FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 1B Study of the Safety and Pharmacokinetics of Ritonavir-Boosted Elvitegravir (GS-9137/r) Plus a Background Regimen (BR) in HIV-1 Infected, Antiretroviral Treatment-Experienced Adolescents
Name of Test Drug:	Elvitegravir (GS-9137)
Dose and Formulation:	85-mg strength tablet, 150-mg strength tablet
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-183-0152
Phase of Development:	Phase 1B
IND No.:	72,177
EudraCT No.:	2008-003917-29
Study Start Date:	21 August 2008 (first subject screened)
Study End Date:	02 July 2010 (last subject observation)
Principal or Coordinating Investigator:	Name: Aditya Gaur, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Steven Chuck, MD Telephone: PPD Fax: PPD
Report Date:	06 December 2010

STUDY SYNOPSIS
Study GS-US-183-0152
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA

Title of Study: Study GS-US-183-0152: A Phase 1B Study of the Safety and Pharmacokinetics of Ritonavir-Boosted Elvitegravir (GS-9137/r) Plus a Background Regimen (BR) in HIV-1 Infected, Antiretroviral Treatment-Experienced Adolescents

Principal Investigator: Aditya Gaur, MD

Study Centers: 10 sites in the United States, United Kingdom, and Canada

Publications: Gaur A, Abadi J, Wiznia A, et al. Pharmacokinetics and Safety of Once-Daily Elvitegravir in HIV-Infected Adolescents. Poster No. 874 presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16–19, 2010; San Francisco, CA.

Study Period:
21 August 2008 (first subject screened)
02 July 2010 (last subject observation)

Phase of Development: Phase 1B

Objectives:

The primary objective of this study was:

- To evaluate the steady-state pharmacokinetics (PK) and confirm the dose of ritonavir-boosted elvitegravir (EVG/r) in Human Immunodeficiency virus type 1 (HIV-1) infected antiretroviral treatment-experienced adolescent subjects.

The secondary objective of this study was:

- To evaluate the safety and tolerability of EVG/r in HIV-1 infected antiretroviral treatment-experienced adolescents.

Methodology: This was a Phase 1B, nonrandomized, open-label, multicenter study of once-daily administration of elvitegravir (EVG) plus an antiretroviral (ARV) background regimen (BR) containing a ritonavir (RTV)-boosted protease inhibitor (PI/r) conducted in 2 phases, a 10-day PK evaluation phase followed by an optional treatment phase through 48 weeks. The PK phase evaluated the steady-state pharmacokinetics of EVG and its metabolites, GS-9200 (M4) and GS-9202 (M1), and RTV; the optional treatment phase evaluated safety and efficacy through 48 weeks' treatment. Eligible subjects were assigned to 1 of 2 EVG dose groups (150 mg/day or 85 mg/day) according to the PI prescribed for the background regimen. All subjects received their RTV dose based on the dosing schedule prescribed for the PI; no additional RTV was required to be taken with EVG.

Group 1: EVG 150 mg plus RTV-boosted darunavir, fosamprenavir, or tipranavir

Group 2: EVG 85 mg plus RTV-boosted lopinavir (LPV) or atazanavir (ATV)

To be eligible for enrollment in the optional treatment phase of the study, a subject must have completed the 10-day PK evaluation phase and had HIV-1 RNA > 1000 copies/mL at screening.

Number of Subjects:	**Planned**	**Analyzed**			
		Safety	EVG PK	GS-9200 PK	RTV PK
Group 1: (BR + EVG 150 mg):	12	11	10	10	10
Group 2: (BR + EVG 85 mg):	12	14	13	9	13

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HIV-1 infected, ARV treatment-experienced adolescents 12 to < 18 years old with plasma HIV-1 RNA levels > 1000 copies/mL or < 400 copies/mL.

Duration of Treatment: 10 days for the PK evaluation phase, 48 weeks total for subjects enrolled in the optional treatment phase.

Test Product, Dose, Mode of Administration, and Lot No.: EVG 150-mg or 85-mg strength tablet co-administered orally, once daily with the prescribed background regimen dosage, together with food.

EVG 150-mg tablet: Lot Numbers. AJ0704E1 and AJ0705E1
EVG 85-mg tablet: Lot Numbers. AJ0704D1 and AJ0802C1

Criteria for Evaluation:

Efficacy: The change from baseline in $\log_{10}$ HIV-1 RNA (copies/mL) and in CD4 cell count (cells/µL) at the end of the study, and the proportions of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL at the end of the study.

Pharmacokinetics: The following plasma PK parameters of EVG and, when appropriate, GS-9200, GS-9202, and RTV, were computed: C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, AUC_{tau}, and $T_{½}$.

Safety: Extent of exposure, adverse events (AEs), routine clinical laboratory tests, complete and symptom-driven physical examinations, vital signs, electrocardiograms (ECGs), and concomitant medications were monitored throughout the study period.

