The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: RES100769
Title: A study to assess disease pathology and key therapeutic targets in severe asthma.
Rationale: This study was designed to validate key therapeutic targets and characterise their response to corticosteroids in severe asthma and other asthma phenotypes.
Phase: I
Study Period: 02-AUG-2005 to 06-JUN-2011.
Study Design: An open-label, parallel-group method study in subjects with asthma and healthy subjects.
Centres: One centre in the United Kingdom.
Indication: None.
Treatment: Subjects were recruited in four groups: (A) intermittent mild steroid-naïve asthma, (B) mild to moderate persistent asthma, (C) severe asthma and (D) healthy volunteers. The healthy volunteer group was renamed as Cohort E for the purposes of study reporting. Healthy volunteers were assessed at baseline; all asthma subject groups underwent a 2-week steroid trial with various assessments before (baseline) and after this trial. All subjects with asthma attended a screening visit (Visit 1) within 30 days of study start (baseline visit) and then went on to a 2-week run-in period immediately prior to the 2-week steroid trial. During this 2-week run-in period subjects continued their usual asthma therapy and were given a diary card to record their asthma symptoms and their concurrent medication, peak expiratory flow rate (PEFR) and any changes in clinical symptoms. On Day 1 (baseline visit/Visit 2/pre-steroid trial), these subjects underwent a series of baseline assessments including sputum induction and a bronchoscopy. Subjects then began the 2-week trial in which they received prednisolone 0.5 mg/kg/day or as close to this as possible using 5 mg tablets and rounding down to the nearest 5 mg. The steroid trial did not exceed the equivalent of 40 mg per day for 14 days. Subjects attended the unit at the end of the steroid trial (Visit 3, Days 13/14) for repeat assessments including bronchoscopy. Healthy volunteers attended a screening visit (Visit 1) followed by a visit for bronchoscopy (Visit 2) within 30 days. Healthy subjects were not required to take part in the 2-week steroid trial and were followed-up by phone within 14 days of the second visit.
Objectives: 1) To evaluate and compare the expression of key severe asthma targets at baseline such as interleukin (IL)-13, inhibitor of nuclear factor-kappaB kinase 2, p38 and chloride channel calcium-activated 1 across the three asthma groups and healthy subjects. 2) To evaluate and compare changes in the expression (from baseline) of key severe asthma targets in response to a 2-week course of corticosteroids (prednisolone) across the three asthma groups. 3) To evaluate and compare airway pathology across the three asthma groups and healthy subjects. 4) To evaluate and compare changes in airway pathology (from baseline) following a 2-week course of corticosteroids (prednisolone) in the three asthma groups.
Statistical Methods: The planned sample size of 100 subjects was based on logistical considerations and thus the study was not powered to detect statistically significant differences. All statistical analysis was therefore deemed to be exploratory in nature. No formal statistical hypothesis testing was conducted. Study population: Subject disposition, demographic and baseline characteristics, cell counts and protein biomarker data were summarised by cohort. The change in response post-treatment was summarised by cohort. Only subjects who had both pre-and post-prednisolone data present were included in these summaries: change in pulmonary function testing responses; change in plethysmography responses; change in biochemical marker data. Summaries by number of concurrent asthma medications were also produced for clinical and biochemical data. A summary by concurrent medications for key clinical and biomarker responses was made within the severe asthma cohort. Safety analyses: Safety data were summarised by cohort. For the purposes of study reporting, subject groups were renamed using the following conventions in order to be consistent with Study RES100767: Group A=Cohort A; Group B=Cohort B; Group C=Cohort C; Group D=Cohort E. The 'All Subjects' population comprised 55 subjects.
Study Population: All subjects were male or female and aged 18–65 years, inclusive. Subjects in the asthma groups had a history of diagnosed asthma documented for a minimum of 6 months prior to entry to the study, with exclusion of other significant pulmonary diseases.

