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: SGN113391

Title: A single-center, randomized, two part, open-label, crossover study to assess the relative bioavailability and food effect of new formulations of GSK2248761 in healthy adult subjects

Rationale: The primary purpose of this study was to provide an estimate of the relative oral bioavailability of new candidate formulations of GSK2248761 in either the fed or fasted state in comparison to the current Gelucire capsule formulation dosing with food. The results of this study were to be used to guide the selection of one formulation to progress into late stage clinical development.

Phase: I

Study Period: 21 December 2009 to 08 March 2010

Study Design: Single-center, randomized, two-part, open-label, crossover study

Centers: One study center in the United States

Indication: Human immunodeficiency Virus Type 1

Treatment:
Part A:
Cohort 1:
Treatment A: GSK2248761 100mg Gelucire capsule administered with a moderate-fat meal
Treatment B: GSK2248761 100mg milled tablet (Formulation 1) administered fasted
Treatment C: GSK2248761 100mg milled tablet (Formulation 1) administered with a moderate-fat meal
Cohort 2:
Treatment A: GSK2248761 100mg Gelucire capsule administered with a moderate-fat meal
Treatment D: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered fasted
Treatment E: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered with a moderate-fat meal
Part B:
Treatment F: GSK2249761 100mg micronized tablet (Formulation 2) administered fasted
Treatment G: GSK2249761 100mg micronized tablet (Formulation 2) administered with a moderate-fat meal

Objectives: The primary objective of this study was to evaluate the single-dose relative bioavailability of up to three oral GSK2248761 formulations administered as single 100mg doses with and without a moderate fat meal compared to the current Gelucire formulation with a moderate fat meal.

Statistical Methods: Following loge-transformation, the PK parameters Cmax, AUC(0-t), AUC(0-∞), t1/2, and CL/F of GSK2248761 were separately analyzed using a mixed effects model with fixed effect terms for Period and Treatment for each cohort. Subject was treated as a random effect in the model. Point estimates and their associated 90% confidence intervals (CIs) were constructed for the differences, test treatments (B, C, D, E, F, or G)-reference treatment (A). Similar models were also used to assess the food effect for each of the test formulation, where point estimates and their associated 90% CIs were constructed for treatments C - B, E - D and G - F. The point estimates and their associated 90% CIs were then back-transformed to provide the ratios of GLS means and associated 90% CIs for the ratios of test/reference for the selected PK parameters.

Study Population: Healthy male or female subjects between 18 and 50 years of age inclusive, with a body weight ≥50kg for men and ≥45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).

Number of Subjects:	**Cohort 1**	**Cohort 2**	**Overall**
Planned N	12	12	24
Dosed N	12	12	24
Completed n (%)	12 (100)	12 (100)	24 (100)
Total Number Subjects Withdrawn N (%)	0	0	0
Demographics	**Cohort 1**	**Cohort 2**	**Overall**
N (Safety Population)	12	12	24
Females: Males	2 : 10	1 : 11	3 : 21
Mean Age in Years (sd)	35.7 (9.15)	29.1 (8.73)	32.4 (9.37)
Mean Weight in Kg (sd)	78.92 (10.191)	75.73 (8.509)	77.33 (9.324)
White n (%)	10 (83)	9 (75)	19 (79)

Pharmacokinetics (PK) Endpoints:

Summary of Selected Plasma GSK2248761 Pharmacokinetic Parameters[1]

Treatment	N	AUC(0-∞) (µg.hr/mL)	Cmax (µg/mL)	tmax (hr)[2]	t1/2 (hr)	C24 (µg/mL)
A	24	8.26 (32)	0.720 (26)	5.00 (3.00-8.00)	9.74 (33)	0.08 (46)
A (Cohort 1)	12	7.51 (27)	0.670 (22)	6.00 (3.00-8.00)	9.46 (36)	0.07 (39)
A (Cohort 2)	12	9.10 (34)	0.780 (29)	4.00 (3.00-8.00)	10.0 (31)	0.09 (52)
B	12[3]	6.42 (28)	0.450 (34)	2.50 (1.00-6.00)	13.2 (36)	0.08 (33)
C	12	9.67 (38)	0.960 (34)	4.00 (2.00-6.00)	7.71 (18)	0.07 (61)
D	12	13.3 (48)	1.39 (41)	3.00 (1.00-6.00)	7.49 (20)	0.11 (68)
E	12	14.7 (37)	1.79 (20)	4.00 (2.00-6.00)	6.89 (18)	0.09 (86)
F	12	9.66 (27)	0.850 (41)	2.50 (1.00-4.00)	10.6 (43)	0.10 (33)
G	12	12.6 (21)	1.62 (23)	2.00 (2.00-4.00)	6.76 (8)	0.07 (41)