Statistical Methods:

Efficacy: Efficacy endpoints were summarized descriptively by HIV-1 RNA level at baseline (< 400 copies/mL and > 1000 copies/mL). The change from baseline in $\log_{10}$ HIV-1 RNA (copies/mL) and in CD4 cell count (cells/µL), and the proportions of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL, were summarized by scheduled study visit.

Pharmacokinetics: The PK analysis was performed after all subjects completed the 10-day PK evaluation phase of the study. Pharmacokinetic concentration data and PK parameters for EVG, GS-9200, GS-9202, and RTV were listed by subject and summarized by treatment using descriptive statistics. To determine whether the adult doses of EVG in adolescents

achieve systemic exposures similar to those in adults, an analysis of variance was carried out for natural log-transformed AUC_{tau} as a primary parameter (other PK parameters such as C_{max} and C_{tau} were explored). Data from the current study were compared to the database for EVG adult PK data using PK equivalence testing with equivalence boundaries of 70% to 143% for the 90% confidence interval (CI).

Safety: All safety data collected on or after the date of the first dose of the study treatment up to 30 days after the last dose of study treatment were listed by subject. All safety data were summarized by treatment group, except for AEs and graded laboratory abnormalities, which were also grouped by study phase, using descriptive statistics.

SUMMARY – RESULTS:

Subject Disposition and Demographics: 11 subjects were enrolled into Treatment Group 1 (BR + EVG 150 mg once daily), and 14 subjects were enrolled into Treatment Group 2 (BR + EVG 85 mg once daily). Two subjects (one in each treatment group) did not complete the study, both because of AEs during the 10-day PK evaluation phase of the study. Eleven of the 23 subjects who completed the 10-day PK evaluation phase of the study were eligible for enrollment in the optional treatment phase; 9/11 eligible subjects enrolled in the optional treatment phase, and each of these subjects completed treatment through 48 weeks.

Of the 25 enrolled subjects, 13 (52.0%) were male, 7 (28.0%) were White, and 18 (72.0%) were African-American. The median age was 16 years (range 12 to 17 years: 80% 15 to < 18 years: 48% Tanner Stage 5). Approximately one-half (14/25, 56.0%) of subjects were asymptomatic at baseline.

Efficacy Results: Efficacy data are summarized in the table below.

Efficacy Endpoint	Day 10		Week 48[b]
	Baseline HIV-1 RNA < 400 copies/mL[a]	Baseline HIV-1 RNA > 1000 copies/mL[a]	
Change from Baseline in HIV-1 RNA (log_{10} copies/mL), median (min, max)	0 (–0.58, 0.04)	–1.84 (–2.41, –1.39)	–1.74 (–2.69, –0.40)
Change from Baseline in CD4 Cell Count (cells/μL), Median (min, max)	–12 (–88, 544)	28 (–86, 172)	215 (–43, 600)
Change from Baseline in CD4 Cell Percentage median (min, max)	0.3 (–6.2, 2.9)	1.7 (–2.1, 4.6)	6.2 (–2.4, 13.2)
Proportion of subjects with HIV-1 RNA < 50 copies/mL, n (%)	9/12 (75.0%)	0/13 (0%)	2/9 (22.2%)
Proportion of subjects with HIV-1 RNA < 400 copies/mL, n (%)	10/12 (83.3%)	8/13 (61.5%)	4/9 (44.4%)

min = minimum, max = maximum
a n = 10 for change in HIV-1 RNA and CD4 cell count and percentage data
b n = 9 for all data; all subjects had baseline plasma HIV-1 RNA levels >1000 copies/mL, as mandated by optional treatment phase enrollment criteria

Pharmacokinetic Results: Elvitegravir PK parameters [mean (%CV)] on Day 10, are presented in the summary table below. Following administration of EVG 85 mg (plus ATV/r or LPV/r) or EVG 150 mg (plus other protocol-specified PI/r), mean EVG plasma concentration at t = 0 (C_0) used as a surrogate for C_{tau} to evaluate 24-hour EVG pharmacokinetics was higher in the 85-mg treatment group (627.0 ng/mL) relative to 150 mg (324.5 ng/mL), which is consistent with EVG 85-mg versus EVG 150-mg data from adult studies. Protocol-defined statistical comparison indicated that the GLS mean ratio (90% CI) in adolescents versus adult healthy subjects for EVG 150 mg AUC_{tau} [93.43 (75.81, 115.14)] was within the predefined equivalence boundaries (data not shown in the table).