Subjects in Group A (Cohort A) were planned to be as follows:
- Steroid-naïve with intermittent asthma (Global Initiative for Asthma 1 and 2) and forced expiratory volume in 1 second (FEV_1) ≥80% predicted
- Asymptomatic with normal PEFR between attacks
- Positive beta-2 agonist reversibility: >12% improvement on FEV_1 (or >200 mL improvement in FEV_1 within 30 minutes following salbutamol 400 mcg inhalation aerosol) or methacholine provocative concentration resulting in 20% reduction of FEV_1 (PC_{20}) <8 mg/mL
- Subjects were not taking regular inhaled steroids, although short-acting inhaled beta-2 agonists were allowed as concurrent medication
- Non-smokers for at least the previous 12 months with a pack history ≤5 pack years

Subjects in Group B (Cohort B) had mild to moderate persistent asthma symptoms and were receiving low to moderate inhaled steroid treatment (fluticasone propionate [FP] 200–500 mcg daily or equivalent). Short- and long-acting beta-2 agonists, anti-cholinergics and leukotriene receptor antagonists were allowed as concurrent medication. Subjects had an FEV_1 ≥80% predicted (post-bronchodilator), no daily symptoms of asthma and a PEFR variability <20%. Beta-2 agonist reversibility and non-smoking status was as for Group A.

Subjects in Group C (Cohort C) had uncontrolled asthma symptoms with daily symptoms and documented exacerbations at least twice a year in at least one of the last 2 years, and were taking high dose inhaled steroids (≥1000 mcg FP daily or equivalent) and/or oral steroids of ≤20 mg prednisolone a day or equivalent. Short- and long-acting beta-2 agonists, anti-cholinergics, leukotriene receptor antagonists and phosphodiesterase inhibitors were allowed as concurrent medication. Subjects were required to satisfy one (if on oral steroids) or two (if only on inhaled steroids) of the following conditions for their asthma control: FEV_1 ≤80% (post-bronchodilator) and FEV_1/forced vital capacity (FVC) ratio <70% predicted. Subjects had PEFR variability >25% and smokers were permitted in this group.

Subjects in Group D (Cohort E) were healthy non-smokers who did not have asthma.

Number of Subjects	Cohort B	Cohort C	Total asthma	Cohort E	Total
Planned N	20	50	85[a]	15	100[a]
Enrolled N	10	32	42	13	55[b]
Completed n (%)	4 (40)	29 (91)	33 (79)	11 (85)	44 (80)
Total Number Subjects Withdrawn N (%)	6 (60)	3 (9)	9 (21)	2 (15)	11 (20)
Withdrawn due to Adverse Events n (%)	0	1 (3)	1 (2)	0	1 (2)
Withdrawn for Other Reasons n (%)					
Subject Decided to Withdraw	4 (40)	2 (6)	6 (14)	1 (8)	7 (13)
Lost to Follow-up	1 (10)	0	1 (2)	0	1 (2)
Protocol Violation	1 (10)	0	1 (2)	0	1 (2)
Unable to Tolerate Bronchoscopy	0	0	0	1 (8)	1 (2)

a. No subjects were dosed in Cohort A (planned number was 15 subjects).
b. Recruitment was stopped after a total of 55 subjects had been enrolled, as the study had exceeded the anticipated time period planned for recruitment.

Demographics	Cohort B	Cohort C	Total asthma	Cohort E	Total
N (All Subjects)	10	32	42	13	55
Females: Males	7: 3	17: 15	24: 18	3: 10	27: 28
Mean Age in Years (SD)	38.2 (9.61)	46.7 (11.88)	44.7 (11.86)	39.7 (12.64)	43.5 (12.12)
Mean BMI in kg/m^2 (SD)	25.0 (3.96)	29.3 (7.37)	28.3 (6.92)	26.1 (5.11)	27.8 (6.56)
Not Hispanic or Latino n (%)					
African American/African Heritage	0	1 (3)	1 (2)	0	1 (2)
White/ Caucasian/European Heritage	10 (100)	31 (97)	41 (98)	13 (100)	54 (98)

