# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203093Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY REVIEW

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|---|---|
| NDA | 203093 |
| Submission Date | 27 June 2012 |
| Brand Name | Vitekta® |
| Generic Name | Elvitegravir |
| Office of Clinical Pharmacology (OCP) Review Team | Leslie Chinn, Ph.D., Dhananjay Marathe, Ph.D., Jeffry Florian, Ph.D., Islam R. Younis, Ph.D. |
| OCP Division | DCP4 |
| OND Division | Division of Antiviral Products |
| Applicant | Gilead Sciences, Inc. |
| Formulation; Strength | IR tablets; 85 and 150 mg |
| Proposed Dosing Regimen | Elvitegravir 85 mg once daily coadministered with one of the following ritonavir-boosted PIs:<br>– atazanavir/ritonavir 300/100 once daily<br>– lopinavir/ritonavir 400/100 twice daily<br><br>Elvitegravir 150 mg once daily coadministered with one of the following ritonavir-boosted PIs:<br>– darunavir/ritonavir 600/100 mg twice daily<br>– fosamprenavir/ritonavir 700/100 twice daily<br>– tipranavir/ritonavir 500/200 twice daily |
| Proposed Indication | Treatment of HIV-1 infection in ARV treatment-experienced patients, in combination with a ritonavir-boosted protease inhibitor and other ARV agents |
| Review Type | 505(b)(1) New Drug Application, standard review |

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# 1. EXECUTIVE SUMMARY

Elvitegravir (EVG) is a novel inhibitor of HIV-1 integrase (INSTI) that prevents the integration of HIV-1 DNA into host genomic DNA, thereby obstructing formation of the HIV-1 provirus. EVG is one component of Stribild® (NDA 203100), a fixed-dose combination tablet approved by the US Food and Drug Administration (FDA) in August 2007 for the treatment of HIV-1 infection in treatment-naïve adults. In addition to EVG, Stribild® also contains the novel pharmacoenhancer cobicistat (Cobi, NDA 203094, PDUFA date 28 Apr 2013) as well as the approved antiretroviral (ARV) drugs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC).

In the current application, the **proposed indication** for EVG is the treatment of HIV-1 infection, in combination with a ritonavir-boosted protease inhibitor (PI/r) and other ARV agents, in treatment-experienced adults. Due to pharmacokinetic interactions, the **proposed dose** of EVG is dependent upon the PI/r with which EVG is administered: if the PI/r is atazanavir/r (ATV/r) or lopinavir/r (LPV/r), the proposed dose of EVG is 85 mg once daily; if the PI/r is darunavir/r (DRV/r), tipranavir/r (TPV/r), or fosamprenavir/r (FPV/r), the proposed dose of EVG is 150 mg once daily. The lower EVG dose is necessary due to a uridine glucuronosyltransferase- [UGT-] mediated pharmacokinetic drug interaction between EVG and LPV/r or ATV/r. These RTV-boosted PIs represent those expected to be commonly used in combination with EVG. No other RTV-boosted PIs have been evaluated.

The safety and efficacy data for EVG were collected during the Phase 3 study GS-US-183-0145 (96 week), the Phase 2 study GS-US-183-0105 (48 week), and the rollover study GS-US-183-0130 (long-term safety). All three studies were conducted in treatment-experienced HIV-1 infected subjects.

The Applicant submitted data characterizing the clinical pharmacology of EVG to support the proposed prescribing information (16 clinical trials conducted using EVG/ritonavir). In addition, these data are supported by right of reference to the Applicant's Stribild®, including 16 clinical trials conducted using EVG/ritonavir, EVG/Cobi, or EVG/Cobi/TDF/FTC as well as 14 *in vitro* studies. These clinical trials and *in vitro* studies were previously evaluated as part of the review process for NDA 203100; NDA 203100 will be referenced throughout the current review when applicable.

## 1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) finds this application acceptable and recommends approval of EVG for the treatment of HIV-1 in treatment-experienced adults pending Applicant agreement on the labeling changes described in Section 3.0 of this review.

## 1.2. POST-MARKETING COMMITMENTS OR REQUIREMENTS

The post-marketing commitments were under discussion at the time this review was completed. Please refer to Sections 2.0 and 2.4.2.9 of this review for details regarding outstanding issues that may require post-marketing commitments or requirements.

## 1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

### Dose Selection

The EVG dose was selected based on results from the Phase 2 dose-finding trial in which EVG/r 125/100 mg demonstrated greater antiviral activity (i.e. decreases in HIV-1 RNA at Week 24) compared to EVG/r 50/100 mg or 20/100 mg. A subsequent relative bioavailability trial demonstrated that exposures of EVG were similar following administration of EVG/r 150/100 mg (Phase 3 EVG formulation) compared to EVG/r 125/100 mg (Phase 2 EVG formulation). The EVG 85 mg dose was selected based on exposure-matching EVG in the presence of ATV/r or LPV/r.

### Exposure-Response Relationship

EVG, administered with an antiretroviral background regimen, has a relatively flat exposure-response relationship across the range of clinically observed EVG exposures ($AUC_{tau}$ Q1-Q3 13641-21254 ng·h/mL, $C_{tau}$ Q1-Q3 1128-1584 ng/mL) with no clear relationship between virologic outcome or virologic failure and EVG exposures.

There was no evidence of a relationship between EVG dose (85 or 150 mg) or exposures ($AUC_{tau}$ and $C_{tau}$) and the most frequently reported study drug-related adverse event (AE) of diarrhea. Higher daily doses of RTV were associated with diarrhea, which is an AE that is commonly observed following RTV administration.

### Absorption, Distribution, Metabolism, and Excretion

The absolute bioavailability of EVG was not determined, but the bioavailability of EVG is expected to be high based on boosted vs. unboosted administration. Ritonavir-boosted EVG is rapidly absorbed with a $T_{max}$ of approximately 4 h post-dose. Absorption is unaffected by local pH.

EVG is highly protein-bound in plasma (98-99%), regardless of EVG concentration. The blood:plasma ratio of EVG is approximately 0.73, indicating that EVG is largely contained in the plasma rather than the cellular components of the blood.

EVG primarily undergoes CYP3A-mediated hydroxylation (generating a chlorofluorophenyl group hydroxide of EVG [GS-9202]) and glucuronidation via UGT1A1/3 (generating an acyl glucuronide of EVG [GS-9200]). In clinical practice, EVG will therefore be coadministered with a pharmacokinetic "booster" – a potent CYP3A inhibitor such as ritonavir or cobicistat – in order to increase EVG exposures. In the presence of RTV, the apparent systemic clearance (CL/F) of EVG is estimated to be low (7.10 L/h based on population PK analyses using Phase 3 data) and GS-9202 concentrations are typically below the lower limit of quantification; the exposures ($AUC_{tau}$) of all observed metabolites constitute less than 10% of parent drug exposure.

EVG is a weak inhibitor of CYP3A, P-gp, and OATP1B1 and a moderate inhibitor of OATP1B3 ($IC_{50}$ 0.44 uM). EVG does not inhibit microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1. It is a weak inducer of CYP3A, but its inductive effects are outweighed by the inhibitory properties of ritonavir.

The primary route of EVG elimination is hepatobiliary excretion. Following administration of a single dose of $^{14}$C-EVG/r 50/100 mg, 94.8% of radioactivity was excreted in the feces (30.8% EVG and 33.8% GS-9202, with limited amounts of other metabolites detected) and 6.7% of radioactivity was excreted in the urine as metabolites. The median half-life of EVG following multiple-dose administration of EVG/r is 9.13 h.

**Intrinsic Factors**

Based on population PK modeling, EVG exposures were not affected by age, gender, race, estimated glomerular filtration rate (eGFR), HIV-1 infection, or hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection. Body surface area was significantly associated with EVG exposures, but differences in exposures were not considered to be clinically relevant.

EVG exposures were similar in subjects with moderate hepatic impairment compared to matched healthy controls, indicating that no EVG dose adjustment is needed in HIV-1 infected patients with mild or moderate hepatic impairment. Ritonavir is not indicated for use in patients with severe hepatic impairment; therefore, the ritonavir-boosted PIs with which EVG will be administered are also not recommended for use in patients with severe hepatic impairment.

EVG exposures were similar in subjects with severe renal impairment compared to matched healthy controls, indicating that no EVG dose adjustment is needed in HIV-1 infected patients with mild, moderate, or severe renal impairment.

