAP are employees and/or hold shares in Atopix Therapeutics Ltd.



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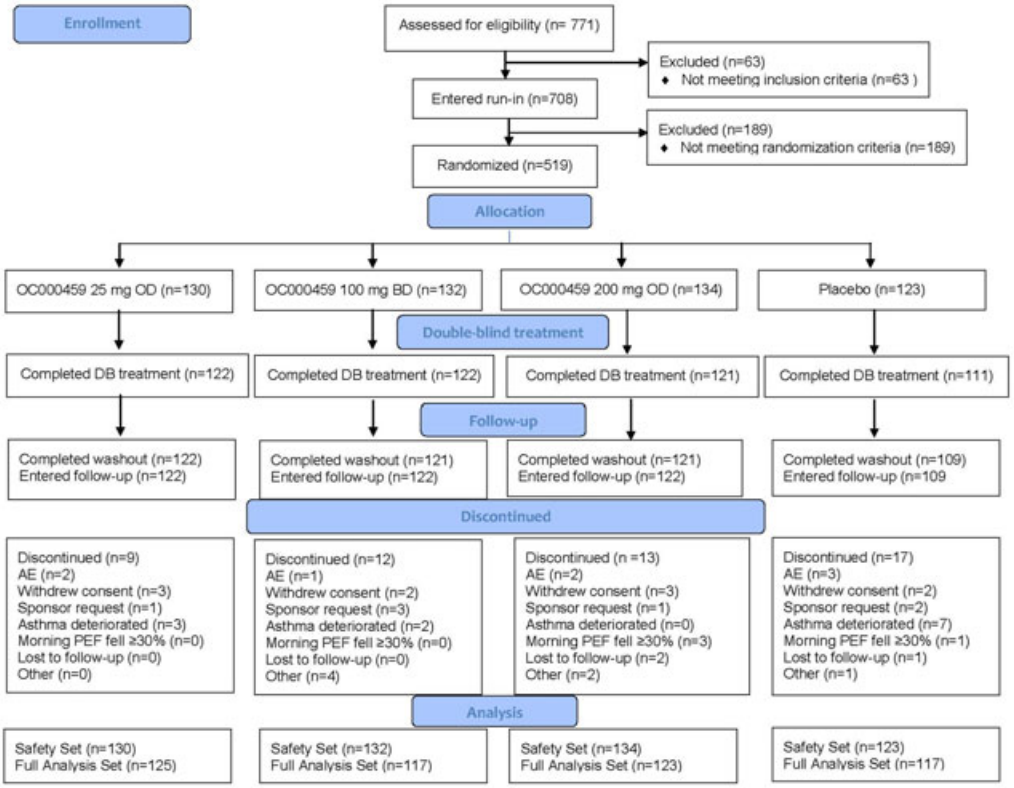

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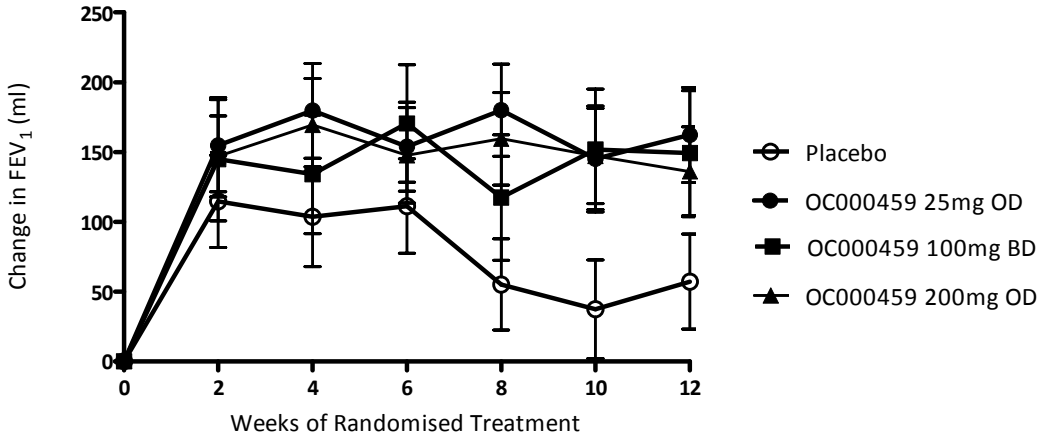
A