Pre-treatment protein biomarkers: Geometric mean (SD logs) bronchoalveolar lavage (BAL) eotaxin-3 (pg/mL) was 10.39 (0.616) in Cohort B, 26.10 (0.772) in Cohort C and 4.97 (0.582) in Cohort E. Increases were also seen in BAL IL-1 beta, IL-8, interferon-inducible protein-10 (IP-10), monocyte chemotactic protein (MCP)-1, prostaglandin D2 (PGD2) and 'regulated on activation, normal T-cell expressed and secreted' (RANTES) for subjects with asthma compared with healthy subjects.

Levels of most serum protein biomarkers (eotaxin, IL-17F, IL-8, IL-23, IP-10, MCP-1, MCP-4, macrophage-derived chemokine [MDC], monocyte inflammatory protein-1 beta [MIP-1 beta], PGD2, thymus and activation-regulated chemokine [TARC]) were higher in Cohort C (n=15) than Cohort B (n=2). No serum protein biomarker results were reported in Cohort E.

Although subject numbers were relatively small, sputum MDC in subjects with asthma (n=14) was higher than in

healthy subjects (n=3). Geometric mean (SD logs) sputum MDC (pg/mL) was 594.24 (0.099) in Cohort B, 598.91 (0.320) in Cohort C and 155.51 (0.516) in Cohort E. Increases were also seen in sputum IL-1 beta and MIP-1 beta for subjects with asthma compared with healthy subjects.

Pre-treatment cell counts: Blood, sputum and BAL eosinophil percentages were generally higher in the asthma cohorts than in healthy subjects, most notably in Cohort C. Geometric mean (SD logs) blood eosinophil percentage was 2.72% (0.306) in Cohort B, 4.54% (0.262) in Cohort C and 2.25% (0.316) in Cohort E. Neutrophil percentages showed no consistent trends for blood, sputum and BAL between cohorts. Eosinophil counts in biopsy submucosa were higher in the asthma cohorts, with mean (SD) values of 3.08 cells/mm^2 (0.933) in Cohort B, 10.76 cells/mm^2 (0.576) in Cohort C and 2.23 cells/mm^2 (0.806) in Cohort E.

Pharmacodynamics (PD):

Clinical responses: Four subjects in Cohort C were responders based on an FEV_1 % predicted increase of ≥15% post-prednisolone. Three of these four subjects had high blood eosinophils [i.e., log blood eosinophil level >log(300) cells/uL] and one of the subjects had low blood eosinophils [≤log(300)] at pre-treatment. Mean percent predicted FEV_1 in Cohort C increased by 5.4% compared with pre-treatment, as did FVC, while PEFR increased by 5.7%. Mean percent predicted FVC in Cohort B increased by 3.2% compared with pre-treatment. In contrast, there was no notable increase in FEV_1 in Cohort B, and percent predicted PEFR decreased by 4.4%. Geometric mean specific airway conductance (sGaw) increased by 46% in Cohort C but only one subject in Cohort B had plethysmography data recorded. Methacholine PC_{20} increased by 75%, on average, across all subjects with asthma. Average exhaled nitric oxide decreased by 41%. Post-treatment changes in clinical responses (mean, SD) are summarised in the table below.