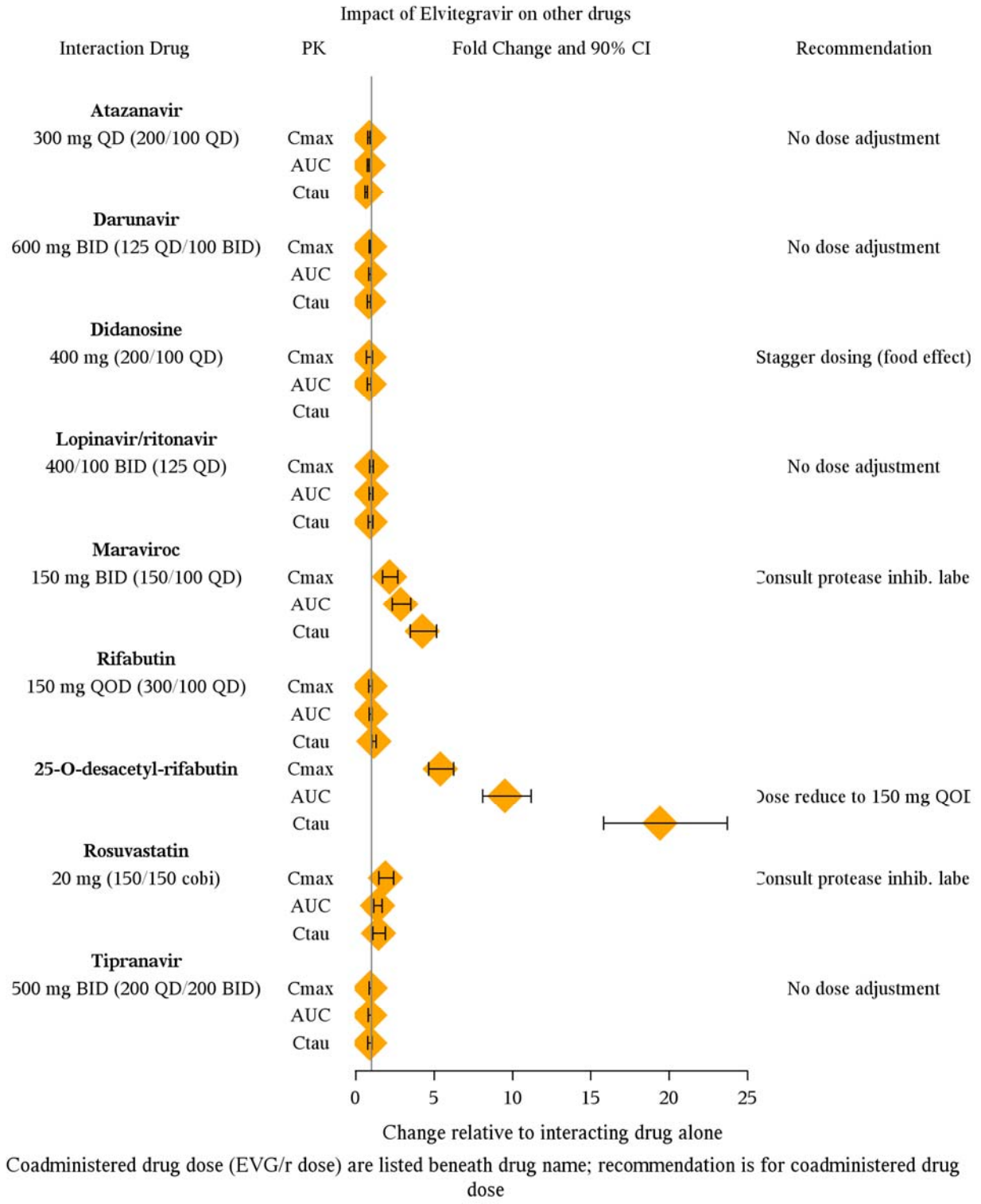
**Extrinsic Factors**

EVG has a low liability to cause drug interactions. In general, ritonavir is expected to be the perpetrator in drug-drug interactions in which EVG is administered. The Vitekta® package insert will recommend review of the potential drug-drug interactions listed in the package insert for the ritonavir-boosted PI with which EVG will be administered.

EVG exposures are maximally boosted by CYP3A inhibition when coadministered with the proposed dose of ritonavir; therefore, EVG exposures are not expected to increase further when EVG is coadministered with other CYP3A inhibitors. Exposures may also be increased when EVG is coadministered with a potent inhibitor of UGT1A1 (such as atazanavir/r or lopinavir/r) via prevention of the formation of the glucuronidation metabolite. Exposures may be decreased when EVG is coadministered with potent CYP3A inducers; coadministration is not recommended.

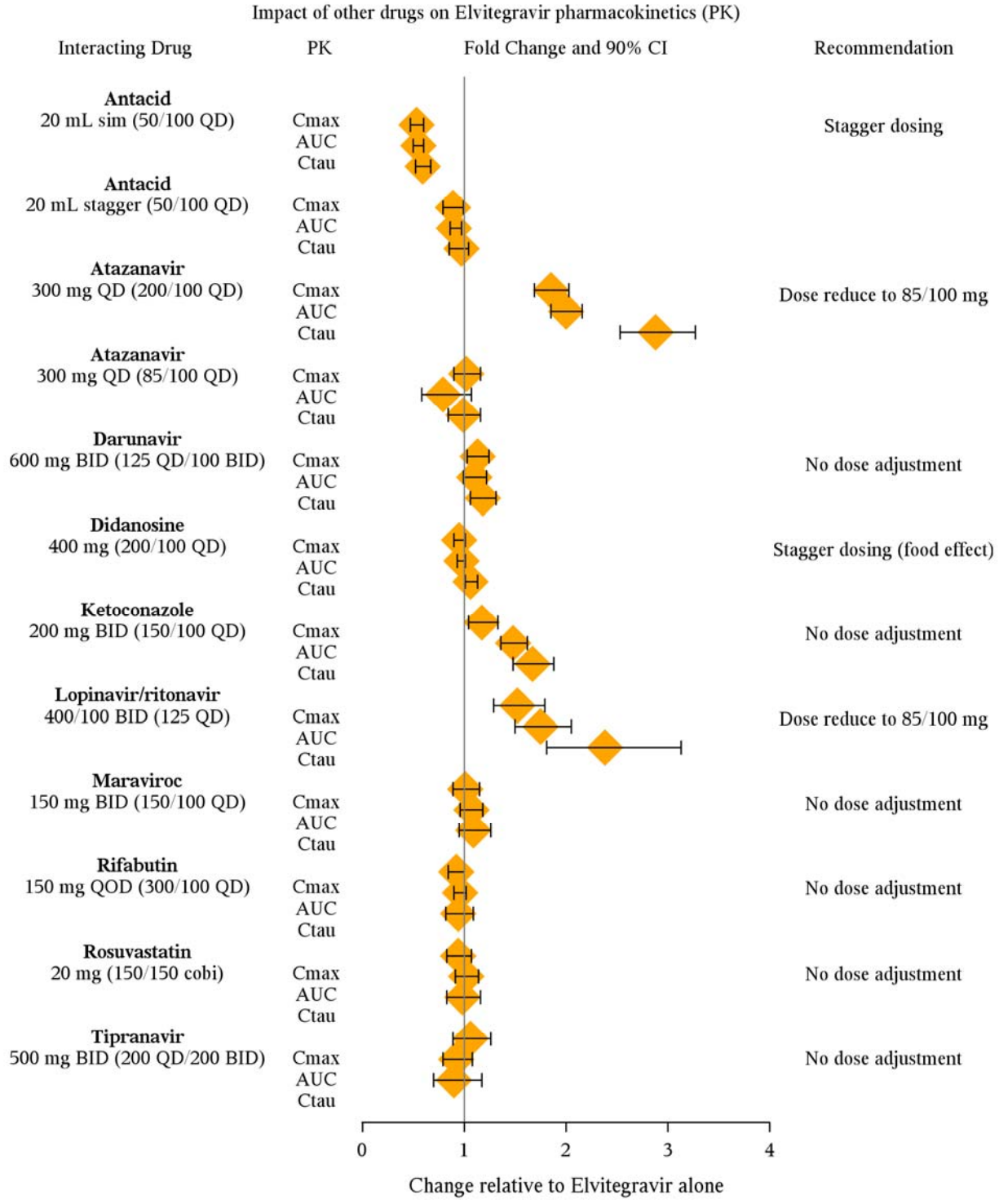
Figures 1 and 2 depict the effect of EVG on concomitant drugs and the effects of concomitant drugs on EVG, respectively.

**Figure 1. The impact of elvitegravir on the pharmacokinetics of concomitant drugs and clinical recommendations regarding the dose of the concomitant drug**




Coadministered drug dose (EVG/r dose) are listed beneath drug name; recommendation is for coadministered drug dose

**Figure 2. The impact of concomitant drugs on the pharmacokinetics of elvitegravir and clinical recommendations regarding elvitegravir dose**




Coadministered drug dose (EVG/r dose) are listed beneath drug name; recommendation is for EVG dose

# 2. QUESTION-BASED REVIEW

## 2.0. APPLICATION-SPECIFIC QUESTIONS

### 2.0.1. Should the proposed indication be extended to include the treatment, in combination with a ritonavir-boosted protease inhibitor, of HIV-1 infection in ARV-treatment experienced adolescents aged 12 to <18 years?

From an efficacy standpoint, the indication should be extended to adolescents (pending the availability of safety data) because the pharmacokinetics of EVG (based on intensive sampling) are comparable in adults and adolescents at the adult doses proposed in this Application (see Sections 2.3.1 and 2.3.2.2). Although the Applicant did not seek the adolescent indication in the current NDA, the Applicant submitted intensive PK data collected following 10 days of EVG 85 mg or 150 mg QD administered with an ARV background regimen containing an appropriate PI/r to adolescents 12 to < 18 years of age (n=23), as well as safety and efficacy data from an optional 48-week treatment phase, in the clinical study report for GS-US-183-0152.

Efficacy data are available from nine adolescent patients who enrolled in the optional 48-week treatment phase. Two of the nine patients (22.2%) had HIV-1 RNA <50 copies/mL at Week 48. This degree of efficacy is low compared to that seen in adults, as 59.8% of adult patients had HIV-1 RNA <50 copies/mL at Week 48. A potential explanation for the differential treatment effect observed in adolescents relative to adults is a lower level of treatment adherence by adolescent patients. This hypothesis is supported by the observation of larger percentage of adolescents (n/N=8/9 i.e. 88%) with multiple EVG concentration samples below the limit of quantification (BLQ) during the 48-week treatment phase as compared to the adults (44%) in Phase 3 trial.

### 2.0.2. Should the proposed indication be extended to include the treatment, in combination with cobicistat and two NRTIs, of HIV-1 infection in ARV-treatment naïve adults?

