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.

GSK Medicine: Vercirnon (GSK1605786A)

Study Number: CCX114151

Title: A Randomised, Double-blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GSK1605786A in the Treatment of Subjects with Moderately-to-Severely Active Crohn's Disease

Rationale: The purpose of this study was to assess the efficacy and safety of GSK1605786A compared with placebo as an induction therapy in subjects with moderately-to-severely active Crohn's disease over 12 weeks.

Phase: III

Study Period: 20 December 2010 – 11 July 2013

Study Design: This study was a multi-centre, randomised, double-blind, placebo-controlled, parallel group study. Following the screening period (max 5 weeks), approximately 600 eligible subjects were randomised in a 1:1:1 ratio at baseline (Week 0) to receive blinded treatment with one of two doses of GSK1605786A (500 mg once daily [QD] or 500 mg twice daily [BID]) or placebo for 12 weeks (treatment period). Treatment allocation was grouped by subjects who had ever received anti-tumour necrosis factor (TNF) therapy or not. Response and remission endpoints, using the Crohn's Disease Activity Index (CDAI), were evaluated at Weeks 4, 8 and 12. Subjects who met the definition of clinical responder (CDAI decrease of ≥100 points from baseline) or who were in clinical remission (CDAI score <150 points) at Week 12 were eligible for randomisation into a separate placebo-controlled maintenance study of 52 weeks (Study CCX114157). Subjects who completed the 12-week treatment period but did not meet the definition of responder or who were not in remission were eligible to enter a separate open-label extension study (Study CCX114644). Subjects who did not enter either of the long-term treatment studies returned for a Follow-up visit at Week 16. Post-study treatment for Crohn's disease was determined at the discretion of the Investigator.

Centres: This study was conducted at 162 centres in 23 countries with sites in North America, Europe, Israel, South Africa, Japan, Australia, Korea and New Zealand.

Indication: Crohn's disease

Treatment: Subjects were assigned to blinded treatment with GSK1605786A capsules (500 mg QD or BID), or placebo for 12 weeks.

Objectives: The primary objective was to assess the efficacy of GSK1605786A compared with placebo as an induction therapy in subjects with moderately-to-severely active Crohn's disease over 12 weeks.

Primary Efficacy Endpoint: The proportion of subjects achieving clinical response, defined by CDAI decrease from baseline of ≥100 points, at Week 12.

Key Secondary Efficacy Endpoint: The proportion of subjects in clinical remission, defined as a CDAI score of <150 points, at Week 12.

Statistical Methods:

Analysis Populations:

The Intent-to-Treat (ITT) population consisted of all subjects randomised to double-blind treatment for 12 weeks. This population was the primary population for the analyses of efficacy measures.

The Safety population consisted of all subjects in the ITT population except those who did not take at least one dose of investigational product. This population was the primary population for safety analyses.

Efficacy Analysis:

For the primary efficacy endpoint (clinical responders at Week 12) and key secondary efficacy endpoint (clinical remission at Week 12), the proportion and 95% confidence interval (CI) using the normal approximation to the binomial distribution was summarized by treatment group. The difference of proportions and 95% CI using the normal approximation to the binomial distribution between each GSK1605786A dose group and placebo was calculated. Proportions of responders between each GSK1605786A dose group and placebo were compared using a Mantel-Haenszel test stratified by prior anti-TNF use.

Safety Analysis:

Safety endpoints were summarized descriptively. The number and percentage of subjects who reported at least one AE in a system organ class and preferred term category, and the total number and percentage of subjects with any AE over all system organ classes were summarised by treatment group.

Study Population:
Key inclusion criteria included having a diagnosis of Crohn's disease for at least 4 months with a documented history of disease in the small bowel and/or colon, and characterised by a CDAI score of ≥220 to ≤450 (at Week 0) with a history of inadequate response or intolerance to Crohn's disease treatment with corticosteroids or immunosuppressants. All subjects were required to have a diagnosis with identification of anatomic location of Crohn's disease, which had been established by visualisation of the gastrointestinal tract within 12 months of screening. Subjects were also required to have evidence of current active inflammation at the time of randomisation confirmed by either endoscopy (adjudicated by a central reader) or by inflammatory biomarkers (elevated C-reactive protein [CRP] greater than the upper limit of normal plus an elevated level of faecal calprotectin).

Key exclusion criteria included known coeliac disease,(those who followed a gluten-free diet to manage symptoms of suspected coeliac disease and subjects with a positive screening test for coeliac disease [elevated anti-tissue transglutaminase antibodies]); diagnosis of ulcerative or indeterminate colitis; enterocutaneous, abdominal or pelvic fistulae with abscesses or fistulae likely to require surgery during the study period; bowel surgery, other than appendectomy, within 12 weeks prior to screening and/or had surgery planned or deemed likely for Crohn's disease during the study period; extensive colonic resection, subtotal or total colectomy; presence of ileostomies, colostomies or rectal pouches; fixed symptomatic stenoses of small bowel or colon; and history of more than 3 small bowel resections or diagnosis of short bowel syndrome. Positive test results for hepatitis B and C and tuberculosis (TB) using Quantiferon TB Gold were also exclusionary.

