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: GSK2586184
Study Number: JAK117171
Title: A two-part healthy volunteer study to investigate both the interaction of GSK2586184 with rosuvastatin and simvastatin and to compare the pharmacokinetics of two different formulations of GSK2586184.
Rationale: The purpose of this study was to evaluate the effect of repeated doses of GSK2586184 on the pharmacokinetics of simvastatin and rosuvastatin in healthy volunteers (Cohort A) and to assess both the impact of poloxamer excipient, and the dosing of GSK2586184 with/without food on the pharmacokinetics of GSK2586184 in healthy male volunteers (Cohort B).
Phase: I
Study Period: 04-OCT-2013 to 10-MAR-2014
Study Design: This was a single-centre, open-label study planned in 37 healthy volunteers. There were two study cohorts. Cohort A was a single sequence dual statin drug interaction study in healthy male and female volunteers, planned to comprise evenly of 14 male and 14 female subjects. Subjects were to reside within the unit for 16 days/15 nights. All subjects were to receive single doses of simvastatin (10 mg) and rosuvastatin (10 mg) on two occasions, once alone and once following administration of repeated doses of GSK2586184 (400 mg BID). PK parameters of simvastatin were to be monitored for 48h following each dose of simvastatin and PK parameters of rosuvastatin were to be monitored for 72h following each dose of rosuvastatin. Steady state pharmacokinetic parameters of GSK2586184 were also to be assessed in this cohort. Cohort B was a randomised 3-way crossover PK study planned in 9 healthy male volunteers (3 subjects per treatment sequence). Subjects were to reside within the unit for 9 days/8 nights. Each subject was planned to receive a single dose of the standard formulation (containing poloxamer) of GSK2586184 (400 mg) following a FDA approved high fat breakfast and two separate doses (400 mg) of a new formulation of GSK2586184 (without poloxamer), once following a FDA approved high fat breakfast and once in a fasted state, according to their treatment sequence, with a 3-day wash out between doses. Pharmacokinetic parameters were to be measured for GSK2586184 for 24h following each dose and additionally at +48h and +72h during the wash out phase following the first two doses. The circulating levels of 2 metabolites, GSK2983628 and GSK3100466 were also to be assessed alongside GSK2586184 at each time point where PK samples for GSK2586184 were analysed, for both Cohorts A and B. Two subjects from Cohort A were prematurely withdrawn from the study on day 14, due to a sponsor decision to terminate the study with immediate effect based upon review of emerging safety data from another study that did not support continued dosing of subjects with GSK2586184. Study dosing was discontinued on 24-FEB-2014 and all follow-up visits were completed by 10-MAR-2014.
Centre: PAREXEL (US) Baltimore, 3001 S. Hanover Street, Baltimore, Maryland, 21225, USA.
Indication: Systemic Lupus Erythematosus
Treatment: Cohort A (open label, single sequence): GSK2586184 400 mg was administered orally (as tablets), with food, twice daily for 9 days (study days 6-14); simvastatin 10 mg was administered orally (as tablets) on two occasions (study day 1 and study day 10); rosuvastatin 10 mg was administered orally (as tablets) on two occasions (study day 3 and study day 12). Cohort B (open label, randomised): GSK2586184 400 mg (standard formulation containing poloxamer excipient, or new formulation without poloxamer, according to treatment sequence) was administered orally (as tablets), with or without food (according to treatment sequence), on three days (study days 1, 4 and 7).

Primary Objectives	Primary Endpoints
Cohort A (Statin DDI) • To determine the pharmacokinetic profile of rosuvastatin in the presence and absence of GSK2586184. • To determine the pharmacokinetic profile of simvastatin and simvastatin acid in the presence and absence of GSK2586184.	• AUC(0-∞), AUC(0-t) and Cmax of rosuvastatin alone and in the presence of GSK2586184. • AUC(0-∞), AUC(0-t) and Cmax of simvastatin/simvastatin acid alone and in the presence of GSK2586184.
Cohort B (Formulation and food effect) • To assess the influence of poloxamer on the pharmacokinetics of GSK2586184.	• AUC(0-∞), AUC(0-24), Tmax and Cmax of GSK2586184 (standard formulation, containing poloxamer) and GSK2586184 (new formulation, without-poloxamer).