At the time of NDA filing, the Applicant did not seek the treatment-naïve indication (in combination with cobicistat and two NRTIs). The proposed indication was expanded to include elvitegravir in combination with cobicistat and two NRTIs for the treatment of HIV-1 infection in treatment-naïve patients in response to a request by the Agency in the Filing Letter of 26 Sept 2012.

The Agency's request was based on the August 2012 approval of Stribild®, a fixed dose combination tablet of EVG, Cobicistat (Cobi), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF), indicated for the of HIV-1 in the treatment-naïve HIV-1 infected population. Because NRTIs, including FTC and TDF, are considered to be clinically interchangeable, it was proposed that EVG and Cobi as single agent formulations (NDAs 203093 and 203094, respectively) in combination with two NRTIs can be indicated for the treatment of HIV-1 in treatment-naïve HIV-1 infected patients, on the basis that safety and efficacy of EVG/Cobi were demonstrated in the pivotal trials conducted using Stribild®.

According to federal regulations, an in vivo bioavailability study should be conducted when "new formulations of active drug ingredients of therapeutic moieties approved for marketing" are under evaluation (21 CFR 320.25). Therefore, a relative BA/BE study is required to establish similarity in EVG exposures following the administration of Stribild® fixed dose combination tablet or coadministration of the EVG and Cobi single agent formulations in order to link the efficacy and safety data in treatment-naïve patients from Stribild® to the EVG and Cobi single agent formulations.

In the absence of a pharmacokinetic bridging study comparing EVG exposures from the single agent formulation to those from Stribild®, the decision regarding an extension of the indication was based on a risk-benefit analysis, taking the following points into consideration:

1. Although a direct comparison cannot be made, a cross-study BA/BE comparison may be evaluated using Studies GS-US-236-0101 (EVG/r + FTC/TDF versus EVG/Cobi/FTC/TDF fixed-dose combination tablet) and GS-US-216-0116 (EVG/r versus EVG/Cobi). Mean EVG exposures from these studies suggests that exposures may be lower following coadministration of the single agents relative to after administration of Stribild, with the lower bound of the 90% confidence intervals falling below the predefined bioequivalence range of 80-125% (Table 1).

**Table 1. Mean EVG exposures after administration of EVG and Cobi as single entities (Study GS-US-216-0116) and Stribild® (Study GS-US-236-0101)**

| | **N** | **EVG + Cobi** GS-US-216-0116 | **N** | **Stribild** GS-US-236-0101 | **EVG Ratio EVG+Cobi:Stribild** (90% CI) |
|---|---|---|---|---|---|
| $AUC_{tau}$ (ng·h/mL) | 22 | 21906 | 42 | 25809 | 85 (75, 96) |
| $C_{max}$ (ng/mL) | 22 | 2216 | 42 | 2565 | 86 (77, 96) |
| $C_{tau}$ (ng/mL) | 22 | 380 | 42 | 415 | 92 (65, 109) |

2. The integrity of the data from Studies GS-US-236-0101 and GS-US-216-0116 cannot be verified because inspections of the bioanalytical sites, where analysis of EVG concentrations in plasma samples was conducted, were not performed because these studies were not initially considered to be pivotal for approval. A risk-based assessment was performed to evaluate the degree of confidence with which data analyzed by these sites could be accepted based on the Agency's inspection history of the bioanalytical sites. Prior inspections of the sites by the Office of Scientific Investigations were inconclusive: some inspections resulted in the issuance of Forms 483, while others generated No Action Indicated (NAI) designations. These discrepant findings add to the uncertainty surrounding the data from the cross-study BA/BE comparison.
3. The formulations cannot be bridged based on in vitro methodologies (e.g. dissolution profiles) in the absence of an in vitro-in vivo correlation. In addition, the formulations

differ in terms of active pharmaceutical ingredients as well as excipients, making a direct comparison impossible.

4. The option to use EVG/Cobi in combination with two NRTIs (compared to the use of the Stribild® fixed dose combination tablet) would benefit HIV-1 infected patients with renal impairment for whom Stribild® cannot be used due to the inability to dose adjust TDF and FTC.

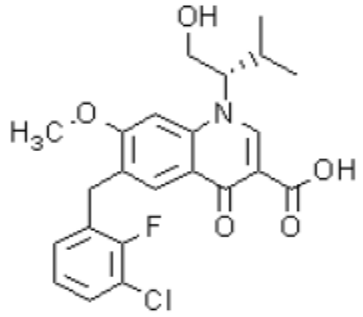
Taken together, the totality of evidence does not conclusively indicate that EVG exposures would be similar following administration of EVG and cobicistat single agent formulations compared to administration of Stribild®. Based on the above considerations, OCP does not recommend extending the indication to include the treatment, in combination with cobicistat and two NRTIs, of HIV-1 infection in ARV-treatment naïve adults. Should the Applicant wish to pursue this indication, a relative BA study should be conducted in order to establish similarity of EVG exposures following co-administration of EVG and cobicistat single agent formulations to EVG exposures following administration of the Stribild® fixed dose combination tablet.

## 2.1. GENERAL ATTRIBUTES OF THE DRUG

### 2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology review?

The molecular weight of EVG is 447.9 Da and the chemical structure is shown in Figure 3.

**Figure 3. Chemical structure of elvitegravir**




EVG tablets are green, film-coated, immediate-release tablets shaped like a pentagon (85 mg EVG) or triangle (150 mg EVG). The former are debossed with "GSI" on one side and "85" on the other, while the latter are debossed with "GSI" on one side and "150" on the other. The composition of EVG 85 and 150 mg tablets are listed in Tables 2 and 3, respectively.

**Table 2. Qualitative and quantitative composition of elvitegravir tablets, 85 mg**

| Components | % w/w | Unit Formula (mg/tablet) | Quality Standard | Function |
|---|---|---|---|---|
| **Tablet Core** | | | | |
| Elvitegravir | (b) (4) | 85.00[a] | In-House | Active |
| Hydroxypropyl Cellulose | | (b) (4) | NF, Ph. Eur. | (b) (4) |
| Sodium Lauryl Sulfate | | | NF, Ph. Eur., JP | |
| Lactose Monohydrate | | | NF, Ph. Eur., JP | |
| Microcrystalline Cellulose | | | NF, Ph. Eur., JP | |
| Croscarmellose Sodium | | | NF, Ph. Eur., JP | |
| Magnesium Stearate | | | NF, Ph. Eur., JP | |
| (b) (4) | | | USP, Ph. Eur. | |
| Total | 100 | (b) (4) | | |
| **Film-Coat** | | | | |
| (b) (4) | | | | |
| (b) (4) | | | | |

**Table 3. Qualitative and quantitative composition of elvitegravir tablets, 150 mg**

| Components | % w/w | Unit Formula (mg/tablet) | Quality Standard | Function |
|---|---|---|---|---|
| **Tablet Core** | | | | |
| Elvitegravir | (b) (4) | 150.0[a] | In-House | Active |
| Hydroxypropyl Cellulose | | (b) (4) | NF, Ph. Eur. | (b) (4) |
| Sodium Lauryl Sulfate | | | NF, Ph. Eur., JP | |
| Lactose Monohydrate | | | NF, Ph. Eur., JP | |
| Microcrystalline Cellulose | | | NF, Ph. Eur., JP | |
| Croscarmellose Sodium | | | NF, Ph. Eur., JP | |
| Magnesium Stearate | | | NF, Ph. Eur., JP | |
| (b) (4) | | | USP, Ph. Eur. | |
| Total | 100 | (D) (4) | | |
| **Film-Coat** | | | | |
| (b) (4) | | | | |
| (b) (4) | | | | |

### 2.1.2. What are the proposed mechanism of action and therapeutic indication(s)?

Elvitegravir is a novel inhibitor of HIV-1 integrase (INSTI) that prevents the integration of HIV-1 DNA into host genomic DNA, thereby obstructing formation of the HIV-1 provirus.

The indication proposed by the Applicant for EVG is for the treatment of HIV-1 infection, in combination with a ritonavir-boosted protease inhibitor (PI/r) and other ARV agents, in treatment-experienced adults.

An additional indication for EVG in combination with a ritonavir-boosted PI in ARV treatment experienced adolescents aged 12 to <18 was considered during the review process. Please refer to Section 2.0 of this review for further discussion.

### 2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed doses are EVG 85 mg once daily in combination with ATV/r 300/100 mg once daily or LPV/r 400/100 mg twice daily, and EVG 150 mg once daily in combination with DRV/r 600/100 mg twice daily, FPV/r 700/100 mg twice daily, or TPV/r 500/200 mg twice daily.

EVG is to be administered orally in combination with a ritonavir-boosted PI and food.

## 2.2. GENERAL CLINICAL PHARMACOLOGY

### 2.2.1. What are the design features of the clinical and clinical pharmacology studies used to support dosing or claims?

The following studies were conducted during the elvitegravir development program. An asterisk (*) denote studies which were reviewed under NDA 203100 (Stribild®) and the number in square brackets [] indicates the EVG formulation, where Formulation 1 is the test formulation and Formulation 2 is the to-be-marketed formulation.