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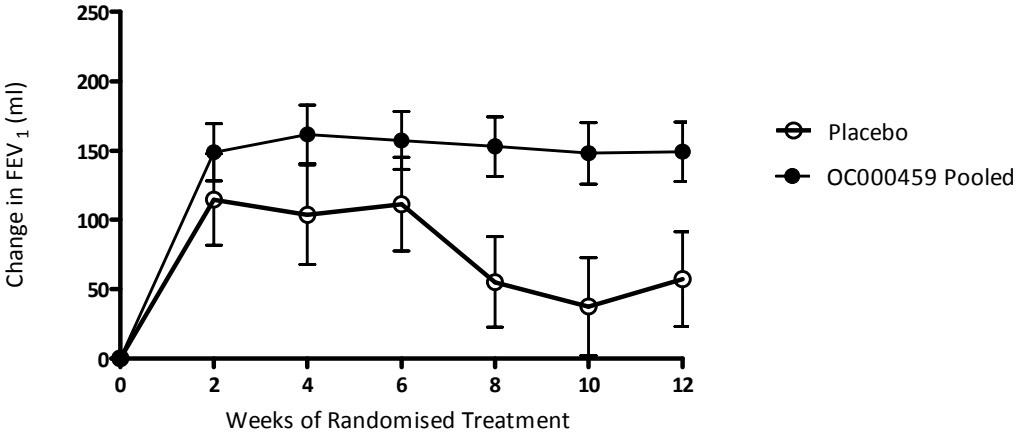

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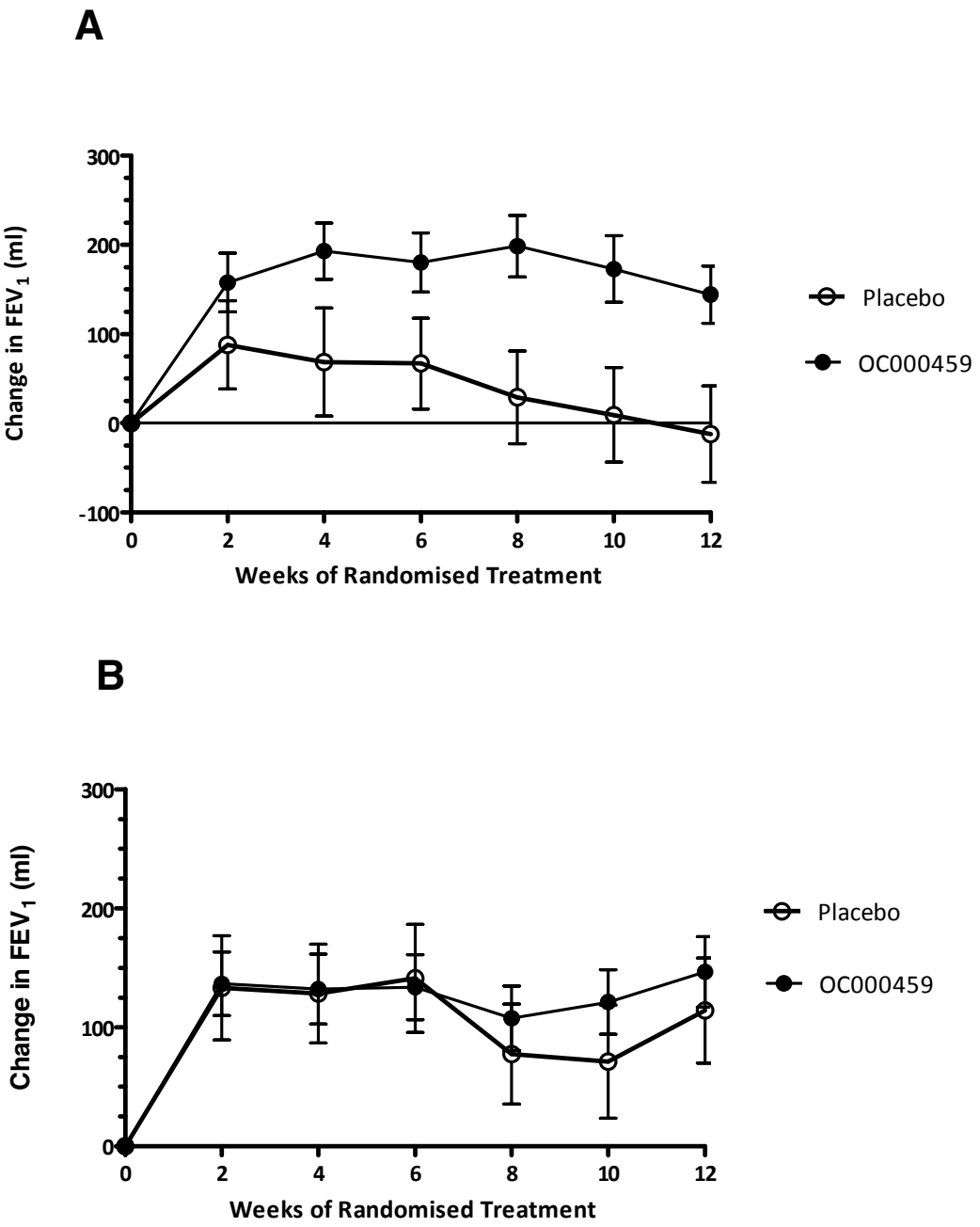