• To assess the impact of dosing with and without food on a new formulation GSK2586184 tablet (without poloxamer).	• AUC(0-∞), AUC(0-24), Tmax and Cmax of GSK2586184 (new formulation, without-poloxamer) dosed with and without food.
Secondary Objectives	Secondary Endpoints
Cohort A (DDI) • To determine the pharmacokinetic profile of GSK2586184 at steady state - following administration of 400 mg BID. • To evaluate levels of metabolites GSK2983628 and GSK3100466 present during steady state GSK2586184 dosing.	 • AUC(0-12) and Cmax. • AUC(0-12) and Cmax of two metabolites of GSK2586184 (GSK2983628 and GSK3100466).
Cohort B (Formulation) • To evaluate pharmacokinetic profile of metabolites GSK2983628 and GSK3100466 following single dose of GSK2586184.	 • AUC(0-∞), AUC(0-24), Cmax, Tmax and t1/2 of two metabolites of GSK2586184 (GSK2983628 and GSK3100466).

Statistical Methods: Cohort A: A total of 28 subjects (14 males and 14 females) were to be enrolled such that at least 24 subjects would complete this part of the study. The sample size was primarily based on feasibility but also on the desire to estimate the treatment ratio with a reasonable precision.

Following $\log_e$-transformation, Cmax, AUC(0-∞) and AUC(0-t) of rosuvastatin, simvastatin and simvastatin acid were separately analysed using a mixed effects model with fixed effect terms for regimen (i.e. statin alone, statin + GSK2586184). Subjects were treated as random effects in the model. Point estimates and their associated two-sided 90 % confidence intervals were constructed for the differences, statin + GSK2586184 *vs* statin alone. The point estimates and their associated two-sided 90 % confidence intervals were then back-transformed to provide point estimates and two-sided 90 % confidence intervals for the ratios.

Cohort B: A total of 9 male subjects were to be enrolled such that at least 9 subjects would complete this part of the study. The sample size was primarily based on feasibility but also the desire to estimate the treatment ratio with a reasonable precision.

Following $\log_e$-transformation, Cmax, AUC(0-∞), AUC(0-24) and AUC(0-t) of GSK2586184 were separately analysed using a mixed effects model with fixed effect terms for treatment and period. Subjects were treated as random effects in the model. Point estimates and their associated two-sided 90 % confidence intervals were constructed for the following differences: 1) Without-poloxamer formulation *vs* standard formulation (containing poloxamer). 2) Without-poloxamer formulation (fasted) *vs* without-poloxamer formulation (fed).

Study Population: Healthy adult non-smoking males and females (of non-child bearing potential)* aged between 18 to 65 years (inclusive), with body mass index within the range 18 to 30 kg/m^2 (inclusive), were included in the study.
*Females were only eligible for Cohort A.

Number of Subjects	Cohort A	Cohort B
Planned, N	28	9
Randomised,[a] N	28	9
Completed, n (%)	22 (79)	9 (100)
Total Number Subjects Withdrawn, n (%)	6 (21)	0 (0)
Withdrawn due to Adverse Events n (%)	3 (11)	0 (0)
Withdrawn for other reasons n (%)	3 (11)	0 (0)
Demographics	**Cohort A**	**Cohort B**
Females, n (%)	14 (50)	0 (0)
Males, n (%)	14 (50)	9 (100)
Mean Age Males, years (SD)	36.6 (9.63)	34.0 (11.18)
Mean Age Females, years (SD)	53.4 (6.86)	-
BMI (kg/m^2), Mean (SD)	26.26 (2.719)	26.71 (2.042)
Height (cm), Mean (SD)	171.0 (9.95)	177.3 (6.73)
Weight (kg), Mean (SD)	77.02 (11.935)	84.21 (9.718)
African American/African Heritage, n (%)	18 (64)	9 (100)
White - White/Caucasian/European Heritage, n (%)	9 (32)	0 (0)
American Indian or Alaska Native, n (%)	1 (4)	0 (0)

a. Only Cohort B was randomised, Cohort A was open label, single sequence.