**Phase 1 (30 studies):**

Biopharmaceutics (1 study)

- GS-US-183-0140* [2] – relative bioavailability of the Phase 3 (to-be-marketed) formulation of EVG boosted with RTV compared to the reference EVG formulation boosted with RTV

Pharmacokinetics (4 studies)

- GS-US-183-0102* [1] – effect of RTV on the steady-state PK of EVG
- GS-US-183-0113* [1] – effect of a range of RTV doses on the PK of EVG and on hepatic CYP3A activity
- GS-US-183-0126* [1] – mass balance of [$^{14}$C]-EVG boosted with RTV
- GS-US-216-0116* [2] – PK of multiple-dose EVG boosted with Cobi

Pharmacodynamics (2 studies)

- GS-US-183-0128* [1] – effect of steady-state EVG/r exposures on QTcF interval
- GS-US-183-0101* [1] – safety, tolerability, antiviral activity, and PK/PD of EVG

Special populations (3 studies)

- GS-US-183-0133* [2] – PK and safety of EVG/Cobi in subjects with moderate hepatic impairment
- GS-US-216-0124* [2] – PK and safety of EVG/Cobi in subjects with severe renal impairment

- GS-US-183-0152 [2] – Steady-state PK and dose confirmation of EVG in adolescent patients

Drug-drug interactions (DDIs; 18 studies)

- GS-US-183-0103 [1] – EVG/r, FTC, and TDF; effect of antacids on EVG/r PK
- GS-US-183-0104 [1] – EVG/r and zidovudine (ZDV)
- GS-US-183-0106 [2] – EVG 85 mg and ATV/r
- GS-US-183-0108 [1] – EVG/r 200/100 mg and ATV
- GS-US-183-0110 [1] – EVG and TPV/r
- GS-US-183-0111 [1] – EVG and didanosine (ddI) or stavudine (d4T)
- GS-US-183-0112 [2] – EVG/r and etravirine (ETV)
- GS-US-183-0115 [1] – EVG/r and abacavir (ABC)
- GS-US-183-0116 [1] – EVG and LPV/r
- GS-US-183-0118 [2] – EVG/r and maraviroc (MVC)
- GS-US-183-0119* [1] – EVG/r and antacid or omeprazole
- GS-US-183-0120 [1] – EVG and DRV/r
- GS-US-183-0123 [1] – EVG and FPV/r
- GS-US-183-0125 [1] – EVG/r and rifabutin
- GS-US-183-0146* [2] – EVG/r and ketoconazole
- GS-US-183-0147 [1] – EVG and ATV/r
- GS-US-216-0120* [2] – EVG/Cobi and famotidine or omeprazole
- GS-US-216-0123* [2] – EVG/Cobi and rosuvastatin or rifabutin

**Phase 2 (2 studies):**

- GS-US-183-0105* [2] – This supportive study was a randomized, partially blinded trial in which EVG/r was compared to a ritonavir-boosted comparator PI (CPI/r), both with a background regimen. The primary endpoint was the time-weighted average change in $\log_{10}$ HIV-1 RNA levels from baseline at Week 24 post-treatment ($DAVG_{24}$). The results of this study demonstrated that EVG/r 50/100 and 125/100 mg QD dose groups met the criteria for noninferiority compared to CPI/r.
- GS-US-183-0130 [2] – This ongoing open-label rollover trial provided subjects who participated in an EVG/r trial (GS-US-183-0105 and GS-US-183-0152) with continued access to EVG/r. The primary objective was to observe the long-term safety of EVG/r.

**Phase 3 (1 study):**

- GS-US-183-0145 [2] – This was a randomized, double-blind, non-inferiority trial in which raltegravir (RAL) was used as an active control. Both EVG/r and RAL were administered in combination with a background regimen in treatment-experienced HIV-1 infected adults. The secondary objectives of the trial were to evaluate efficacy, safety, and tolerability of EVG administered with a BR through 96 weeks of treatment and in the longer term. The treatment outcomes at Week 48 are displayed in Table 4. The proportions of subjects who achieved and maintained virologic response were similar between the EVG and RAL treatment arms.

**Table 4. Treatment outcomes at Week 48** (HIV-1 RNA cutoff at 50 copies/mL, snapshot analysis)

| Virologic Response at Week 48 | EVG (N=351) | RAL (N=351) | EVG vs. RAL | |
|---|---|---|---|---|
| | | | p-value[a] | Prop Diff (95% CI)[b] |
| Virologic Success at Week 48 | | | | |
| HIV-1 RNA < 50 copies/mL | 210 ( 59.8%) | 202 ( 57.5%) | 0.55 | 2.2% (-5.0% to 9.3%) |

a The p-value is estimated from a 2-sided Cochran-Mantel-Haenszel test adusted by baseline HIV-1 RNA level and the class of second agent. This is the superiority p-value.
b The difference in proportions and its 95% CIs between randomized treatment groups are based on stratum-adjustment [by baseline HIV-1 RNA level (<=100,000 or >100,000 copies/mL) and the class of second agent (NRTI or other classes)] Mantel Haenszel (MH) proportions and normal approximation.

### 2.2.2. What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was the proportion of subjects achieving and maintaining HIV-1 RNA <50 copies/mL through Week 48. The quantitation of plasma HIV-1 RNA (i.e. HIV-1 viral load) has been validated as a surrogate marker for the efficacy of antiretroviral drugs.

### 2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

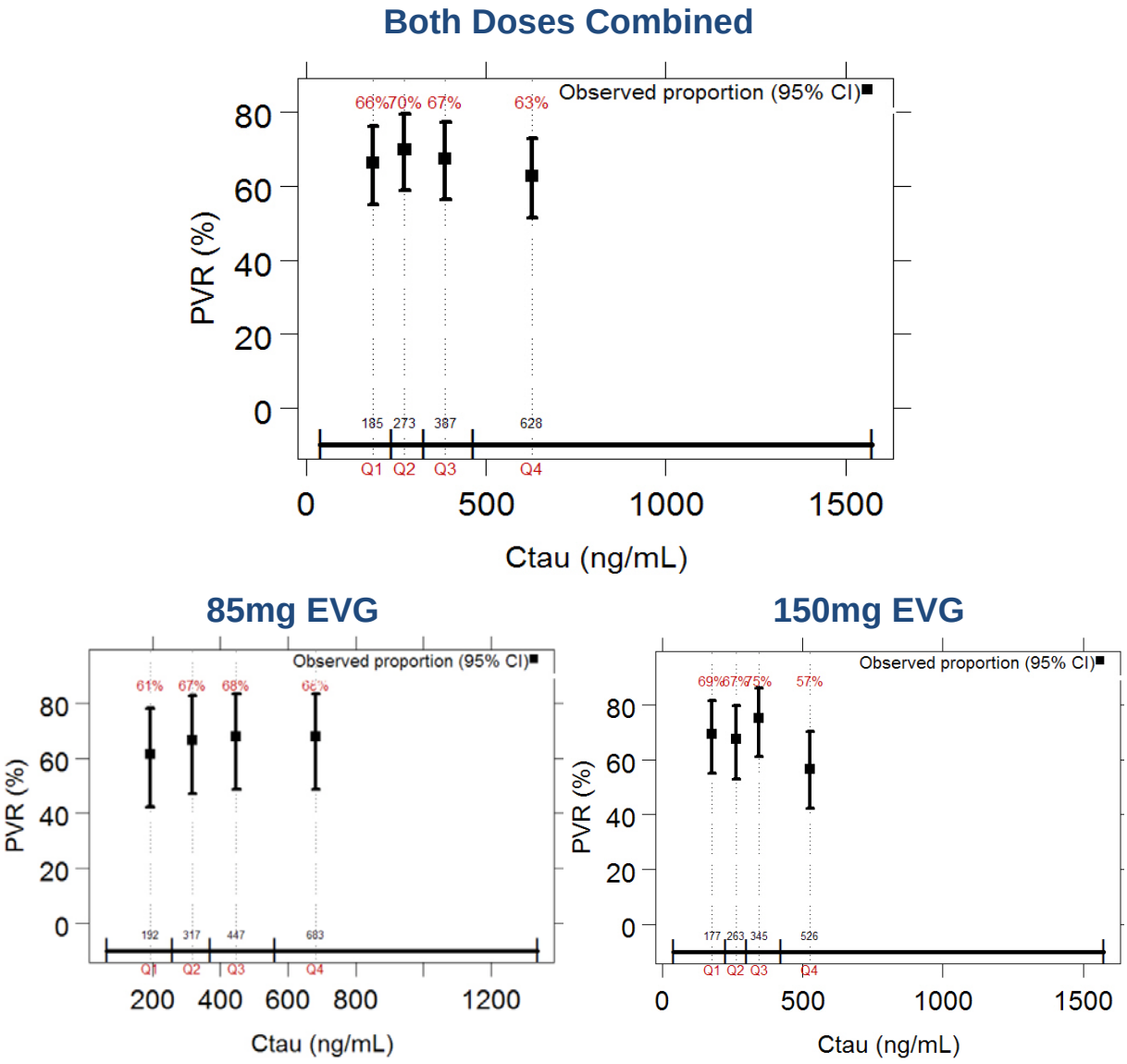
Plasma concentrations of EVG and its metabolites GS-9200 and GS-9202 were quantified in samples from all trials using validated LC-MS/MS analytical methods. Plasma concentrations of ritonavir and other coadministered drugs were calculated in one or more trials (depending on the trial objectives) using validated LC-MS/MS analytical methods.

### 2.2.4. Exposure-Response

### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

A flat exposure-response relationship was observed between elvitegravir $C_{tau}$ and the efficacy endpoint of pure virologic response (PVR, with plasma viral load <50 HIV-1 RNA copies/mL) in trial GS-US-183-0145 (Figure 4). The observed PVR was 66% in the first exposure quartile, which is within the range of PVR values observed in 2$^{nd}$ to 4$^{th}$ exposure quartiles (70-63%). Separate E-R efficacy relationships for PVR were also evaluated for the 85 mg QD and 150 mg QD EVG dose groups and a similar flat exposure-response relationship was identified between elvitegravir $C_{tau}$ and PVR.