Parameter	Cohort B (N=10)	Cohort C (N=32)	Total asthma (N=42)
Pulmonary function tests (actual)			
FEV_1/FVC	-0.03 (0.06) [n=3]	0.00 (0.06) [n=28]	0.00 (0.06) [n=31]
FEV_1 (L)	0.00 (0.06) [n=3]	0.16 (0.22) [n=29]	0.15 (0.21) [n=32]
FVC (L)	0.12 (0.25) [n=3]	0.21 (0.39) [n=29]	0.20 (0.38) [n=32]
PEFR (L/min)	-18.44 (20.95) [n=3]	25.08 (52.09) [n=26]	20.58 (51.34) [n=29]
Plethysmography			
EPMax (cmH_2O)	3.0 [n=1]	7.0 (61.86) [n=11]	6.7 (58.99) [n=12]
IPMax (cmH_2O)	40.0 [n=1]	-5.5 (39.31) [n=11]	-1.7 (39.71) [n=12]
RV (L)	0.07 [n=1]	-0.29 (0.68) [n=12]	-0.26 (0.66) [n=13]
TLC (L)	0.26 [n=1]	0.04 (0.49) [n=12]	0.06 (0.47) [n=13]
sGaw (L/sec/cmH_2O)[a]	0.85 [n=1]	1.46 (0.35) [n=12]	1.40 (0.34) [n=13]
Methacholine challenge			
PC_{20} (mg/mL)[a]	1.71 (0.21) [n=3]	1.76 (0.68) [n=16]	1.75 (0.62) [n=19]
Exhaled NO (ppb)			
50 mL/sec[a]	0.55 (0.23) [n=4]	0.60 (0.21) [n=25]	0.59 (0.21) [n=29]

a. Presented as geometric mean (SD logs) ratio of post-treatment to pre-treatment.

Protein biomarkers: -There was a 32% decrease in sputum IL-1 beta following prednisolone treatment in Cohort C (n=5) compared with pre-treatment.

-A number of the serum analytes changed following prednisolone treatment. There were decreases of 28–59% in IP-10, MCP-1, MCP-4 and MDC in Cohort C (n=4) compared with pre-treatment.

-There was an 80% decrease in BAL eotaxin-3 in Cohort C (n=21).

Cell counts: -There was a 90% decrease in sputum eosinophil differential counts in Cohort C (n=5) compared with pre-treatment. There were increases of 40–140% in sputum epithelial cells, macrophages and neutrophils in Cohort C. Only one subject in Cohort B provided sputum cell count data.

-There was a 90% decrease in BAL eosinophil differential counts and a 120% increase in neutrophil differential counts in Cohort C (n=22) compared with pre-treatment. In Cohort B (n=4) there was a 33% decrease in BAL eosinophils and a 227% increase in neutrophils.

-There was a 90% decrease in blood eosinophil differential counts and a 20% increase in neutrophil differential counts in Cohort C (n=28) compared with pre-treatment. Similar results were obtained for Cohort B (n=3).

-There was a 90% decrease in bronchial wash eosinophil differential counts and a 60% increase in neutrophil differential counts in Cohort C (n=26) compared with pre-treatment. Only two subjects in Cohort B provided bronchial wash data.

Safety results: All AEs were recorded from the administration of first dose of investigational product until the follow-up visit. All SAEs were recorded from the time the subject signed the informed consent until the follow-up visit. The most frequently reported AEs are summarised below.

Preferred Term	Cohort B	Cohort C	Total asthma	Cohort E	Total
N (All Subjects)	10	32	42	13	55
No. subjects with AEs n (%)	2 (20)	6 (19)	8 (19)	0	8 (15)
Most frequent AEs n (%) (more than one subject)					
Chest discomfort	0	2 (6)	2 (5)	0	2 (4)
Headache	1 (10)	1 (3)	2 (5)	0	2 (4)
Lower respiratory tract infection	0	2 (6)	2 (5)	0	2 (4)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:					
	Cohort B	**Cohort C**	**Total asthma**	**Cohort E**	**Total**
No. Subjects with SAEs	0	2 (6) [0]	2 (5) [0]	0	2 (4) [0]
Asthma exacerbation	0	1 (3) [0]	1 (2) [0]	0	1 (2) [0]
Anaphylaxis	0	1 (3) [0]	1 (2) [0]	0	1 (2) [0]
Lower respiratory tract infection	0	1 (3) [0]	1 (2) [0]	0	1 (2) [0]