Primary Results:

Cohort A - Summary of Statistical Analysis of Derived Plasma Simvastatin Pharmacokinetic Parameters[b]

Parameter	Simvastatin SD + GSK2586184 BID		Simvastatin SD		Ratio	90% Confidence Interval	Sq Root MSE
	Geo. LSMean	n[d]	Geo. LSMean	n[d]			
AUC(0-t) (ug*hr/L)	5.1	23	7	27	0.73	(0.6005, 0.8943)	0.4
AUC(0-∞) (ug*hr/L)	7	16	9.9	19	0.71	(0.5808, 0.8599)	0.307
Cmax (ng/mL)	1.4	24	2.1	28	0.66	(0.4758, 0.9029)	0.658

Cohort A - Summary of Statistical Analysis of Derived Plasma Simvastatin Acid Pharmacokinetic Parameters[b]

Parameter	GSK2586184 BID + Simvastatin SD		Simvastatin SD		Ratio	90% Confidence Interval	Sq Root MSE
	Geo. LSMean	n[d]	Geo. LSMean	n[d]			
AUC(0-t) (ug*hr/L)	4.2	23	3.8	28	1.12	(0.8832, 1.4213)	0.475
AUC(0-∞) (ug*hr/L)	7.5	8	7.3	11	1.03	(0.6521, 1.6343)	0.498
Cmax (ng/mL)	0.8	24	0.7	28	1.07	(0.8471, 1.3434)	0.472

Cohort A - Summary of Statistical Analysis of Derived Plasma Rosuvastatin Pharmacokinetic Parameters[b,c]

Parameter	GSK2586184 BID + Rosuvastatin SD		Rosuvastatin SD		Ratio	90% Confidence Interval	Sq Root MSE
	Geo. LSMean	n[d]	Geo. LSMean	n[d]			
AUC(0-t) (ug*hr/L)	96.2	24	21.2	28	4.55	(3.9962, 5.1777)	0.264
AUC(0-∞) (ug*hr/L)	100.8	23	25.6	18	3.93	(3.3805, 4.5759)	0.244
Cmax (ng/mL)	13.7	24	2.1	28	6.64	(5.8425, 7.5452)	0.26

Cohort B - Summary of Statistical Analysis of Derived Plasma GSK2586184 Pharmacokinetic Parameters for two formulations of GSK2586184, under Fed conditions.

Parameter	GSK2586184 New formulation SD		GSK2586184 Standard formulation SD		Ratio	90% Confidence Interval	Sq Root MSE
	Geo. LSMean	n[d]	Geo. LSMean	n[d]			
AUC(0-24) (ug*hr/L)	7313.2	9	7568.5	8	0.97	(0.8901, 1.0490)	0.094
AUC(0-t) (ug*hr/L)	7229.3	9	7196.5	9	1	(0.9107, 1.1081)	0.118
AUC(0-∞) (ug*hr/L)	7332.7	9	7546.1	8	0.97	(0.9048, 1.0435)	0.078
Cmax (ng/mL)	1894.9	9	1871.7	9	1.01	(0.8181, 1.2529)	0.257
t1/2 (h)	2	9	1.8	8	1.12	(0.8990, 1.4011)	0.244

Cohort B - Summary of Statistical Analysis of Derived Plasma GSK2586184 Pharmacokinetic Parameters for GSK2586184 (New formulation) under Fed ***vs.*** Fasted conditions.