**Figure 4. Percentage of patients achieving Pure Virologic Response (<50 copies/mL) versus elvitegravir $C_{tau}$ with both elvitegravir doses combined or in separate dosing groups (85 mg and 150 mg)** (EVG $C_{tau}$ values [derived from population PK analysis] are represented as quartiles)

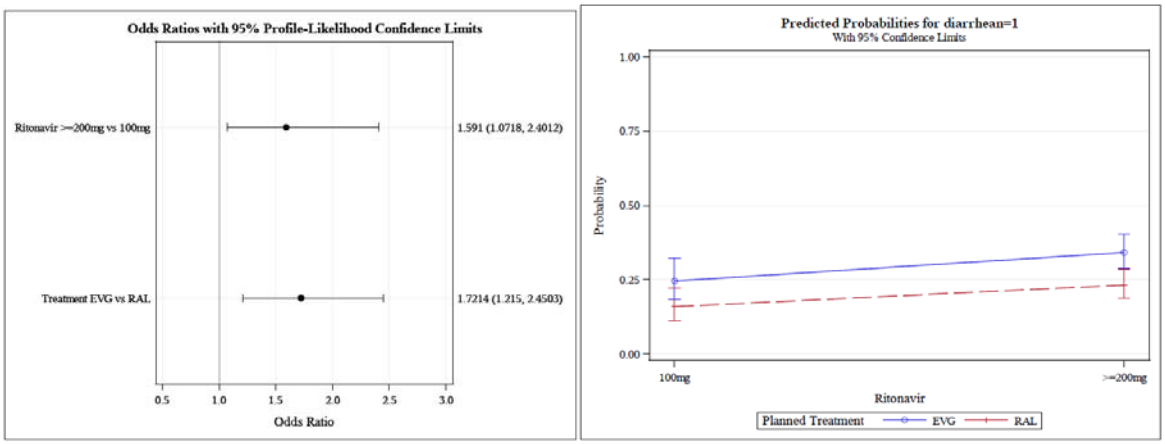



### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Once-daily EVG had no exposure-response relationship for safety adverse events of interest in treatment-experienced HIV-1 infected subjects in the pivotal Phase 3 trial (GS-US-183-0145). For diarrhea, difference in RTV doses in the background ARV regimens across both treatment arms was responsible for 59% increased odds of diarrhea occurrence for subjects receiving ≥200 mg RTV compared to 100 mg RTV. Within the EVG arm, an exposure-safety relationship for

diarrhea was absent, although diarrhea events were more common in the EVG arm (72% increased odds of occurrence) compared to the RAL arm after accounting for RTV dosing (Figure 5).

**Figure 5. Dose/exposure-response relationship for EVG treatment or RTV dose on diarrhea adverse events**




### 2.2.4.3 Does this drug prolong the QT or QTc interval?

EVG does not prolong the QT interval. There is no significant relationship between QT interval and plasma EVG concentrations at EVG/r doses of 125/100 (therapeutic) or 250/100 (supratherapeutic) mg QD (Study GS-US-183-0128). This study was evaluated during review of Stribild®; please refer to the OCP review of NDA 203100 for details.

### 2.2.4.4 Are the dose and dosing regimen selected by the Applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes, the dose and dosing regimen selected by the Applicant are consistent with the known dose-concentration-response relationship. A dose of EVG 125 mg QD was found to provide EVG exposures in the target range when coadministered with RTV 100 mg QD in the Phase 2 dose-finding study GS-US-183-0105. The dose of EVG 150 mg (to-be-marketed formulation) provided similar exposures to the earlier EVG 125 mg formulation (GS-US-183-0140). Modeling and simulations conducted by the Applicant suggested that EVG 85 mg coadministered with LPV/r or ATV/r would provide similar exposures to EVG/r 150/100 mg. The PK, efficacy, and safety of the selected doses were verified in GS-US-183-0145.

The minimum RTV dose of 100 mg QD was selected because this dose provides exposures that produce near-maximal CYP3A inhibition. Ritonavir doses ranging between 20 and 200 mg QD were evaluated (Study GS-US-183-0113); increases in RTV dose above 100 mg QD or corresponding exposure will not result in additional increases in EVG exposure.

There are no unresolved dosing or administration issues.

### 2.2.5. What are the PK characteristics of the drug and its major metabolite?

#### 2.2.5.1 What are the single-dose and multiple-dose PK parameters?

The pharmacokinetics of EVG have been evaluated following administration of the test formulation of EVG (Formulation 1) alone or in combination with RTV. The pharmacokinetics of EVG after administration of the Phase 3 formulation of EVG (Formulation 2; to-be-marketed) have only been evaluated in combination with ritonavir or cobicistat. The pharmacokinetics of EVG following unboosted administration of Formulation 2 have not been evaluated.

EVG pharmacokinetics were evaluated following single- and multiple-dose BID administration of EVG 100 mg (Formulation 1) alone or with RTV 100 mg in healthy subjects (Study GS-US-183-0102). EVG $AUC_{tau}$ was approximately 20% lower after multiple dosing of EVG 100 mg than after a single dose, suggesting autoinduction of its own metabolism. RTV increased EVG exposures (20-fold increase in AUC) due to decreased first-pass metabolism and reduced systemic clearance (Table 5).

**Table 5. Summary of PK parameters after single- or multiple-dose administration of EVG alone or with ritonavir**

| | EVG Alone (N = 12) | | EVG + RTV (N = 12) | |
|---|---|---|---|---|
| Plasma PK Parameter | Day 1 (Single Dose) | Day 10 (Multiple Dose) | Day 11 (Single Dose) | Day 20 (Multiple Dose) |
| **EVG** | | | | |
| AUC (ng•h/mL)[a] | 908.1 (28.3) | 719.3 (26.2) | 6167.3 (29.1)[b] | 14,302.1 (23.7) |
| $C_{max}$ (ng/mL) | 200.1 (30.4) | 164.1 (28.8) | 795.3 (38.4) | 1826.4 (26.4) |
| $C_{tau}$ (ng/mL)[c] | 19.2 (52.5) | 12.4 (63.7) | 543.3 (30.4) | 1035.6 (32.0) |
| $T_{½}$ (h) | 3.1 (2.2, 4.8) | 3.5 (2.2, 4.1) | 18.2 (9.0,42.6)[b] | 9.5 (5.9, 78.2) |
| **RTV** | | | | |
| AUC (ng•h/mL)[d] | — | — | 4979.4 (57.8)[e] | 9402.5 (46.9) |
| $C_{max}$ (ng/mL) | — | — | 616.3 (53.5) | 1686.5 (46.5) |
| $C_{tau}$ (ng/mL)[c] | — | — | 219.8 (61.8) | 544.8 (44.3) |
| $T_{½}$ (h) | — | — | 5.1 (2.2, 8.3)[e] | 4.8 (4.3, 6.9) |

Data are presented as mean (%CV), except for $T_{½}$, which is presented as median (min, max).

a For EVG, AUC represents $AUC_{inf}$ on Day 1 and $AUC_{tau}$ on Days 10, 11, and 20.

b n = 10

c $C_{tau}$ represents the concentration at the end of the dosing interval for Days 1, 10, 11, and 20.

d For RTV, AUC represents $AUC_{inf}$ on Day 11 and $AUC_{tau}$ on Day 20.

e n = 11

The single- and multiple-dose PK of EVG following coadministration of RTV 100 mg and the Phase 3 formulation (Formulation 2) of EVG 150 mg or the test formulation (Formulation 1) of EVG 125 mg in healthy subjects were evaluated in Study GS-US-183-0140. Results demonstrated that EVG exposures (AUC and $C_{max}$) were similar following single- or multiple-

dosing of the Phase 3 formulation (Formulation 2) of EVG/r 150/100 mg, indicating substantial CYP3A inhibition was achieved after a single dose of RTV (Table 6).

**Table 6. Summary of single- and steady-state EVG PK parameters following coadministration of EVG/r 150/100 mg (Phase 3 EVG formulation)**

| Elvitegravir PK Parameter | Single dose (N=12) | Steady-state (N=24) |
|---|---|---|
| $C_{max}$ (ng/mL), Mean (%CV) | 1414.1 (49.7) | 2126.3 (37.6) |
| $T_{max}$ (h), Median (Min, Max) | 4.25 (4.00, 5.00) | 4.00 (2.00, 6.00) |
| $AUC_{0\text{-}last}$ (ng·h/mL), Mean (%CV) | 14430.5 (51.8) | – |
| $AUC_{inf}$ (ng·h/mL), Mean (%CV) | 19977.9 (55.8) | – |
| $AUC_{tau}$ (ng·h/mL), Mean (%CV) | – | 22120.7 (32.3) |
| $T_{1/2}$ (h), Median (Min, Max) | 11.19 (7.34, 14.31) | 9.13 (6.03, 13.96) |

### 2.2.5.2 How does the PK of the drug and its active metabolites in healthy volunteers compare to that in patients?

EVG pharmacokinetics are similar following administration of the EVG 150 mg Phase 3 formulation boosted with RTV 100 mg in healthy subjects and HIV patients based on population PK analysis (Table 7).

**Table 7. Steady-state EVG PK parameters after once-daily administration of EVG in HIV-1 infected subjects or in healthy subjects**

| | HIV-1 Infected Subjects (Population PK) | | | Healthy Subjects |
|---|---|---|---|---|
| EVG PK Parameter | EVG Overall (N = 334) | EVG 85 mg (N = 125) | EVG 150 mg (N = 209) | EVG 150 mg (N = 24) |
| $AUC_{tau}$ (ng•h/mL) | 18,000 (37) | 17,600 (40) | 18,300 (36) | 22,100 (32) |
| $C_{max}$ (ng/mL) | 1380 (28) | 1210 (30) | 1470 (25) | 2130 (38) |
| $C_{tau}$ (ng/mL) | 378 (57) | 422 (56) | 351 (57) | 440 (48) |

Data are mean (%CV) and are shown to 3 significant digits.

