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: GSK1399686

Study Number: MCA111407

Title: A Double-Blind, Double-Dummy, Placebo- and Active-Controlled Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Anti-Inflammatory Effects of GSK1399686 in Patients with Mild to Moderately Active Ulcerative Colitis

Rationale:
GSK1399686 is a novel locally-acting anti-inflammatory compound, consisting of a corticosteroid moiety that is covalently linked to a macrolide moiety. GSK1399686 is characterized by topical anti-inflammatory activity, which is not associated with typical glucocorticoid side-effects. Based on efficacy observed in several *in vivo* models of inflammation, including 2,4, 6-trinitrobenzene sulphonic acid (TNBS)-induced colitis, its non-clinical safety profile and anticipated low oral bioavailability in humans, GSK1399686 was being developed as an oral locally-acting drug for inflammatory bowel disease (IBD).
This study was the first-time-in-patient trial of GSK1399686, aimed at obtaining initial information on the tolerability, safety, pharmacokinetics and anti-inflammatory activity of GSK1399686 upon oral dosing in subjects with active ulcerative colitis

Phase: IIA

Study Period: 15Sep2009 to 29Jul2012

Study Design: This was a randomized, double-blind, double-dummy, placebo-controlled, dose escalating trial, with an active control group as internal control. Subjects with mild-moderately active ulcerative colitis not limited to the rectum were randomized to receive GSK1399686, placebo, or Asacol, respectively in a 3:1:1 ratio in one of four cohorts (Cohorts 1 to 4). In all cohorts, GSK1399686 (or placebo) was dosed once daily (QD), in the morning, over 28 days and Asacol (or placebo) three times a day (t.i.d) over six weeks. A double-dummy design was applied to mask the difference in dosing frequency and duration for the two treatments.

Up to four dose levels were planned for assessment; the starting dose level of GSK1399686 was 10 mg. Dose escalation occurred after assessment of adequate tolerability and safety results from the previous dose. A formal safety and efficacy interim analysis was performed at the end of the Cohort 3 (when four-week efficacy data from at least eight subjects treated with GSK1399686 was available). Based on results, the study was continued by recruiting an additional cohort of subjects.

Centres: Twenty one centres in Europe and five centres in Canada

Indication: Ulcerative colitis

Treatment: GSK1399686 was randomized with placebo and Asacol in a 3:1:1 ratio in Cohorts 1 to 4. Each dose of Asacol (or placebo) was administered three times daily, whereas each dose of GSK1399686 (or placebo) was administered QD in the morning. A double-dummy method was implemented to allow full blinding.

Objectives: Evaluate the Safety, Tolerability, Pharmacokinetics and Anti-Inflammatory Effects of GSK1399686 in Patients with Mild to Moderately Active Ulcerative Colitis

Primary Outcome/Efficacy Variable:

- Safety and tolerability as determined by:
  - Adverse events (AEs);
  - Treatment effects on blood pressure, heart rate, electrocardiography (ECG) parameters and haematology, clinical chemistry and urinalysis findings;
  - Treatment effects on basal morning cortisol and adrenocorticotropic hormone (ACTH)-stimulated cortisol levels at Week 4 in comparison with baseline.
- Concentration of GSK1399686 in colon biopsy obtained within 24 hours after the last dose.

Secondary Outcome/Efficacy Variable(s):

- SCCAI score over time (with and without* the component of general well being).
- Clinical response rate (proportion of subjects with SCCAI score decreased >2 points in comparison with baseline) at Week 4 and Week 6.
- Time to clinical response (defined as the number of days between the first dose of study medication and the first day of at least three consecutive days with SCCAI score decreased >2 points in comparison with baseline).

- Clinical remission rate (proportion of subjects with SCCAI score <3) at Week 4 and Week 6.
- Time to clinical remission, defined as the number of days between the first dose of study medication and the first day of at least three consecutive days with SCCAI score <3.
- Faecal calprotectin and faecal lactoferrin levels over time.
- PK parameters for GSK1399686 derived from observed plasma concentrations of GSK1399686 after repeated oral dosing:
    - The maximum observed concentration (Cmax) on Day 1 and Day 28;
    - Trough concentration ($C\tau$) on Day 28;
    - Plasma clearance and volume of distribution estimated based on population pharmacokinetic analysis of healthy volunteers (historical data) and subject data, if possible.

Statistical Methods:

Cohorts 1-4 were designed to primarily estimate the effect of GSK1399686 relative to placebo and an active control (Asacol) on safety and tolerability endpoints, and to estimate the effect of dose level on concentrations of GSK1399686 in colon biopsy.