Parameter	GSK2586184 SD Fed		GSK2586184 SD Fasted		Ratio	90% Confidence Interval	Sq Root MSE
	Geo. LSMean	n[d]	Geo. LSMean	n[d]			
AUC(0-24) (ug*hr/L)	7313.2	9	4245.9	9	1.72	(1.5928, 1.8626)	0.094
AUC(0-t) (ug*hr/L)	7229.3	9	4342.6	9	1.66	(1.5092, 1.8363)	0.118
AUC(0-∞) (ug*hr/L)	7332.7	9	4787.7	5	1.53	(1.4054, 1.6691)	0.078
Cmax (ng/mL)	1894.9	9	779.8	9	2.43	(1.9637, 3.0073)	0.257
t1/2 (h)	2	9	9.7	5	0.21	(0.1592, 0.2717)	0.244

b. Cohort A subject 1026 withdrew from the study on day 9 due to an AE, however PK samples were taken on day 10. The day 10 samples for this subject have been excluded from the PK analyses.
c. Cohort A subjects 1027 and 1028 were withdrawn from the study on day 14, due to a sponsor decision to terminate the study early. The PK samples for both subjects are included in analysis and were complete apart from their final day 15 Rosuvastatin+GSK2586184 72hr sample, which was not taken.
d. Number of subjects contributing raw data to the model.

Secondary Outcome Results:

Cohort A - Summary of Log-Transformed Derived Plasma GSK2586184 PK Pharmacokinetic Parameters following GSK2586184 BID dosing.

Parameter	Geo. Mean (95% CI)	n	SD Logs	CVb (%)
AUC(0-12) (ug*hr/L)	8403.67 (6999.68,10089.28)	25	0.443	46.5

AUC(0-t) (ug*hr/L)	8399.95 (6996.08,10085.52)	25	0.443	46.6
Cmax (ng/mL)	1843 (1462.8,2322.0)	25	0.56	60.7

Cohort A - Summary of Log-Transformed Derived Plasma GSK2983628 (GSK2586184 Metabolite) Pharmacokinetic Parameters following GSK2586184 BID dosing.

Parameter	Geo. Mean (95% CI)	n	SD Logs	CVb (%)
AUC(0-12) (ug*hr/L)	56956.2 (49594.90,65410.12)	25	0.335	34.5
AUC(0-t) (ug*hr/L)	56952.6 (49590.56,65407.79)	25	0.335	34.5
Cmax (ng/mL)	6601.1 (5873.7,7418.6)	25	0.283	28.9

Cohort A - Summary of Log-Transformed Derived Plasma GSK3100466 (GSK2586184 Metabolite) Pharmacokinetic Parameters following GSK2586184 BID dosing.

Parameter	Geo. Mean (95% CI)	n	SD Logs	CVb (%)
AUC(0-12) (ug*hr/L)	4887.35 (4110.79,5810.61)	25	0.419	43.8
AUC(0-t) (ug*hr/L)	4887.35 (4110.79,5810.61)	25	0.419	43.8
Cmax (ng/mL)	522.8 (437.3,625.1)	25	0.433	45.4

Cohort B - Summary Statistics of Log-Transformed Derived Plasma GSK2983628 (GSK2586184 Metabolite).