### 2.2.5.3 What are the characteristics of drug absorption?

EVG appears to be a highly permeable compound and a substrate for P-gp. Absorption is unaffected by local pH, but EVG is subject to chelation by high concentrations of divalent and trivalent cations. Dissolution appears to be limited by solubility.

In LLC-PK1 cells transfected with control vector, permeability was 6- to 12-fold higher than the low-permeability control mannitol and independent of direction (B:A/A:B ratios <2) (Study JTK303-AD-026). EVG was also transported across MDR1-expressing LLC-PK1 cells in a polarized manner (B:A/A:B ratios ≥13.6), indicating that it is a P-gp substrate (for comparison, the B:A/A:B ratios for the P-gp probe substrate digoxin were ≥9.1; please refer to Section 2.4.2.4

of this review for further details). However, nonclinical studies in rats and dogs showed no evidence for greater than dose-proportional increases in exposures (which would have been indicative of saturation of intestinal P-gp), possibly due to additional mechanisms of EVG transport.

Coadministration of EVG/r and the proton pump inhibitor omeprazole demonstrated no effect of intragastric pH on EVG absorption (GS-US-183-0119).

Cross-study comparisons of EVG exposures following multiple doses of EVG/r showed that exposures of EVG increased in a less-than-proportional manner (doubling the EVG 150 mg dose [GS-US-183-0140] to 300 mg [GS-US-183-0128 and GS-US-183-0147] led to 1.1- to 1.4-fold increases in mean EVG $C_{trough}$), which could be due to solubility-limited dissolution.

Please see Section 2.5.3 of this review for information regarding the effect of food administration on EVG exposures.

#### 2.2.5.4 What are the characteristics of drug distribution?

EVG is 98-99% bound to plasma proteins over an EVG concentration range of 0.1-10 ug/mL (JTK303-AD-014). EVG preferentially bound to human serum albumin (HSA) over α1-acid glycoprotein (AAG; JTK303-AD-013). The blood:plasma ratio is approximately 0.73 over the timecourse evaluated (GS-US-183-0126), indicating that EVG and its metabolites are predominantly distributed to plasma relative to the cellular components of blood.

Population PK analyses using data from 876 subjects (485 healthy subjects and 391 HIV-1 infected subjects across 22 clinical studies) provided an estimated apparent volume of distribution (V/F) of 197.9 L.

#### 2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The mass balance trial (GS-US-183-0126) demonstrated that the majority of the RTV-boosted [$^{14}$C]-EVG dose was recovered in the feces (94.8%), suggesting that the primary route of EVG elimination is hepatobiliary. A small fraction of the radioactive dose was recovered in the urine (6.7%). The radioactivity in feces consisted mainly of EVG (30.8%) and hydroxylation products (GS-9202 33.8%). No parent drug was detected in the urine.

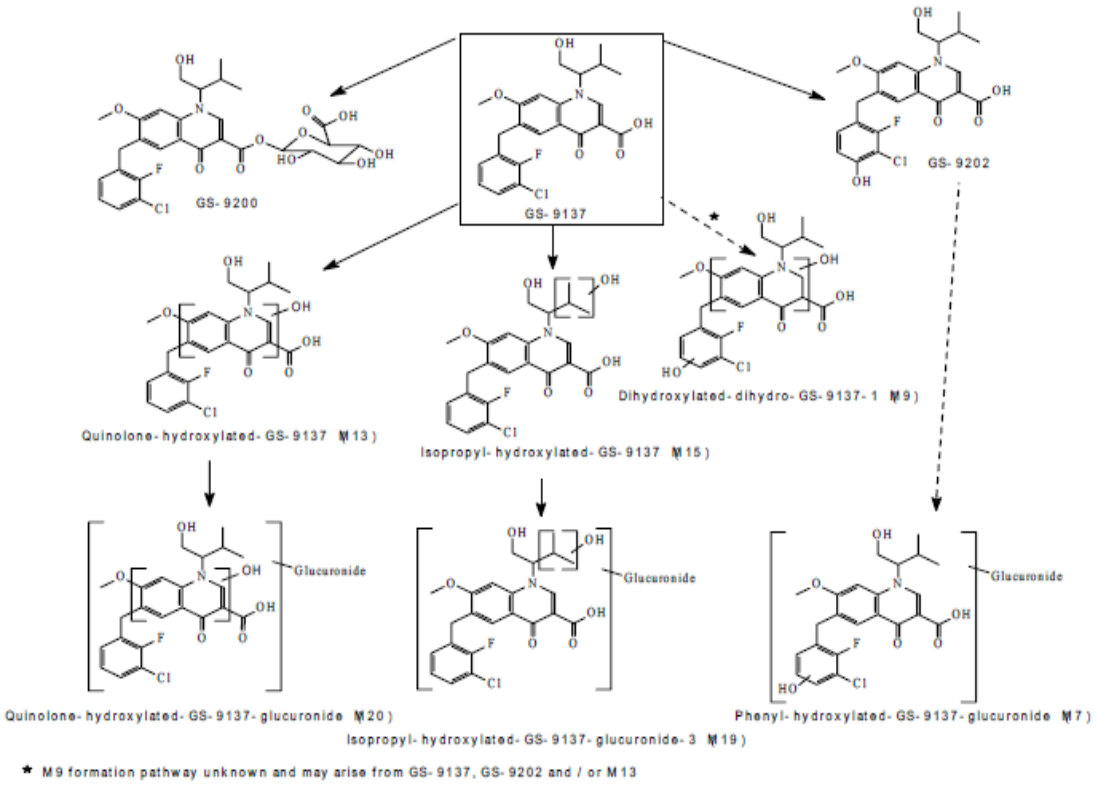
#### 2.2.5.6 What are the characteristics of drug metabolism?

The biotransformation of EVG primarily occurs via CYP3A4-mediated hydroxylation and UGT1A1/3-mediated primary and/or secondary glucuronidation (Figure 5). The primary route of metabolism is supported by the significant increase in EVG exposures in the presence of the potent CYP3A inhibitors RTV or Cobi.

There are two primary metabolites: M1 (GS-9202), a chlorofluorophenyl group hydroxide of EVG formed by CYP3A4 in the absence of a CYP3A4 inhibitor (M1 concentrations are generally below the limit of quantification when EVG is coadministered with RTV or Cobi); and M4 (GS-9200), an acyl glucuronide of EVG formed by UGT1A1/3. Plasma exposures of GS-9200 are generally <10% of EVG exposures and are unaffected by boosting. M1 is 5- to 18-fold and M4 is 10- to 38-fold less potent than EVG; as such, the metabolites are not considered to contribute to the antiviral activity of EVG.

Data from the mass balance trial indicated that the predominant circulating species in plasma is EVG (approximately 94% of radioactivity). EVG and GS-9202 were the primary species in the feces, while glucuronidation metabolites of EVG were the primary species in the urine.

**Figure 5. Proposed biotransformation pathway of EVG in humans**




### 2.2.5.7 What are the characteristics of drug excretion?

Please refer to Section 2.2.5.5 of this review.

### 2.2.5.8 Based on the PK parameters, what is the degree or linearity or nonlinearity in the dose-concentration relationship?

Cross-study analyses (GS-US-183-0119, GS-US-183-0125, GS-US-183-0128, and GS-US-183-0147) demonstrate less-than-proportional increases in exposures over the EVG dose range of 50 to 300 mg (adjusted for formulation) coadministered with RTV 100 mg (Table 8).

**Table 8. Summary of EVG PK parameters across the EVG/r dose range in healthy subjects**

| EVG PK Parameter | EVG/r 50/100 mg[a] (N = 48) | EVG/r 125/100 mg[a] (N = 41) | EVG/r 250/100 mg[a] (N = 42) | EVG/r 300/100 mg[b] (N = 19) | EVG/r 300/100 mg[b] (N = 15) |
|---|---|---|---|---|---|
| $AUC_{tau}$ (ng•h/mL) | 10,700 (28) | 24,200 (36) | 35,700 (27) | 33,500 (25) | 30,700 (16) |
| $C_{max}$ (ng/mL) | 930 (31) | 2270 (35) | 3660 (33) | 2950 (20) | 2770 (17) |
| $C_{tau}$ (ng/mL) | 211 (40) | 450 (49) | 632 (38) | 614 (40) | 485 (26) |

Note: Data are mean (%CV) and are shown to 3 significant digits.

a Data from Studies GS-US-183-0119 and GS-US-183-0128 were generated using the EVG Phase 2 formulation. The 125-mg EVG Phase 2 formulation provides similar exposures as 150 mg of the Phase 3 formulation; the 250-mg dose is expected to provide exposures corresponding to 300 mg of the Phase 3 formulation.

b Data from Studies GS-US-183-0125 and GS-US-183-0147 were generated using the EVG Phase 3 formulation.

#### 2.2.5.9 How do the PK parameters change with time following multiple dosing?

Please refer to Section 2.2.5.1 of this review.

#### 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The intersubject variability of EVG PK parameters was generally low in both healthy and HIV-1 infected subjects. In healthy subjects, following administration of multiple doses of EVG 150 mg coefficient of variation (%CV) values were 37.6%, 47.8%, and 32.3% for EVG $C_{max}$, $C_{tau}$, and $AUC_{tau}$ (Study GS-US-183-0140). The degree of interindividual variability (IIV) was similar in HIV-1 infected patients: population PK analysis generated %CV values of 28%, 57%, and 37% for EVG $C_{max}$, $C_{tau}$, and $AUC_{tau}$, respectively. Based on the population PK analysis, the IIV (%CV) for apparent oral clearance (CL/F) and apparent volume of distribution ($V_c$/F) were 39.1% and 37.5%, respectively.