The rectal and sigmoid colon concentrations of GSK1399686 were summarized by treatment, site and inflammation status (responder or non-responder based on endoscopy) in appropriate tables and plots. Plasma GSK1399686 concentration-time data was analyzed by non-compartmental methods with WinNonlin 5.1 or higher at the end of each cohort.

Study Population: Study participants were male or female subjects 18 years of age or older at the time of signing the informed consent, with mild-to-moderately active ulcerative colitis spread beyond the rectum (inflammation extending ≥15 cm from anal verge) as evidenced by clinical signs, endoscopy and a Ulcerative Colitis Disease Activity Index (UCDAI) score 4-10 (inclusive) with rectal bleeding score ≥1, endoscopy score ≥1 and Physician's rating of disease activity <3.

Number of Subjects	Placebo	GSK1399686				Asacol
		10 mg	30 mg	100 mg	300 mg	

Number of subjects planned, N:	12	12	12	12	12	12
Number of subjects randomized, N:	15	11	12	12	12	16
Number of subjects included in All subjects (safety) population, n (%):	15 (100%)	11 (100%)	12 (100%)	12 (100%)	12 (100%)	16 (100%)
Number of subjects included in rectal PK population, n (%):	NA	11 (100%)	12 (100%)	12 (100%)	12 (100%)	NA
Number of subjects completed as planned, n (%):	13 (87%)	7 (64%)	8 (67%)	10 (83%)	9 (75%)	13 (81%)
Number of subjects withdrawn (any reason), n (%):	2 (13%)	4 (36%)	4 (33%)	2 (17%)	3 (25%)	3 (19%)
Number of subjects withdrawn for SAE, n (%):	1 (7%)	2 (18%)	0	0	0	1 (6%)
Number of subjects withdrawn for AE, n (%):	1 (7%)	3 (27%)	2 (17%)	1 (8%)	0	2 (13%)
Reasons for subject withdrawal, n (%)						
Lack of efficacy	1 (7%)	1 (9%)	1 (8%)	0	1 (8%)	1 (6%)
Adverse events	1 (7%)	3 (27%)	2 (17%)	1 (8%)	0	2 (13%)
Investigator discretion	0	0	1 (8%)	0	0	0
Withdrew consent	0	0	0	1 (8%)	2 (17%)	0
Demographics						
Age in Years, Mean (SD)	43.0 (13.56)	51.9 (9.59)	53.4 (13.53)	39.0 (11.17)	42.0 (13.99)	47.8 (13.34)
Sex, n (%)						
Female:	2 (13%)	5 (45%)	2 (17%)	2 (17%)	5 (42%)	8 (50%)
Male:	13 (87%)	6 (55%)	10 (83%)	10 (83%)	7 (58%)	8 (50%)
BMI (kg/m^2), Mean (SD)	24.5 (3.81)	25.8 (2.33)	27.1 (5.29)	26.3 (3.56)	24.2 (3.62)	27.0 (4.16)
Height (cm), Mean (SD)	181.3 (8.65)	174.4 (12.36)	173.6 (7.91)	174.0 (7.52)	172.3 (10.65)	172.8 (14.18)
Weight (kg), Mean (SD)	83.9 (14.70)	78.7 (11.55)	82.1 (18.48)	79.7 (12.54)	72.5 (16.22)	81.2 (17.70)
Ethnicity, n (%)						
Hispanic or Latino:	0	2 (18%)	1 (8%)	0	0	2 (13%)
Not Hispanic or Latino:	15 (100%)	9 (82%)	11 (92%)	12 (100%)	12 (100%)	14 (88%)
Race, n (%)						
African American/African Heritage	0	0	0	2 (17%)	0	1 (6%)
Asian – Central / South Asian Heritage	1 (7%)	0	0	0	1 (8%)	1 (6%)

Asian – South East Asian Heritage	0	0	0	0	0	1 (6%)
White – White/Caucasian/European Heritage	14 (93%)	11 (100%)	12 (100%)	10 (83%)	11 (92%)	13 (81%)

Conclusions: Safety

- There were no obvious safety concerns from study MCA111407.
- The ACTH data was difficult to interpret.

Pharmacokinetic

- The plasma and colonic exposure was highly variable in patients
- While GSK1399686 does reach the systemic circulation, GSK1399686 does not appear to reach the colonic mucosa in sufficient concentrations to achieve local activity with the current formulation.

Efficacy

- There was no robust evidence of efficacy using a variety of biomarker or clinical endpoints (even in a subset of patients with more severe disease at baseline [endoscopic score >1, calprotectin >150µg/g, SCCAI ≥5]).
- The efficacy signal seen at the interim analysis was not apparent with full data set.
- The clinical trial design was responsive since some benefit was detected with Asacol (internal control) on most clinical endpoints (at 6 weeks).