Parameter	GSK2586184 Standard formulation SD Fed		GSK2586184 New formulation SD Fed		GSK2586184 New formulation SD Fasted	
	Geo. Mean (95% CI)	n	Geo. Mean (95% CI)	n	Geo. Mean (95% CI)	n
AUC(0-24) (ug*hr/L)	39081.71 (30537.82,50016.01)	9	37254.76 (29020.03,47826.19)	9	25540.82 (21749.32,29993.28)	9
AUC(0-t) (ug*hr/L)	42200.68 (30747.03,57920.94)	9	38893.42 (30466.85,49650.62)	9	32683.16 (24661.21,43314.54)	9
AUC(0-∞) (ug*hr/L)	45398.55 (33355.88,61789.07)	9	37828.36 (32845.03,43567.77)	8	36460.45 (27691.31,48006.55)	6
Cmax (ng/mL)	3410.1 (2883.9,4032.3)	9	3257.8 (2765.3,3838.0)	9	1569.9 (1342.3,1836.2)	9
t1/2 (h)	7.005 (5.910,8.304)	9	6.315 (5.332,7.478)	8	13.818 (9.657,19.772)	6

Cohort B - Summary Statistics of Log-Transformed Derived Plasma GSK3100466 (GSK2586184 Metabolite).

Parameter	GSK2586184 Standard formulation SD Fed		GSK2586184 New formulation SD Fed		GSK2586184 New formulation SD Fasted	
	Geo. Mean (95% CI)	n	Geo. Mean (95% CI)	n	Geo. Mean (95% CI)	n
AUC(0-24) (ug*hr/L)	4128.02 (2504.79,6803.17)	9	4041.94 (2533.37,6448.82)	9	2504.12 (1234.19,5080.78)	9
AUC(0-t) (ug*hr/L)	4490.95 (2633.47,7658.58)	9	4351.27 (2616.65,7235.79)	9	3167.33 (1488.02,6741.85)	9
AUC(0-∞) (ug*hr/L)	5944.89 (4634.07,7626.51)	7	5872.29 (4524.22,7622.06)	7	5868.23 (3361.49,10244.30)	4
Cmax (ng/mL)	290.3 (171.7,490.8)	9	283.7 (170.0,473.4)	9	142.3 (72.3,280.1)	9
t1/2 (h)	8.22 (7.458,9.073)	7	8.06 (7.099,9.170)	7	16.44 (8.261,32.736)	4

Safety Results: AEs were collected from the start of study treatment and until the follow-up contact. SAEs were collected over the same time period. In addition, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product were recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

Summary of AEs occurring in two or more subjects in any group	Cohort A	Cohort B
Most Frequent Adverse Events	n (%)	n (%)
Subjects with any AE(s), n (%)	15 (54)	1 (11)
Headache, n (%)	6 (21)	-
Somnolence, n (%)	3 (11)	-
Back pain, n (%)	3 (11)	-
Myalgia, n (%)	2 (7)	-
Catheter site pain, n (%)	2 (7)	-
Nausea, n (%)	2 (7)	-

Serious Adverse Events: One procedure-related serious adverse event (Thrombophlebitis septic) was recorded in Cohort A. This occurred in a single subject in Cohort A during the baseline statin dosing phase (day 4), this was not related to study treatment and GSK2586184 was not dosed to this subject. No serious adverse events occurred in Cohort B.
Conclusion: In Cohort A, decreases in PK parameters AUC(0-t), AUC(0-∞) and Cmax for simvastatin were observed following dosing of the statin in combination with GSK2586184 compared to when the statin was dosed alone. Increases in PK parameters AUC(0-t), AUC(0-∞) and Cmax were observed for rosuvastatin when dosed in the presence of GSK2586184 compared to dosing alone. The PK parameters for simvastatin acid were similar when simvastatin was dosed in combination with GSK2586184 compared to when the statin was dosed alone. In Cohort B, the comparison between the two different formulations of GSK2586184 (with and without poloxamer) resulted in similar PK parameters. In the evaluation of food effect, increases were observed in AUC(0-24), AUC(0-t), AUC(0-∞) and Cmax when GSK2586184 was dosed with food compared to fasted conditions. T1/2 was lower when GSK2586184 was dosed with food compared to fasted dosing. Overall, 15 subjects reported AEs in Cohort A and one subject reported an AE in Cohort B. One procedure-related SAE was reported in Cohort A, this was not considered related to study treatment.