The Potent And Selective CRTH2 Antagonist OC000459 Is Effective In The Treatment Of Eosinophilic Asthma When Given Once Daily.

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Introduction

CRTH2 mediates activation of Th2 cells, type 2 innate lymphoid cells, eosinophils and basophils in response to prostaglandin D_2. The CRTH2 antagonist OC459 has been shown to reduce airway inflammation and improve lung function in a 1 month study of allergic asthmatics with moderate persistent disease (Barnes et al, 2012). The current study was conducted to determine whether OC459 was effective when dosed once a day over 3 months in a study population containing both allergic and non-allergic asthmatics. A post hoc analysis was performed to define the phenotype most responsive to treatment.

Method

The study was a randomized, placebo-controlled, double-blind parallel group study of 3 dose levels of OC459 in patients with mild-to-moderate persistent asthma (% FEV_1 60-85%). The study included steroid-free subjects allowed to use the short acting β_2 agonist salbutamol as a reliever therapy.

Adult subjects were randomized to OC459 (25 mg OD, 200 mg OD or 100 mg BD) or placebo for 12 weeks (n=117-125 per group). The primary endpoint was change from baseline in pre-bronchodilator FEV_1 and secondary endpoints included ACQ, AQLQ(S), incidence of exacerbations and respiratory infections. Change in FEV_1 was studied in atopic subjects with blood eosinophilia ≥250/µl.

ClinicalTrials.gov | Number. NCT00890877

Results

Effect of OC459 on FEV_1 in all comers

All doses of OC459 caused a similar improvement in FEV_1 (95 ml greater than placebo, p=0.024 from ANCOVA model)

	PLACEBO	OC000459			
		25 mg OD	100 mg BID	200 mg OD	Pooled
N	116	122	117	112	361
Mean (SD)	57 (369)	162 (377)	149 (484)	136 (357)	149 (408)
LSmean		176	158	141	158
P-value *		0.028	0.068	0.128	0.024

Effect of OC459 on ACQ and AQLQ(S)

Treatment with OC459 led to a significantly increased number of patients with a minimally important difference in ACQ and AQLQ(S), an effect that was more pronounced in the 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

Patient demographics

	PLACEBO	OC000459		
		25 mg OD	100 mg BD	200 mg OD
Full Analysis Set				
N	117	125	117	123
Male/Female	43/74	55/70	41/76	42/81
Age (years) Mean (SD) Min to max	40.4 (11.03) 19 to 55	40.4 (11.4) 18 to 55	38.9 (11.4) 18 to 55	39.7 (10.2) 18-55
Baseline FEV_1 (l) Mean (SD) Min to max	2.35 (0.58) 1.25 to 4.37	2.43 (0.57) 1.32 to 3.87	2.37 (0.54) 1.34 to 3.61	2.34 (0.55) 1.33 to 3.74

Study design

Primary end point

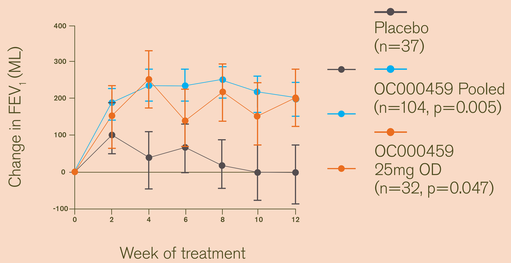
- To establish efficacy over a range of doses of OC459 on improvement in FEV_1.

Secondary end points

- Clinic FEV_1 and PEF
- Diaries: PEF, FEV_1 β_2-agonist use, symptoms.
- Juniper score (AQLQ(S),(ACQ)
- Safety and tolerability

Effect of OC459 in a subgroup of patients with uncontrolled atopic eosinophilic asthma

In skin prick test positive patients with uncontrolled (ACQ≥1.5) eosinophilic (blood eosinophils≥250/µl) asthma, each dose group caused a significant improvement in FEV_1 (with 199-244 ml difference compared to placebo across all the dose groups). The effect of the 25 mg OD dose group and the pooled dose group are shown below. An improvement of 220ml was observed in pooled dose group compared to placebo (p=0.005). Further improvements in FEV_1 were observed in younger patients – in eosinophilic patients aged ≤40 an increase in FEV_1 of 355 ml was seen vs placebo (p=0.007).



Effect of OC459 on respiratory tract infections

All dose groups caused a significant reduction in the incidence of respiratory tract infections.

	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)
Respiratory tract infections (%)	23.1	12.8*	13.7*	10.6*	12.3*

(* indicates statistically significantly reduced compared with placebo, p<0.05 using the log-rank test)

Conclusion

OC459 given once a day at a dose of 25 mg caused a substantial improvement in lung function in eosinophilic asthmatics with atopy, particularly in younger patients. Treatment with OC000459 was also associated with a reduction in respiratory tract infections, the dominant cause of exacerbations in asthmatic patients.

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References

Barnes N | Pavord I | Chuchalin A | Bell J | Hunter M | Lewis T et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. Clin Exp Allergy 2012; 42:38-48.