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: I13106870

Title : A multi-centre, randomized, double-blind, placebo-controlled, repeat-dose study to evaluate the efficacy and safety of intravenous GSK679586 in patients with severe asthma

Rationale: There is a significant unmet medical need for a treatment that is effective in controlling asthma symptoms in patients whose symptoms are not controlled by high dose inhaled corticosteroids (ICS). Accumulating data suggest that neutralization of interleukin-13 (IL-13) signaling may provide clinical benefit in these patients. The current study was intended to establish proof-of-concept with respect to the clinical efficacy of GSK679586, a humanized anti-human IL-13 monoclonal IgG1 antibody, in subjects with severe refractory asthma.

Phase: II

Study Period: 09 December 2008 to 19 July 2010

Study Design: Double-blind, randomized, placebo-controlled, multi-centre, multi-national

Centres: Subjects were enrolled and treated at 34 study centers in France (7 sites), the United States (6), the United Kingdom (4), Poland (5), South Africa (4), Germany (3), The Netherlands (3), and Norway (2).

Indication: Severe asthma

Treatment: Subjects received 3 once-monthly IV infusions of 10 mg/kg GSK679586 or a sodium chloride placebo, each administered over 1 hour.

Objectives: The primary objective was to evaluate the efficacy of repeat intravenous (IV) dose administration of GSK679586 in patients with severe asthma.

Statistical Methods: The ITT population comprised all subjects who received at least 1 dose of study medication, and was used for all efficacy and safety analyses. Change from baseline in ACQ-7 over 12 weeks (the primary endpoint) was analyzed using a mixed model for repeated measures (MMRM) that included data at 4, 8, and 12 weeks after the first dose. The model included fixed terms of treatment, visit, gender, and baseline oral corticosteroid (OCS) use; continuous covariates of baseline and age; subject as a random effect, and visit was the repeated measure term. An unstructured covariance matrix was used to model the error structure. No categorical covariate by treatment interaction was found to be significant at the 10% level. For each timepoint and overall, the adjusted mean change from baseline for each treatment group, and the adjusted treatment difference and 95% confidence intervals (CIs) were reported. Change from baseline at 2 weeks after the first dose were analyzed using an analysis of covariance (ANCOVA) model fitted with fixed categorical terms for treatment, gender, and baseline OCS use, and fixed continuous covariates for baseline and age. ACQ-6 and FEV1 were analyzed in similar manner to ACQ-7; a treatment*visit interaction was found to be statistically significant at the 10% level and was retained in the final model for FEV-1. Other efficacy data were summarized for all subjects by treatment and time (or time interval for diary data). Safety data were listed and summarized; no formal statistical analyses were performed.

The PK population comprised all subjects in the ITT population who provided a GSK679586 plasma PK concentration at one or more timepoints; all data available for these subjects at the time of the first database soft-lock were included in the population PK analysis. The full PK profile for each subject receiving GSK679586 was reconstructed from sparse PK sampling using Bayesian prediction obtained from a population PK model using non-linear mixed effects methods. Individual GSK679586 plasma concentrations and PK parameters estimated from the model were listed and summarized.

Study Population: Male and female subjects 18-75 years of age, inclusive, who had been diagnosed with asthma for ≥6 months and required ICS ≥500 μg/day or equivalent (with or without long-acting β-agonists [LABA]).

- Symptomatic (i.e. ACQ-7 ≥1.5) at screening and at the end of the run-in period during which each subject's ICS dose was increased to 1000 μg/day fluticasone propionate or equivalent (subjects already taking ≥ 1000 μg/day fluticasone propionate or equivalent remained on their pre-study dose).
- Pre-bronchodilator FEV1 >35% and <80% of predicted normal with ≥12% reversibility within 30 minutes after administration of short-acting β2-agonist.
- Up to 30% of enrolled subjects could be taking OCS maintenance therapy provided their usual daily dose was ≤25mg/day and ≥5mg/day prednisolone or equivalent.
- Subjects were excluded if they had received omalizumab within 4 months of the start of treatment.

Number of Subjects:	**Placebo**	**GSK679586**
Planned N	80	80
Dosed N	99	99
Completed n (%)	91 (92)	88 (89)
Total Number Subjects Withdrawn N (%)	8 (8)	11 (11)
Withdrawn due to Adverse Events n (%)	2 (2)	4 (4)
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for Other Reasons n (%)	6 (6)	7 (7)
Demographics	**Placebo**	**GSK679586**
N (ITT)	99	99
Females: Males	50: 49	48: 51
Mean Age in Years (sd)	51.2 (11.78)	51.2 (11.13)
Mean Weight in Kg (sd)	78.4 (15.93)	79.0 (13.78)
White n (%)	95 (96)	96 (97)

Efficacy, Pharmacokinetics (PK), Pharmacodynamics (PD), PK/PD, and Immunogenicity:
No statistically significant, clinically meaningful treatment differences were noted in ACQ-7 or FEV1. The treatment difference in the change from baseline over 12 weeks was -0.14 (p = 0.058) for ACQ-7 and -0.04 (p= 0.28) for FEV1.