Subject Disposition

	Placebo	**GSK1605786A 500 mg QD**	**GSK1605786A 500 mg BID**
Number of Subjects:			
Planned, N	200	200	200
Randomised, N	203	203	202
Completed, n (%)	158 (77.8)	144 (70.9)	153 (75.7)
Total Number Subjects Withdrawn, N (%)	45 (22.2)	59 (29.1)	49 (24.3)
Withdrawn due to Adverse Events, n (%)	26 (12.8)	25 (12.3)	21 (10.4)
Withdrawn due to Lack of Efficacy, n (%)	8 (3.9)	20 (9.9)	12 (5.9)
Withdrawn for other reasons, n (%)	11 (5.4)	14 (6.9)	16 (7.9)

Demographics

	Placebo	**GSK1605786A 500 mg QD**	**GSK1605786A 500 mg BID**
N (ITT)	203	203	202
Females: Males	103:100	130:73	106:96
Mean Age, years (SD)	36.1 (12.62)	37.0 (12.60)	35.9 (12.51)
White, n (%)	177 (87.2)	177 (87.2)	179 (89.5)
Prior Anti-TNF use, n (%)	141 (69.5)	143 (70.4)	138 (68.3)
Baseline CDAI score, mean (SD)	313.7 (57.71)	314.6 (59.15)	321.8 (59.30)

Primary Efficacy Results:

CDAI Response (ITT Population)	**Placebo N=203**	**GSK1605786A 500 mg QD N=203**	**GSK1605786A 500 mg BID N=202**
n (%)	51 (25.1)	56 (27.6)	55 (27.2)
95% CI	19.2%, 31.1%	21.4%, 33.7%	21.1%, 33.4%
Treatment Difference (95% CI)	-	2.5% (-6.1%, 11.0%)	2.1% (-6.5%, 10.7%)
p-value		0.546	0.648

Key Secondary Efficacy Results:			
CDAI Remission (ITT Population)	**Placebo N=203**	**GSK1605786A 500 mg QD N=203**	**GSK1605786A 500 mg BID N=202**
n (%)	31 (15.3)	27 (13.3)	26 (12.9)
95% CI	10.3%, 20.2%	8.6%, 18.0%	8.3%, 17.5%
Treatment Difference (95% CI)	-	-2.0% (-8.8%, 4.8%)	-2.4% (-9.2%, 4.4%)
Safety Results: On-therapy adverse events (AEs) and serious adverse events (SAEs) were defined as an AE or SAE, respectively, with onset on or after the start of study treatment. SAEs related to study participation were collected from the time of informed consent and those occurring prior to the treatment start date were referred to as Pre-treatment SAEs.			
Most Frequent Adverse Events– On-Therapy (Safety Population) (the most frequent 10 events in each treatment group) **Preferred term, n (%)**	**Placebo N=202**	**GSK1605786A 500 mg QD N=202**	**GSK1605786A 500 mg BID N=201**
Subjects with any AE(s)	141 (69.8)	148 (73.3)	157 (78.1)
Headache	31 (15.3)	32 (15.8)	28 (13.9)
Abdominal pain	14 (6.9)	18 (8.9)	22 (10.9)
Crohn's disease	18 (8.9)	20 (9.9)	15 (7.5)
Nasopharyngitis	18 (8.9)	15 (7.4)	20 (10.0)
Nausea	14 (6.9)	19 (9.4)	18 (9.0)
Arthralgia	13 (6.4)	13 (6.4)	10 (5.0)
Dyspepsia	5 (2.5)	7 (3.5)	23 (11.4)
Vomiting	4 (2.0)	12 (5.9)	17 (8.5)
Pyrexia	8 (4.0)	10 (5.0)	10 (5.0)
Fatigue	4 (2.0)	9 (4.5)	10 (5.0)
Abdominal pain upper	8 (4.0)	9 (4.5)	5 (2.5)
Oropharyngeal pain	7 (3.5)	10 (5.0)	5 (2.5)
Dizziness	6 (3.0)	3 (1.5)	9 (4.5)
Serious Adverse Events - On-Therapy (Safety Population) **n (%) [n considered by the investigator to be related to study medication]**			
Preferred Term, **n (%) [related]**	**Placebo N=202**	**GSK1605786A 500 mg QD N=202**	**GSK1605786A 500 mg BID N=201**
Subjects with non-fatal SAEs	18 (8.9) [4]	12 (5.9) [7]	11 (5.5) [5]
Crohn's disease	5 (2.5) [2]	4 (2.0) [2]	1 (0.5) [0]
Abdominal pain	1 (0.5) [0]	1 (0.5) [1]	1 (0.5) [0]
Anal abscess	0	0	2 (1.0) [1]
Intestinal obstruction	1 (0.5) [0]	1 (0.5) [1]	0
Pyrexia	0	0	2 (1.0) [2]
Vomiting	0	0	2 (1.0) [1]
Acute myocardial infarction	0	0	1 (0.5) [0]
Anaemia	0	1 (0.5) [0]	0
Anal fissure	1 (0.5) [0]	0	0
Bacteraemia	0	1 (0.5) [0]	0
Body temperature increased	0	0	1 (0.5) [0]
Clostridium difficile colitis	0	1 (0.5) [0]	0
Clostridium difficile infection	1 (0.5) [0]	0	0
Constipation	0	0	1 (0.5) [1]
Depression	0	1 (0.5) [0]	0
Dyspnoea	1 (0.5) [0]	0	0

