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: OSM104972

Title : A randomised, double-blind, placebo-controlled, Bayesian adaptive dose finding study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat intravenous infusions of GSK315234A in patients with active rheumatoid arthritis (RA)

Rationale: OSM104972 was a proof of concept study. Administration of GSK315234 [an anti-human Oncostatin M (OSM) IgG1 monoclonal antibody] to patients with active RA was expected to reduce the signs and symptoms of RA due to the inflammatory effects of OSM, reduce pannus formation and synovial cellular infiltrate, and reduce joint damage due to the destructive effects of OSM on cartilage and bone.

Phase: II

Study Period: 21 April 2008 – 06 December 2010

Study Design: This was a 3-part (Parts A, B and C), multicenter study. Part A and Part B were randomised, double-blind, placebo-controlled, Bayesian adaptive dose finding studies to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of single (Part A) and 3 repeat (Part B) IV infusions of GSK315234 in subjects with active RA on a background of MTX. Part B was powered to detect a 0.95 unit DAS28 change from placebo. Part C was a single dose, randomised, single-blind, placebo-controlled study to assess the relative bioavailability of subcutaneously administered GSK315234 to subjects with active RA on a background of MTX

Centres: Twenty-two (22) investigative sites in 6 countries participated in the study. Twenty-one (21) sites in 5 countries screened at least one subject, but only 15 sites in 4 countries enrolled (i.e., dosed) one or more subjects.

Indication: Rheumatoid arthritis

Treatment: Eight (8) cohorts of 8 subjects each were enrolled in Part A (Cohorts 1 through 8) and randomized to GSK315234 (n=6) or placebo (n=2). Subjects in Part B were randomized to GSK315234 or placebo in a 2:1 ratio; each dose was administered approximately 4 weeks apart. Subjects in Part C were randomized on a 3:1 basis to GSK315234A or placebo. In Parts A, B and C, subjects received either GSK315234 or placebo in accordance with the randomization schedule prepared prior to the start of the study.

Treatment	Concentration/Form/Route	Frequency/Duration/Dose[1]	Batch Numbers
GSK315234	100 mg/mL / liquid / intravenously (Part A and Part B) or subcutaneously (Part C)	Part A: Single intravenous (IV) administration of 0.03, 0.06, 0.3, 3, 10, 20 and 30 mg/kg of GSK315234. Part B: Three (3) repeat IV administrations of 6 mg/kg GSK315234 each. Part C: Single subcutaneous (SC) administration of 500 mg of GSK315234 (5 SC injections of 1 mL each)	061119459 061129887 091234937
Placebo	Not applicable / liquid / intravenously or subcutaneously	Part A: Single IV administration Part B: Three (3) repeat IV administrations Part C: Single subcutaneous administration	071144412 091234940

1. In Parts A and B, study medication was administered intravenously at a fixed rate over 2 hours.

Objectives: The primary objectives were 1) to assess the safety and tolerability of GSK315234A after single and repeat IV infusions in subjects with active RA on a background of methotrexate (MTX); 2) to assess the effect of GSK315234A on disease activity [as defined by Disease Activity Score (DAS) 28 score] on Day 28 after a single IV infusion in subjects with active RA on a background of MTX (Part A); and 3) to assess the effect of GSK315234A on disease activity (as defined by DAS 28 score) on Day 56 in subjects with active RA on a background of MTX (Part B and Part C).

Statistical Methods: The primary safety endpoints included adverse events (AEs), vital signs [heart rate (HR) and

blood pressure (BP)], electrocardiograms (ECGs) and clinical laboratory tests (haematology, biochemistry and urinalysis). Extent of exposure including the total volume administered during the infusions (Part A and B) or injections (Part C) were summarised. AEs were summarised by frequency and proportion of total subjects (number of patients) by each treatment group. Vital signs/values of 12-Lead ECG and changes from baseline were summarised by treatment group at each time point. Summary statistics of clinical laboratory data at each time point and changes from baseline were provided for chemistry data and haematology data. Haematological events were graded using an OMERACT (Outcome Measures in Rheumatology) Rheumatology Common Toxicity Criteria scale. Chemistry events were graded using CTCAE criteria scale.