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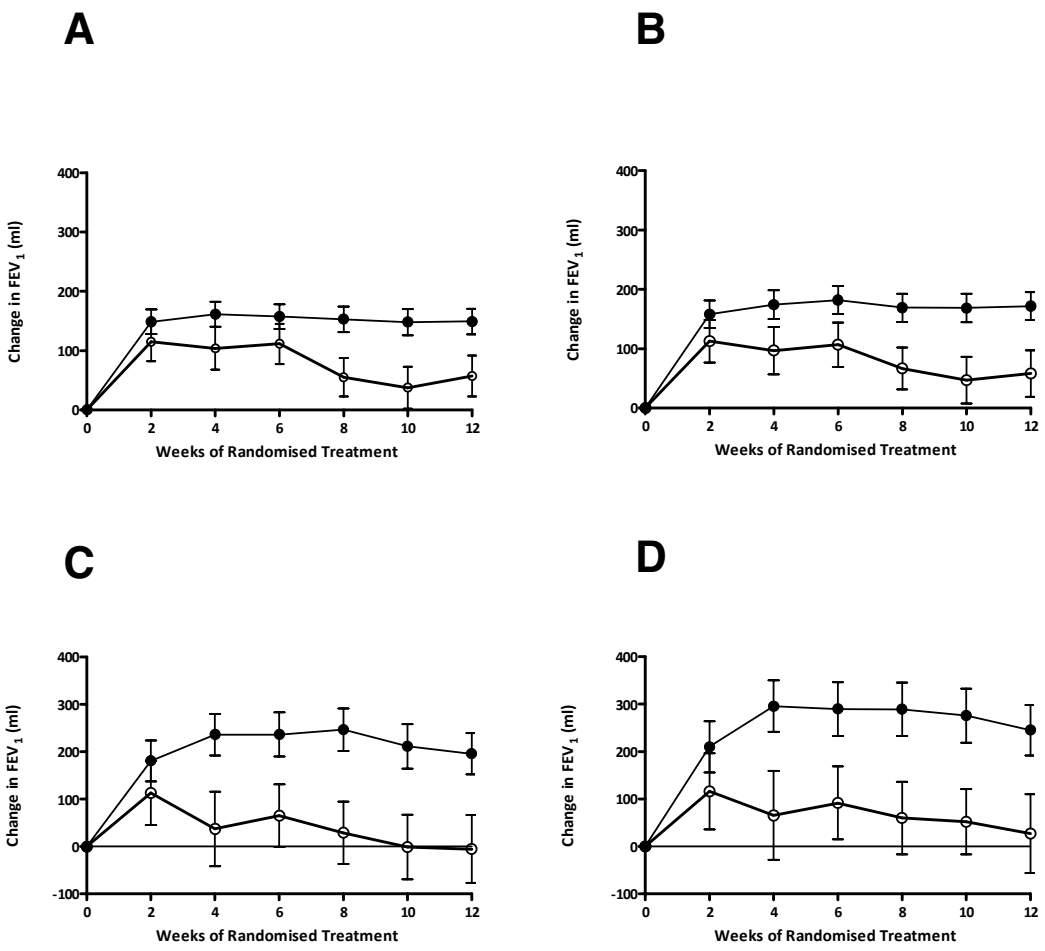

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