Asthma exacerbations were reported by similar numbers of subjects in the GSK679586 group and placebo group during the treatment period and post-treatment period. For subjects in the GSK679586 group only, the number of exacerbations reported was higher during the post-treatment period (21 events) compared to the treatment period (14 events). No significant or potentially clinically meaningful differences between treatment groups were noted for other efficacy endpoints, or for the health outcomes measure (AQLQ).

GSK679586 plasma concentration-time data were well described by a 2-compartment model with first order elimination. Estimates of population PK parameters from the final model are presented in the table below.

Parameter	Estimate (95% CI)		BSV
CL (mL/day/kg)	2.33	(2.12, 2.56)	25.0%
V1 (mL/kg)	35.8	(33.2, 38.6)	37.9%
Q (mL/day/kg)	9.54	(5.70, 16.0)	NA
V2 (mL/kg)	29.6	(23.0, 38.1)	NA
RESIDUAL	0.381	(0.319, 0.434)	

BSV= between-subject variability

A majority of subjects in each treatment group had free serum IL-13 levels below LLQ at baseline, and free serum IL-13 levels remained below LLQ in most of these subjects throughout the study. Mean serum total IL-13 levels increased over time in the GSK679586 group (with measurable increases in serum total IL-13 observed for 51 of the 99 subjects, as defined by at least 2 measurements >2x the upper limit of normal), consistent with binding of free IL-13 by GSK679586 to form an antibody-cytokine complex. Mean serum total IL-13 was essentially unchanged over time in the placebo group. On average, treatment with GSK679586 did not lead to any change in serum total IgE concentration or blood eosinophil count over the 12 weeks of treatment.

No trends were apparent in plots of plasma GSK679586 concentrations versus serum total IgE and serum free IL-13 or plots of cumulative plasma GSK679586 AUC versus weighted mean (AUC/12 weeks) for ACQ-7, ACQ-6, and FEV1 over 12 weeks.

Seventeen subjects tested positive for anti-drug antibodies (ADAs) at one or more sampling timepoints. Of these 17 subjects, 6 subjects (2 active, 4 placebo) had treatment-emergent ADAs. The two GSK679586-treated subjects had confirmed positive ADA results at Day 169 (16 weeks after last study drug administration) and the final follow-up visit, with titers ≤ 16. Given that the 4 placebo subjects had occasional ADA titers of up to 128, the titers in GSK679586-treated subjects were considered low and unremarkable. The 17 subjects with a confirmed positive ADA result were also tested for neutralizing antibodies; all results were negative.

Safety results:
An adverse event (AE) was defined as an AE with onset after the first dose of study medication and on or before the follow-up visit. In addition, serious AEs (SAEs) that occurred at any time after a subject consented to participate in the study and prior to the first dose of study medication, and which were related to study participation, were also to be reported.

The most frequently reported AEs (i.e., those occurring in ≥3 subjects in the study) are summarized in the table below.

Adverse Events:	**Placebo**	**GSK679586**
N (ITT)	99	99
No. subjects with AEs n (%)	49 (49)	52 (53)
Most Frequent AEs		
Headache	6 (6)	13 (13)
Nasopharyngitis	5 (5)	10 (10)
Upper respiratory tract infection	6 (6)	4 (4)
Fatigue	3 (3)	4 (4)
Pharyngitis	2 (2)	5 (5)
Back pain	2 (2)	4 (4)
Diarrhoea	3 (3)0	3 (3)
Arthralgia	1 (1)	4 (4)
Dyspnoea	3 (3)	1 (1)
Hypertension	3 (3)	1 (1)
Myalgia	2 (2)	2 (2)
Sinusitis	3 (3)	1 (1)
Abdominal pain	1 (1)	2 (2)
Bronchitis	1 (1)	2 (2)
Laryngitis	3 (3)	0
Nausea	2 (2)	1 (1)
Oedema peripheral	1 (1)	2 (2)
Urinary tract infection	0	3 (3)
Vertigo	1 (1)	2 (2)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

Serious Adverse Events	**Placebo**	**GSK679586**
Asthma	2 (2) [0]	0
Colon cancer	0	2 (2) [0]
Bronchitis	1 (1) [0]	0
Cholecystitis	1 (1) [0]	0
Fall	1 (1) [0]	0
Hypertension	0	1 (1) [0]
Lethargy	0	1 (1) [1]
Morphine intoxication	0	1 (1) [0]
Myocardial infarction	0	1 (1) [0]
Rectal haemorrhage	0	1 (1) [0]
Rib facture	1 (1) [0]	
Supraventricular extrasystoles	0	1 (1) [1]
Wrist fracture	1 (1) [0]	0