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.: SGN113404

Title: A Phase 2b study to select a once daily oral dose of GSK2248761 administered with tenofovir/emtricitabine or abacavir/lamivudine in HIV-1 infected antiretroviral therapy naive adult subjects

Rationale: SGN113404 was designed to select the optimal once daily dose of GSK2248761 for Phase 3 studies and provide an early assessment of antiviral activity and durability of GSK2248761 in combination with backbone NRTIs. Efavirenz (EFV) in combination with tenofovir/emtricitabine or abacavir/lamivudine served as the control arm. This study was conducted in ART-naive HIV-1 infected subjects.

Phase: IIb

Study Period: 18 NOV 2010 – 04 JUL 2011

Study Design: Study SGN113404 was a phase 2b randomized, partially blinded, multicenter, parallel group, dose-ranging study. The study was to be conducted in approximately 150 HIV-1 infected ART naïve subjects. The background NRTIs to be co-administered with GSK2248761 or EFV were selected by Investigators prior to randomization and were either abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) fixed dose combination (FDC) tablets.

Subjects participated in a Screening period (Day -28 to Day -1). Subjects were randomized 1:1:1 to receive 100 mg of GSK2248761 once daily (50 subjects), 200 mg of GSK2248761 once daily (50 subjects) or 600 mg of EFV once daily (50 subjects). All three arms were combined with either 300 mg/200 mg TDF/FTC or 600 mg/300 mg ABC/3TC, as chosen by the Investigator. The Investigators and subjects were blinded to the dose of GSK2248761 being administered but knew whether they receive EFV or GSK2248761. The randomization was stratified by HIV-1 viral load (VL) at screening, <100,000 copies/mL or ≥100,000 copies/mL as well as the choice of backbone NRTI, TDF/FTC or ABC/3TC.

Analyses were planned for Week 4,16, 24, and 96. The Week 16 and Week 24 analyses were to be used respectively to select and confirm the optimal dose of GSK2248761 for continuation.

Enrollment in study SGN1133404 was terminated prematurely due to a safety finding (convulsion) in 5/20 subjects receiving GSK2248761 in the treatment experience partner study, SGN113399. There were no convulsions suffered during the conduct of SGN113404. All subjects taking GSK2248761 as of February 2, 2011 were instructed to discontinue GSK2248761 and by February 3, 2011, all subjects in SGN113404 had discontinued GSK2248761. Investigators were instructed to have all subjects return for follow-up at 1, 2, and 4 weeks after switching off GSK2248761. In a follow-up communication, investigators were instructed to withdraw all subjects from study SGN113404 as of April 1, 2011, and to conduct follow-up visits at 4, 8, and 12 weeks after study withdrawal.

Centres: A total of 6 Investigational sites enrolled subjects in Germany and France.

Indication: HIV infection

Treatment: Subjects randomized to GSK2248761 were to take GSK2248761 orally at 100mg or 200mg once daily. To blind subjects and investigators to the GSK2248761 doses, all subjects randomized to receive GSK2248761 took two tablets per day; those subjects receiving 200 mg per day received two active 100mg tablets and those subjects receiving 100mg per day received one active 100mg tablet and one matching placebo. Subjects randomized to EFV were to take 600 mg orally once daily. All subjects received either 300 mg/200 mg TDF/FTC or 600 mg/300 mg ABC/3TC as selected by the Investigator.

Objectives: To select a once daily dose of GSK2248761 for further evaluation in Phase 3 based on a comparison of the Week 16 antiviral activity and tolerability of two oral doses of GSK2248761 in HIV-1 infected therapy-naïve adult subjects.

Primary Outcome/Efficacy Variable: The endpoint for the primary efficacy comparison was the proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at Week 16.