The primary efficacy endpoints were DAS28 scores on Day 28 (Part A) and DAS28 scores on Day 56 (Part B and Part C). A repeated measure analysis was used to analyze the mean change from baseline in DAS28 scores.

Study Population: Eligible subjects were males or females between 18 and 75 years of age (inclusive) with a body mass index between 18.5 and 35 kg/m^2 (inclusive) and a diagnosis of RA according to the revised 1987 criteria of the ACR; subjects did not receive prior treatment with any biological therapy. Subjects also had a DAS28 disease activity score of >4.2 at screening and pre-dose, a CRP serum level of ≥0.5 mg/dl or an ESR level ≥28 mm/hour at screening and pre-dose.

Number of Subjects:

	Part A	Part B	Part C
Number of subjects planned, N:	64	54	16
Number of subjects randomized, N:	64	54	17
Number of subjects included in the safety population, n (%):	64 (100)	54 (100)	16 (100)
Number of subjects included in PK population, n (%):	64 (100)	54 (100)	16 (100)
Number of subjects completed as planned, n (%):	64 (100)	51 (94.4)	16 (100)
Number of subjects withdrawn (any reason), n (%):	0	3 (5.6)	1 (6)
Lack of efficacy	0	1 (1.85) [1]	0
Investigator discretion	0	1 (1.85) [2]	0
Subject withdrew consent	0	1 (1.85) [1]	0
Protocol violation (DAS28 <4.2 at pre-dose)	0	0	1 (6) [1]

1. Placebo group
2. GSK315234 (6 mg/kg) group

Demographics:

	Part A	Part B	Part C
Age in Years, Mean (SD)	52.8 (9.90)	55.3 (10.06)	54.7 (13.49)
Gender, n (%)			
Female:	47 (73)	37 (68.5)	15 (88)
Male:	17 (27)	17 (31.5)	2 (12)
Height in cm, Mean (SD)	165.1 (9.24)	166.5 (9.39)	165.6 (10.0)
Weight in kg, Mean (SD)	71.74 (11.409)	73.69 (12.140)	77.51 (14.984)
BMI in kg/m^2, Mean (SD)	26.38 (4.050)	26.57 (3.709)	28.25 (4.641)
Ethnicity, n (%)			
Not Hispanic or Latino:	64 (100)	54 (100)	17 (100)
Race, n (%)			
White –White/Caucasian/European Heritage	64 (100)	54 (100)	17 (100)

Safety results:

Adverse event (AE) and serious adverse event (SAE) data were collected and recorded on the CRF starting at the time the consent form was signed and continuing until the end of the study (including any follow-up period). Overall, the most commonly reported AEs (occurring in 5 or more subjects) were worsening rheumatoid arthritis, alanine transferase elevation and pyrexia. All AEs were Grade 1, 2 or 3; there were no subjects with Grade 4 or higher AEs. There were more treatment-related AEs in the GSK315234 treated subjects (16/64, 25%) as compared to the placebo treated subjects (0%). AEs are summarized by study part below (any AE reported by ≥2 subjects):