The major causes of variability were subject body surface area (BSA) and RTV exposure (RAUC), both of which were included in the final population PK model. Relative to the median BSA, the observed range ($5^{th}$ to $95^{th}$ percentile) corresponded to differences of -24% to +27% in EVG clearance, resulting in +29% to -23% change in EVG exposures ($AUC_{tau}$), which was not considered to be clinically significant. Relative to the mean RAUC, the observed range ($5^{th}$ to $95^{th}$ percentile) corresponded to differences of -15% to +12% in EVG bioavailability, which was not considered to be clinically significant.

There were insufficient data to evaluate the intrasubject variability of EVG PK parameters.

### 2.3. INTRINSIC FACTORS

#### 2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on

**pharmacodynamics? What dosage regimen adjustments are recommended for each of these subgroups, if any?**

Following administration of RTV-boosted EVG, EVG exposures were not affected by age, race, estimated glomerular filtration rate (eGFR), HIV-1 disease status, or hepatitis B virus (HBV) and/or hepatitis C virus (HCV) coinfection. Based on population PK analysis, females had approximately 21% lower clearance compared to males; however, this change did not result in any corresponding increase in virological success for females. A statistically significant relationship between EVG exposures and body surface area was identified during population PK analyses, but the extent of change in EVG exposure is not clinically relevant.

The effect of age on EVG exposures was also evaluated in Study GS-US-183-0152, in which EVG was coadministered with a RTV-boosted PI (PI/r) in a background regimen to adolescents at an EVG dose of 85 or 150 mg QD (depending on the PI/r). EVG exposures in adolescents were comparable to those in adults (Table 9 and Figure 6; also refer to Section 2.3.2.2 of this review). Within the adolescent population, there were no relevant changes in EVG exposure with age.

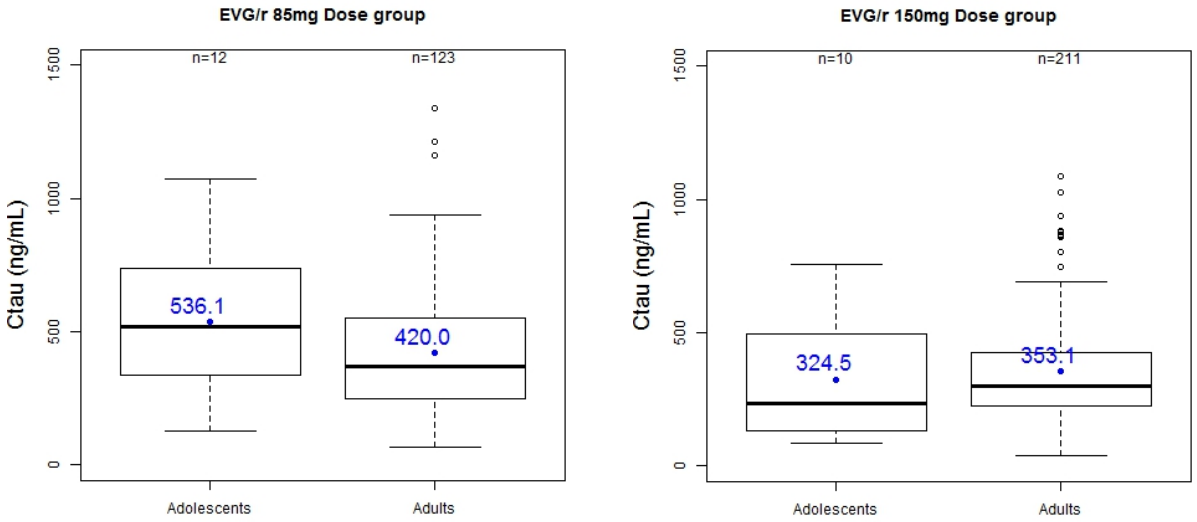
**Table 9. Statistical comparisons of EVG PK parameters for adolescent versus adult subjects**

| Plasma PK Parameter | Adolescent Mean (%CV) | | Exploratory Statistical Comparisons Adolescent (Test) vs HIV-1 Infected Adult (Reference)[a] GLSM Ratio (%) (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

a n = 24 HIV-1 infected adults from Study GS-US-183-0105 (EVG 125 mg) and Study GS-US-236-0104 (EVG 150 mg) combined (m5.3.5.1, GS-US-183-0105 CSR; QUAD STR NDA 203100, Sequence 0000, m5.3.5.1, GS-US-236-0104 CSR). 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 (m5.3.1.2, GS-US-183-0140 CSR).

**Figure 6. EVG $C_{tau}$ in adolescents (Trial GS-US-183-0152*) and adults (Phase 3 Trial GS-US-183-0145)**




* A very high concentration outlier is excluded in this analysis

Based on these findings, no dose adjustments are recommended based on the intrinsic factors discussed above.

**2.3.2. Based upon what is know about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

**2.3.2.1 Elderly**

The pivotal Phase 3 trial GS-US-183-0145 (total N=334) included 36 subjects aged 55 years old or above. Population PK analysis indicated that age did not have a significant effect on EVG exposures (Table 10); no EVG dose adjustments are recommended for this subpopulation.

**Table 10. Mean (%CV) EVG exposures by age following administration of EVG in HIV-1 infected subjects**

| Age | $AUC_{tau}$ (ng•h/mL) | $C_{max}$ (ng/mL) | $C_{trough}$ (ng/mL) |
|---|---|---|---|
| < 55 years of age (N = 298) | 17,900 (38) | 1360 (29) | 374 (58) |
| ≥ 55 years of age (N = 36) | 19,300 (28) | 1480 (22) | 410 (50) |

Data are mean (%CV) and are shown to 3 significant digits.

There were six subjects aged 65 years old or above included in the analysis, providing insufficient data to compare EVG exposures in this group to those in the general population.

### 2.3.2.2 Pediatrics

EVG PK were evaluated in HIV-1 infected adolescents (aged 12 years old to <18 years old) after 10 days of treatment in Study GS-US-183-0152. The EVG dose and allowed ARV BR containing a PI/r were identical to those evaluated in GS-US-183-0145. The results of this study showed that EVG exposures in both the 85 mg and 150 mg dose groups were comparable in adolescents relative to adults (Table 11). When the 85 mg and 150 mg dose groups were analyzed collectively, EVG $AUC_{tau}$ and $C_{max}$ values were slightly higher (by 22.3% and 29.6%, respectively) and $C_{tau}$ was also higher (by 64.8%) in adolescents compared to adults (Table 9). The minor changes in EVG exposures are not clinically relevant and may be explained by the inverse relationship between body surface area and EVG exposure; the higher mean $C_{tau}$ remains below the mean $C_{max}$ and does not pose a safety concern. No EVG dose adjustments are recommended for adolescents.

**Table 11. Multiple-dose EVG exposures following administration of EVG 85 mg or 150 mg in combination with RTV 100 mg and a PI-containing BR in HIV-1 infected adolescent versus adult subjects**

| | Adolescents | | Adults[a,b] | |
|---|---|---|---|---|
| EVG PK Parameter | EVG 85 mg (n = 13) | EVG 150 mg (n = 10) | EVG 85 mg (n = 12) | EVG 150 mg (n = 19) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 25,299.2 (44.7) | 21,199.7 (35.7) | 21,918.1 (56.4) | 20,298.1 (51.5) |
| $C_{max}$ (ng/mL) Mean (%CV) | 2142.3 (44.6) | 2067.0 (35.8) | 1514.4 (49.7) | 1721.5 (43.3) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 627.0 (68.9) | 324.5 (72.5) | 759.6 (73.3) | 378.2 (67.4) |

a The PK substudy analysis set for EVG includes all subjects who received at least 1 dose of EVG and for whom steady-state PK parameters at Week 2 were evaluable for EVG.

b Values below the lower limit of quantitation were treated as 0 for summary statistics.

GS-US-183-0152 had an optional 48-week treatment phase in which the safety and tolerability of EVG/r were evaluated. EVG was well-tolerated in the nine subjects who enrolled in and completed the treatment phase. (b) (4)

(b) (4)

(b) (4)

### 2.3.2.3 Gender

Based on a population PK analysis of pooled data from 22 studies, females had approximately 21% lower clearance compared to males. The Phase 3 study GS-US-183-0145 (N=334 in the PK/PD analysis set) included 58 female subjects. Analysis of population PK-derived exposure metrics for Phase 3 subjects indicated that females had ~17% higher EVG exposures ($C_{tau}$) than males (Table 12, Figure 7). However, this higher exposure did not result in any corresponding higher efficacy (PVR) for females. In fact, the PVR were 11-18% lower in females compared to males in the Phase 3 study across the two dose subgroups (Figure 7). The analysis with actual concentrations measured through 48 weeks for each individual showed that there were 54% female subjects who had one or more BLQ (below level of quantitation) concentrations compared to 41% of males. Thus the lower efficacy (PVR) in females can be partially attributable to lower adherence to dosing regimen observed in females compared to males. Since gender differences did not have a clinically significant effect on EVG exposures and EVG exposures did not contribute to difference in efficacy responses across genders, no dose adjustments are recommended based on gender.