Secondary Outcome/Efficacy Variable(s):

- Change in CD4+ cells
- Pharmacokinetic and pharmacodynamic parameters
- Development of viral resistance over time

- Assessment of safety and tolerability measures

Statistical Methods: The primary efficacy analysis was to be performed at Week 16 based on the proportion of subjects in the ITT-E population with plasma HIV-1 RNA <50 copies/mL according to the MSDF algorithm. This analysis was never preformed due to the early termination of the study. Instead we looked at the proportion of subjects in the ITT-E population with plasma HIV-1 RNA <50 copies/mL by visit according to the observed analysis while subjects were on randomized treatment and then also for visits after the subjects randomized to GSK2248761 switched to the control treatment. Other efficacy endpoints that were summarized included CD4+ cell counts. Measures of safety and tolerability were used to compare the doses as detailed in the RAP. The following AEs were summarized overall and by treatment group: all AEs, drug-related AEs, AEs by grade, serious SAEs, and AE withdrawals were summarized by randomized treatment.

Study Population:

	GSK2248761		EFV	Total
	100 mg	200 mg		
Number of Subjects:	8	7	8	23
Planned, N	50	50	50	150
Randomised, N	8	7	8	23
Completed, N	0	0	0	0
Total Number Subjects Withdrawn, N	8	7	8	23
Withdrawn due to Adverse Events, n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0
Study Terminated, n (%)	8 (100)	5 (71)	8 (100)	21 (91)
Withdrew Consent, n (%)	0	2 (29)	0	2 (9)
Demographics				
N (ITT-E)	8	7	8	23
Females: Males	0:8	1:6	0:8	1:22
Median Age, years (SD)	39.5 (24, 51)	33.0 (27, 44)	37.5 (25, 47)	37.0 (24, 51)
White/Caucasian/European, n (%)	7 (88)	7 (100)	8 (100)	22 (96)
IP Exposure (Weeks)				
Less than 2 weeks, n (%)	1 (13)	2 (29)	0	
Greater than or equal to 2 to 4 weeks, n (%)	4 (50)	2 (29)	0	
Greater than or equal to 4 to 8 weeks, n (%)	3 (38)	3 (43)	4 (50)	
Greater than or equal to 8 to 12 weeks, n (%)	0	0	1 (13)	
Greater than or equal to 12 to16 weeks, n (%)	0	0	3 (38)	

Primary Efficacy Results:

Due to the premature discontinuation of the study which limited both the number of subjects randomized as well as the duration of exposure, efficacy results are summarized using an Observed analysis and no comparisons by treatment arm have been performed. The proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit while on randomized treatment (ITT-E Population) is presented.

Proportion of Subjects Responding based on Plasma HIV-1 RNA <50 c/mL by Visit (ITT-E Population)	GSK2248761 100 mg	GSK2248761 200 mg	Efavirenz
Baseline, n/N (%)	0/8	0/7	0/8
Week 2, n/N (%)	0/8	0/5	0/8
Week 4, n/N (%)	1/5 (20)	0/4	3/8 (38)
Week 8, n/N (%)	0	1/1 (100)	3/8 (38)
Week 12, n/N (%)	0	0	2/4 (50)

Most Frequent Adverse Events – While Taking Randomized Therapy	GSK2248761 100 mg	GSK2248761 200 mg	GSK2248761 Subtotal	Efavirenz
Subjects with any AE(s), n (%)	6 (75)	5 (71)	11 (73)	8 (100)
Nightmare	0	2 (29)	2 (13)	3 (38)
Somnolence	1 (13)	1 (14)	2 (13)	0
Nasopharyngitis	1 (13)	0	1 (7)	3 (38)
Fatigue	1 (13)	0	1 (7)	1 (13)
Vertigo	1 (13)	0	1 (7)	2 (25)

Dizziness	0	0	0	6 (75)
Abnormal dreams	0	0	0	2 (25)
Diarrhoea	0	0	0	2 (25)
Nausea	0	0	0	2 (25)
Musculoskeletal stiffness	0	0	0	2 (25)
Subjects with Any Serious Adverse Events (SAE)				
Subjects with non-fatal SAEs, n (%)	1 (13)	0	1 (7)	1 (13)
Subjects with fatal SAEs, n (%)	0	0	0	0
Subjects with drug related SAE, n (%)	0	0	0	0

Conclusion:
SGN113404 was terminated prematurely due to an unexpected safety finding of convulsions in the concurrently run treatment-experienced study, SGN113399. The relatively short duration of GSK2248761 use in this study limits the ability to evaluate the standard HIV efficacy parameters of GSK2248761. The clinical development of GSK2248761 has been terminated.