	Adolescent EVG PK Parameters Mean (%CV)		**Exploratory Statistical Comparisons Adolescent (Test) vs. HIV-1 Infected Adult (Reference)[a] GLS Means Ratio as % (90% CI)**		
	BR+EVG 85 mg (n = 13)	**BR+EVG 150 mg (n = 10)**	**BR+EVG 85 mg (n = 13)**	**BR+EVG 150 mg (n = 10)**	**BR+EVG 85 or 150 mg Combined (n = 23)**
AUC_{tau} (ng•h/mL)	25,299.2 (44.7)	21,199.7 (35.7)	130.36 (102.98, 165.04)	112.55 (89.53, 141.50)	122.30 (101.83, 146.88)
C_{max} (ng/mL)	2142.3 (44.6)	2067.0 (35.8)	130.82 (105.17, 162.72)	127.95 (101.11, 161.90)	129.56 (108.49, 154.72)
C_{tau} (ng/mL)	627.0 (68.9)	324.5 (72.5)	222.11 (145.24, 339.66)	111.74 (69.02, 180.89)	164.76 (113.01, 240.19)

BR = background regimen, CV = coefficient of variation, EVG = elvitegravir, GLS = geometric least-squares
PK = pharmacokinetic.

a n = 24 HIV-1 infected adults from Study GS-US-236-0104 (EVG 150 mg) and Study GS-US-183-0105 (EVG 125 mg) combined. The Phase 2 EVG 125-mg dose/formulation has been shown previously to provide bioequivalent EVG exposures to the Phase 3 150-mg dose/formulation in a multiple-dose clinical study (GS-US-183-0140).

Exploratory statistical comparisons of exposure between EVG 150 mg in adolescents versus EVG 150 mg in adult HIV-1 infected subjects (shown in the table above) indicated comparable EVG AUC_{tau} and C_{tau} and a modest difference in C_{max}. The EVG 85-mg adolescent dose provided modestly higher AUC_{tau} and C_{max} compared to EVG 150-mg adult data. These differences are not considered to be clinically relevant based on the favorable long-term safety profile for EVG in adults at doses up to 300 mg once daily (Study GS-US-183-0130).

Overall, statistical comparisons between HIV-1 infected adolescents and healthy or HIV-1 infected adults indicated comparable and clinically equivalent EVG exposures. EVG/r mean C_{tau} was 7- to 13-fold above the in vitro protein binding-adjusted IC_{95} (45 ng/mL).

Consistent with data from adult studies, GS-9200 was a minor metabolite with low exposures relative to EVG, and GS-9202 levels were below the lower limit of quantitation.

Safety Results: All 25 enrolled subjects received at least 1 dose of EVG; 23/25 subjects completed the 10-day PK evaluation phase of the study, 13/14 subjects in the EVG 85-mg treatment group and 10/11 subjects in the EVG 150-mg treatment group. The 9 subjects participating in the optional treatment phase of the study received a median 48.3 weeks of EVG (range 47.6 weeks to 49.6 weeks).

During the 10-day PK evaluation phase of the study, treatment-emergent AEs were reported in 10/14 subjects (71.4%) in the EVG 85-mg treatment group and in 8/11 subjects (72.7%) in the EVG 150-mg treatment group. Overall, nausea (6/25 subjects, 24.0%) and dizziness (3/25 subjects, 12.0%) were the most frequently reported AEs; all other AEs were reported in 2 or fewer subjects in either treatment group. Most AEs were mild or moderate in severity (Grade 1 or 2) and were deemed by the investigator to be not related to study treatment. Grade 3 was the highest severity AE reported during the 10-day PK evaluation phase of the study; Grade 3 AEs were reported in 2/25 subjects, one in each treatment group, and included treatment-related nausea, vomiting, dizziness and chills. Both of these subjects discontinued EVG because of the AEs. No additional subject prematurely discontinued EVG. There was no death or study treatment-related SAE. No Grade 3 or 4 AE, and no SAE, was reported for the 9 subjects enrolled in the optional treatment phase through 48 weeks. No relationship between AE frequency and EVG dose was observed.

There was no apparent study treatment-related change over time in hematology, clinical chemistry, urinalysis, or safety serology results. During the 10-day PK evaluation phase of the study, 23/25 subjects had treatment-emergent graded laboratory abnormalities. All except one of these laboratory abnormalities were Grade 1 or 2; one subject in the EVG 85-mg treatment group (whose BR included ATV/r) had a Grade 3 abnormality (total bilirubin) on Day 14, during the posttreatment follow-up period. All 9 subjects enrolled in the optional treatment phase of the study had treatment-emergent graded laboratory abnormalities at some time point through 48 weeks; most of these laboratory abnormalities were Grade 1 or 2. No notable change in vital signs, ECGs, or physical findings was observed during the study. No pregnancy occurred during the study.

CONCLUSIONS: In adolescent subjects (12 to < 18 years), EVG once daily was well tolerated and provided comparable plasma exposures as in HIV-1 infected adults when added to a PI/r background regimen.