	Part A - Number of Subjects (%)						
Preferred Term	**GSK315234 0.03/0.06mg/ kg IV (n=4)**	**GSK315234 0.3mg/kg IV (n=8)**	**GSK315234 3mg/kg IV (n=12)**	**GSK315234 10mg/kg IV (n=12)**	**GSK315234 20mg/kg IV (n=6)**	**GSK315234 30mg/kg IV (n=6)**	**Placebo (n=16)**
Any AE	2 (50)	2 (25)	7 (58)	6 (50)	5 (83)	4 (67)	4 (25)
Rheumatoid arthritis	0	0	1 (8)	1 (8)	2 (33)	0	2 (13)
Arthralgia	1 (25)	0	2 (17)	0	0	0	1 (6)
Blood pressure increased	1 (25)	0	0	1 (8)	2 (33)	0	0
Diarrhea	0	0	0	0	1 (17)	2 (33)	1 (6)
Pyrexia	0	0	1 (8)	1 (8)	1 (17)	0	1 (6)
Rash	0	1 (33)	1 (8)	1 (8)	0	1 (17)	0
ALT increased	0	1 (13)	1 (8)	0	0	1 (17)	0
Headache	0	0	0	0	2 (33)	1 (17)	0
WBC count increased	0	0	2 (17)	1 (8)	0	0	0
Anemia	0	0	0	0	2 (33)	0	0
Asthenia	1 (25)	0	1 (8)	0	0	0	0
AST increased	0	1 (13)	1 (8)	0	0	0	0
Bilirubin urine	0	0	0	1 (8)	1 (17)	0	0
Cough	0	0	0	1 (8)	0	0	1 (6)
CRP increased	1 (25)	0	0	0	0	1 (17)	0
GGT increased	0	1 (13)	0	0	1 (17)	0	0
Respiratory tract infection	0	0	1 (8)	1 (8)	0	0	0
Upper respiratory tract infection	0	0	0	1 (8)	0	1 (17)	0

	Part B - Number of Subjects (%)	
Preferred Term	**GSK315234 6mg/kg repeat IV (n=37)**	**Placebo (n=17)**
Any AE	15 (41)	4 (24)
Rheumatoid arthritis	4 (11)	1 (6)
Bronchitis	1 (3)	1 (6)
Nasopharyngitis	0	2 (12)

Preferred Term	Part C - Number of Subjects (%)	
	GSK315234 500mg SC (n=12)	Placebo (n=5)
Any AE	6 (50)	4 (80)
Dizziness	1 (8)	1 (20)

Efficacy Endpoints:

Although one of the primary endpoints in Part A was to assess the effect of GSK315234 on disease activity on Day 28, the data from Day 56 in Part A was thought to be more meaningful and is presented below. There was a significant difference in DAS28 between 3 mg/kg and placebo in Part A (adjusted mean was -0.71 and p-value was 0.0378) at Day 56. Part B was a repeat dose phase of the study and was powered to detect a 0.95 unit DAS28 change from placebo. No significant difference was detected on Day 56 in Parts B or C. The treatment comparisons and results for the analysis of the change from baseline in DAS28 at Day 56 are summarized by study part in the table below.

Part A					
Treatment Comparison[1]	**Day**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
0.3 / Placebo	Day 56	-0.27	0.39	(-1.03,0.50)	0.4913
3 / Placebo	Day 56	-0.71	0.34	(-1.39,-0.04)	0.0378
10 / Placebo	Day 56	-0.43	0.34	(-1.10,0.25)	0.2121
20 / Placebo	Day 56	-0.01	0.43	(-0.84,0.85)	0.9844
30 / Placebo	Day 56	-0.05	0.43	(-0.90,0.79)	0.8978
Part B					
Treatment Comparison	**Day**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
6 / Placebo	Day 56	-0.15	0.28	(-0.71,0.41)	0.5962
Parts A and B Combined					
Treatment Comparison	**Day**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
6 / Placebo	Day 56	-0.23	0.22	(-0.66,0.19)	0.2852
Part C					
Treatment Comparison	**Day**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
500 / Placebo	Day 56	-0.65	0.43	(-1.50,0.21)	0.1393

1. Statistical analysis was not performed for data from the 0.03/0.06 mg/kg dose level due to the small sample size.

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: 2 (1.5) [0]

Non-fatal SAEs were reported for 2 subjects. One subject in the 3 mg/kg group of Part A experienced an SAE of breast cancer. Another subject in Part B (6 mg/kg) experienced an SAE of acute sinusitis. Neither event was considered related to treatment with study medication.