Enterovesical fistula	1 (0.5) [1]	0	0
Fistula	1 (0.5) [0]	0	0
Gastrointestinal stoma complication	1 (0.5) [0]	0	0
Haematochezia	1 (0.5) [0]	0	0
Hepatic enzyme increased	0	1 (0.5) [1]	0
Humerus fracture	0	0	1 (0.5) [0]
Ileus	1 (0.5) [0]	0	0
Intermittent claudication	0	1 (0.5) [0]	0
Intestinal fistula	1 (0.5) [1]	0	0
Lumbar radiculopathy	1 (0.5) [0]	0	0
Nausea	0	0	1 (0.5) [0]
Osteomyelitis	0	1 (0.5) [0]	0
Postoperative adhesion	1 (0.5) [0]	0	0
Prostatism	0	1 (0.5) [1]	0
Retinal detachment	1 (0.5) [0]	0	0
Salmonellosis	0	1 (0.5) [1]	0
Sepsis	1 (0.5) [0]	0	0
Subcutaneous abscess	1 (0.5) [0]	0	0
Subileus	1 (0.5) [0]	0	0
Urinary tract infection	0	0	1 (0.5) [0]
Varicella	1 (0.5) [0]	0	0
Subjects with fatal SAEs	0	0	1 (0.5) [0]
Cardiac arrest	0	0	1 (0.5) [0]
Coronary artery stenosis	0	0	1 (0.5) [0]
Ventricular fibrillation	0	0	1 (0.5) [0]

Conclusion:

- GSK1605786A (500 mg once daily and 500 mg twice daily) was not effective as an induction agent in the treatment of moderately-to-severely active Crohn's disease over 12 weeks. Non-significant treatment differences (active vs placebo) in the proportion of subjects achieving a clinical response (defined by CDAI decrease from baseline of ≥100 points) at Week 12 were observed for the 500 mg once daily and 500 mg twice daily treated groups (2.5% and 2.1%, respectively) compared with the placebo treated group (25.1% response rate); no dose response was observed.
- Non-significant treatment differences (active vs placebo) in the proportion of subjects achieving clinical remission (CDAI score <150 points) at Week 12 were observed for the GSK1605786A 500 mg once daily and GSK1605786A 500 mg twice daily treated groups (-2.0% and -2.4%, respectively) compared with the placebo treated group (15.3% response rate); no dose response was observed.
- In the placebo treated group 141/202 (69.8%) subjects reported non-serious adverse events with the most frequently reported being headache, Crohn's disease, nasopharyngitis, nausea, and abdominal pain. In the GSK1605786A 500 mg once daily treated group 148/202 (73.3%) subjects reported non-serious adverse events with the most frequently reported being headache, Crohn's disease, nausea, and abdominal pain. In the GSK1605786A 500 mg twice daily treated group 157/201 (78.1%) subjects reported non-serious adverse events with the most frequently reported being headache, dyspepsia, abdominal pain, and nasopharyngitis.
- In the placebo treated group 18/202 (8.9%) subjects reported serious non-fatal adverse events with the most frequently reported being Crohn's disease. In the GSK1605786A 500 mg once daily treated group 12/202 (5.9%) subjects reported serious non-fatal adverse events with the most frequently reported being Crohn's disease. In the GSK1605786A 500 mg twice daily treated group 11/201 (5.5%) subjects reported serious non-fatal adverse events with the most frequently reported being anal abscess, pyrexia, and vomiting.
- There was one fatality in the GSK1605786A 500 mg twice daily treated group, no fatalities in the GSK1605786A 500 mg once daily treated group and no fatalities in the placebo treated group.