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.: SGN113399

Title: A Phase 2b study to select a once daily oral dose of GSK2248761 in HIV-1 infected antiretroviral therapy experienced adults with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance

Rationale: SGN113399 was designed to select the optimal once daily dose of GSK2248761 and provide an early assessment of antiviral activity and durability of GSK2248761 in combination with DRV/r and RAL. Etravirine (ETV) in combination with DRV/r and RAL served as the control arm. This study was conducted in ART-experienced HIV-1 infected subjects with documented NNRTI resistance.

Phase: IIb

Study Period: 09 October 2010-19 July 2011

Study Design: Study SGN113399 is a Phase 2b randomized, partially-blinded, multicenter, parallel-group, dose-ranging study to be conducted in HIV-1 infected ART-experienced adults with documented NNRTI resistance. Subjects were randomized 1:1:1 to one of two GSK2248761 doses (100 mg or 200 mg once daily) or a control regimen containing ETV (200 mg twice daily); all subjects also received darunavir (DRV)/ritonavir (RTV) (600 mg/100 mg twice daily) and raltegravir (RAL) (400 mg twice daily). The trial was partially blinded, i.e. subjects receiving GSK2248761 and the investigators were blinded to the dose they received. Subjects were not blinded to whether they receive GSK2248761 or ETV. Randomization was stratified by HIV-1 VL at screening, <50,000 copies/mL or ≥50,000 copies/mL and by darunavir susceptibility, screening phenotype fold change <7 or ≥7 to 20. Background ART was administered open-label.

Once randomized and enrolled into the study subjects were scheduled to attend clinic visits at Day 1, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 36, 48 then every 12 weeks thereafter. All subjects were to participate in a Follow-up (FU) evaluation performed 4 weeks after permanent discontinuation of investigational product (IP).

Enrollment in study SGN113399 was terminated prematurely due to a safety finding (convulsion) in 5/20 subjects receiving GSK2248761. All subjects taking GSK2248761 as of February 2, 2011 were instructed to discontinue GSK2248761 as soon as possible and within one week, and to switch to the comparator arm of the study (ETV). 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 SGN113399 as of April 1, 2011, and to conduct follow-up visits at 4, 8, and 12 weeks after study withdrawal.

Centres: A total of 17 investigational sites enrolled subjects in this multicenter study: 1 center in Romania and 16 in the USA.

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 ETV were to take 200 mg orally twice daily (2 tablets twice daily; 4 tablets total daily).

Objectives: To select a GSK2248761 once daily dose for further evaluation in Phase 3 based on a comparison of the Week 16 antiviral activity and tolerability of a range of oral doses of GSK2248761 in HIV-1 infected antiretroviral therapy experienced adults with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance

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. Additional safety analyses were conducted to further explore and summarize safety and tolerability issues particularly around the group of subjects that had convulsions. 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		ETV	Total
	100mg	200mg		
Number of Subjects:	9	11	10	30
Planned, N	50	50	50	150
Randomised, N	9	11	10	30
Completed, N	0	0	0	0
Total Number Subjects Withdrawn, N	9	11	10	30
Withdrawn due to Adverse Events n (%)	0	1 (9)	0	1 (3)
Study Terminated n (%)	7 (78)	9 (82)	7 (70)	23 (77)
Lost to Follow-up n (%)	0	0	2 (20)	2 (7)
Withdrawn at Investigator Discretion n (%)	0	1 (9)	1 (10)	2 (7)
Withdrawn for Other reasons n (%)	2 (22)	0	0	2 (7)
Demographics				
Females: Males	2:7	2:9	5:5	9:21
Median Age, years	45	44	43	44
White, n (%)	5 (56)	5 (50)	4 (40)	14 (48)
Median Extent of Exposure (range), days	50 (6,81)	42 (7,80)	83 (57,114)	NA

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.

Visit	GSK2248761 100mg	GSK2248761 200mg	ETV
Baseline, n/N (%)	0/9	0/11	1/10 (10)
Week 2, n/N (%)	4/8 (50)	2/10 (20)	3/9 (33)
Week 4, n/N (%)	2/4 (50)	2/6 (33)	4/9 (44)
Week 8, n/N (%)	5/5 (100)	3/4 (75)	3/9 (33)
Week 12, n/N (%)	3/3 (100)	1/1 (100)	3/7 (43)
Week 16, n/N (%)	0	0	1/3 (33)

Most Frequent Adverse Events – While Taking Randomized Therapy	GSK2248761 100mg	GSK2248761 200mg	GSK2248761 Subtotal	ETV
Subjects with any AE(s), n(%)	6 (67%)	8 (73%)	14 (70%)	6 (60%)
Influenza	1 (11%)	0	1 (5%)	1 (10%)
Sinusitis	2 (22%)	0	2 (10%)	0
Diarrhoea	1 (11%)	3 (27%)	4 (20%)	2 (20%)
Convulsion*	1 (11)	4 (36%)	4 (20%)	0
Headache	0	1 (9%)	1 (5%)	1 (10%)
Pruritus	1 (11%)	1 (9%)	2 (10%)	0
Decreased appetite	1 (11%)	0	1 (5%)	1 (10%)

*The case of convulsion reported in the GSK2248761 100mg arm occurred 4 days after stopping randomized therapy and is included here for completeness.

Subjects with Any Serious Adverse Events (SAE)

Subjects with any SAEs, n (%) [drug related]	GSK2248761 100mg	GSK2248761 200mg	GSK2248761 Subtotal	ETV

Convulsion	1 (11) [1]	4 (36) [4]	5 (25) [5]	0
Facial Bone Fracture	1 (11) [0]	0	1 (5) [0]	0
Schizophrenia	0	1 (9) [0]	1 (5) [0]	0

Conclusion:
Due to the development of convulsions in five subjects, the study SGN113399 was terminated and the clinical development of GSK2248761 has been discontinued.