1. Geometric Mean (cv%)
2. Median (range)
3. 11 subjects for AUC(0-∞) and t1/2

Treatment A: GSK2248761 100mg Gelucire capsule administered with a moderate-fat meal
Treatment B: GSK2248761 100mg milled tablet (Formulation 1) administered fasted
Treatment C: GSK2248761 100mg milled tablet (Formulation 1) administered with a moderate-fat meal
Treatment D: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered fasted
Treatment E: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered with a moderate-fat meal
Treatment F: GSK2249761 100mg micronized tablet (Formulation 2) administered fasted
Treatment G: GSK2249761 100mg micronized tablet (Formulation 2) administered with a moderate-fat meal

Summary of GSK2248761 Relative Bioavailability Analyses						
Plasma GSK2248761 PK Parameter	Ratio of GLS Means (90% CI)					
	Part A				Part B	
	B/A	C/A	D/A	E/A	F/A	G/A
AUC(0-∞)	0.869 (0.764, 0.990)	1.28 (1.12, 1.46)	1.46 (1.37,1.56)	1.62 (1.51, 1.72)	1.13 (1.03, 1.23)	1.47 (1.34, 1.61)
Cmax	0.666 (0.562, 0.789)	1.44 (1.21, 1.70)	1.78 (1.55, 2.05)	2.28 (1.98, 2.62)	1.16 (0.959, 1.39)	2.21 (1.84, 2.67)
C24	1.16 (0.968, 1.40)	0.907 (0.755, 1.09)	1.22 (1.03, 1.46)	1.03 (0.865, 1.23)	1.20 (1.04, 1.39)	0.844 (0.729, 0.976)

Summary of GSK2248761 Food Effect Analyses			
Plasma GSK2248761 PK Parameters	**Ratio of GLS Means (90% CI)**		
	Part A		**Part B**
	C/B	**E/D**	**G/F**
AUC(0-∞)	1.47 (1.29 ,1.68)	1.10 (1.04 ,1.18)	1.31 (1.17 , 1.47)
Cmax	2.16 (1.82 , 2.56)	1.28 (1.12 ,1.47)	1.92 (1.53 , 2.40)
C24	0.780 (0.650, 0.937)	0.844 (0.707, 1.01)	0.703 (0.589, 0.839)

Treatment A: GSK2248761 100mg Gelucire capsule administered with a moderate-fat meal
Treatment B: GSK2248761 100mg milled tablet (Formulation 1) administered fasted
Treatment C: GSK2248761 100mg milled tablet (Formulation 1) administered with a moderate-fat meal
Treatment D: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered fasted
Treatment E: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered with a moderate-fat meal
Treatment F: GSK2249761 100mg micronized tablet (Formulation 2) administered fasted
Treatment G: GSK2249761 100mg micronized tablet (Formulation 2) administered with a moderate-fat meal

Safety results: Adverse events were collected from the time of first dose to the end of follow-up. All adverse events reported in the study are presented below.

Adverse Events:	**A**	**B**	**C**	**D**	**E**	**F**	**G**
N (Safety Population)	24	12	12	12	12	12	12
No. subjects with AEs n (%)	5 (21)	1 (8)	0	4 (33)	1 (8)	2 (17)	0
Headache	2 (8)	1 (8)	0	2 (17)	1 (8)	1 (8)	0
Rectal hemorrhage	1 (4)	0	0	0	0	0	0
Influenza like illness	0	0	0	1 (8)	0	0	0
Nasopharyngitis	0	0	0	0	0	1 (8)	0
Post procedural complication	0	0	0	1 (8)	0	0	0
Musculoskeletal stiffness	0	0	0	0	0	1 (8)	0
Insomnia	1 (4)	0	0	0	0	0	0
Cough	1 (4)	0	0	0	0	0	0

Treatment A: GSK2248761 100mg Gelucire capsule administered with a moderate-fat meal
Treatment B: GSK2248761 100mg milled tablet (Formulation 1) administered fasted
Treatment C: GSK2248761 100mg milled tablet (Formulation 1) administered with a moderate-fat meal
Treatment D: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered fasted
Treatment E: GSK2248761 100mg wet bead milled capsule (Formulation 3) administered with a moderate-fat meal
Treatment F: GSK2249761 100mg micronized tablet (Formulation 2) administered fasted
Treatment G: GSK2249761 100mg micronized tablet (Formulation 2) administered with a moderate-fat meal

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: No serious adverse events were reported during this study.