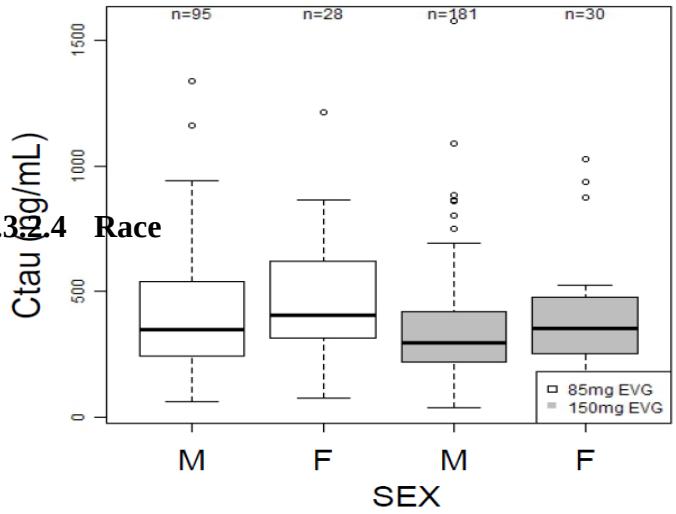
**Table 12. Mean (%CV) EVG exposures by gender following administration of EVG in HIV-1 infected subjects**

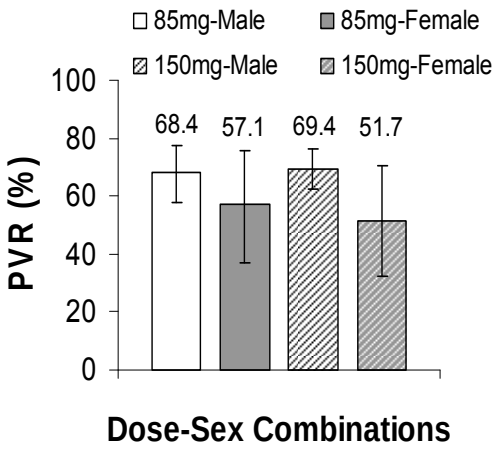
| Gender | $AUC_{tau}$ (ng•h/mL) | $C_{max}$ (ng/mL) | $C_{trough}$ (ng/mL) |
|---|---|---|---|
| Female (N = 58) | 20,000 (39) | 1480 (30) | 429 (55) |
| Male (N = 276) | 17,600 (37) | 1350 (27) | 367 (58) |

Data are mean (%CV) and are shown to 3 significant digits.

**Figure 7. (A) EVG $C_{tau}$ derived from population PK analysis versus gender; (B) percentage PVR versus gender relationship in different dose subgroups in Phase 3 data**

**A.** **B.**




**2.3.2.4 Race**

**2.3.2.5 Race**

The majority of subjects enrolled in GS-US-183-0145 (total N=334) were white (60.2%), with 35.3% of subjects who were black and 2.7% who were Asian. Population PK analysis indicated that race did not have a significant effect on EVG exposures (Table 13), although the sample size for Asian subjects was limited. A population PK analysis also showed no change in clearance based on race. No dose adjustments are recommended based on race.

**Table 13. Mean (%CV) EVG exposures by race following administration of EVG in HIV-1 infected subjects**

| Race | $AUC_{tau}$ (ng•h/mL) | $C_{max}$ (ng/mL) | $C_{trough}$ (ng/mL) |
|---|---|---|---|
| Asian (N = 9) | 19,000 (37) | 1480 (30) | 380 (51) |
| Black (N = 118) | 17,900 (37) | 1360 (30) | 382 (52) |
| White (N = 201) | 17,900 (38) | 1380 (27) | 373 (62) |

Data are mean (%CV) and are shown to 3 significant digits.

### 2.3.2.6 Renal impairment

Steady-state EVG pharmacokinetics were evaluated in subjects with severe renal impairment (eGFR <30 mL/min) not on dialysis and matched healthy controls with normal renal function (eGFR ≥90 mL/min) following multiple-dose administration of EVG/Cobi 150/150 mg QD (Study GS-US-216-0124). Since RTV and Cobi are both mechanism-based inhibitors of CYP3A, the effect of renal impairment on EVG exposure following EVG/r administration is expected to be the same as that following administration of EVG/Cobi. Steady-state EVG plasma concentrations were lower in subjects with severe renal impairment (Table 14). It should be noted that for unexplained reasons, mean EVG exposures in the normal renal function group had substantially higher exposures compared to historical data. However, based on the EVG exposure-response relationship, the differences between EVG exposures in patients with severe renal impairment relative to those in subjects with normal renal function are not considered to be clinically relevant. In addition, severe renal impairment was found to have no effect on EVG protein binding (% free fraction was 1.16 in control subjects vs. 1.42 in subjects with severe renal impairment). Therefore, no EVG dose adjustment is recommended in patients with mild, moderate, or severe renal impairment.

**Table 14. Statistical comparison of elvitegravir PK parameters for Test (severe renal impairment) versus Reference (normal matched control) treatments**

| EVG PK Parameter | Geometric Least-Squares Mean | | Geometric Least-Squares Means Ratio (%) (90% CI) |
|---|---|---|---|
| | Test Severe Renal Impairment $eGFR_{CG}$ < 30 mL/min (N = 12) | Reference Normal Renal Function $eGFR_{CG}$ ≥ 90 mL/min (N = 11) | |
| $AUC_{tau}$ (ng•h/mL) | 25316.69 | 33530.63 | 75.50 (62.82, 90.75) |
| $C_{max}$ (ng/mL) | 2154.03 | 3200.46 | 67.30 (54.78, 82.68) |
| $C_{tau}$ (ng/mL) | 491.26 | 711.29 | 69.07 (51.82, 92.06) |

#### 2.3.2.7 Hepatic impairment

Steady-state EVG pharmacokinetics were evaluated in subjects with moderate hepatic impairment and matched healthy controls following administration of EVG/Cobi 150/150 mg QD for 10 days in Study GS-US-183-0133. Steady-state EVG plasma concentrations were higher in subjects with moderate hepatic impairment (Table 15). Based on the EVG exposure-response and -safety relationships, the effect of mild or moderate hepatic impairment is not considered to be clinically relevant and no EVG dose adjustment is recommended in these patient populations.

**Table 15. Statistical comparison of elvitegravir PK parameters for Test (moderate hepatic impairment) versus Reference (normal matched control) treatments**

| PK Parameter | GLSMs | | GLSM Ratio (%) (90% CI) |
|---|---|---|---|
| | Reference Treatment: Normal Matched Control Group (N=10) | Test Treatment: Moderate Hepatic Impairment Group (N=10) | |
| $AUC_{tau}$ (ng•h/mL) | 20537.29 | 27722.39 | 134.99 (103.09, 176.75) |
| $C_{tau}$ (ng/mL) | 335.30 | 602.29 | 179.63 (111.03, 290.60) |
| $C_{max}$ (ng/mL) | 1880.67 | 2657.00 | 141.28 (108.80, 183.45) |

GLSMs were obtained using a mixed-effects model. The model included treatment, sequence, and period as fixed effects, and subject-within-sequence as a random effect.

Neither RTV (Norvir®) nor EVG has been studied in patients with severe hepatic impairment. Per the approved Norvir® labeling, RTV is not recommended for use in patients with severe hepatic impairment, therefore; to the pharmacokinetics and safety of EVG/r in subjects with severe hepatic impairment were not evaluated in this development program.

#### 2.3.2.8 What pregnancy and lactation use information is there in the application?

No information regarding the use of EVG in pregnant or lactating women was included in the application.

### 2.4. EXTRINSIC FACTORS

#### 2.4.1. What extrinsic factors influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

The effects of two extrinsic factors – the administration of EVG with food and the administration of EVG with other drugs (antacids, zidovudine, atazanavir/r, didanosine, stavudine, etravirine, abacavir, lopinavir/r, maraviroc, omeprazole, darunavir/r, fosamprenavir/r, rifabutin, ketoconazole, famotidine, rosuvastatin, and norgestimate plus ethinyl estradiol) – were evaluated by the Applicant. The first is discussed in Section 2.5.3 and the second is discussed in Section 2.4.2 of this review.

### 2.4.2. Drug-drug interactions

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, EVG is a substrate for CYP3A4, UGT1A1/3, and P-gp. It is also an inhibitor of OATP1B1 and OATP1B3.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

EVG is a substrate of CYP3A4 and UGT1A1. It is primarily metabolized by CYP3A4, although metabolism by CYP3A5 and CYP1A1 was also detected (Study JTK303-AD-017). In liver microsomes from rats, dogs, monkeys, and humans, the primary metabolite of EVG in the presence of NADPH was M1, a chlorofluorophenyl group hydroxide of EVG (Study JTK303-AD-015), while the primary metabolite of EVG in the presence of uridine diphosphoglucuronic acid was M4, an acyl-glucuronide of EVG (Study JTK303-AD-016), which is formed by UGT1A1.

CYP3A4 is (b) (4) metabolism is not substantially influenced by genetics.

UGT1A1 (b) (4) Two common haplotypes, UGT1A1*28 (a promoter repeat with an allele frequency of approximately 40-45% in African Americans and Caucasians) and UGT1A1*6 (a missense mutation in exon 1 with an allele frequency of 20-25% in Asians), are associated with decreased enzymatic expression and function, respectively. Based on in vitro studies, UGT1A1*6 is expected to be approximately 30-70% less active than the reference enzyme (Udomuksorn *et al* Pharmacogenet Genomics 17:1017-29), while UGT1A1*28 is expected to be 50-70% less active than the reference enzyme (Iyer *et al* Clin Pharm Ther 65:876-582). Patients with the UGT1A1*28 and UGT1A1*6 haplotypes are expected to have higher EVG exposures compared to patients with the reference haplotype.

Atazanavir is an inhibitor of UGT1A1 ($K_i$ 1.9 uM). In Study GS-US-183-0108, EVG exposures increased following 14 days of administration of EVG 200 mg plus ATV/r 300/100 mg QD (geometric means: $C_{max}$ 5460 ng/mL, $AUC_{tau}$ 57037 ng·h/mL, $C_{tau}$ 1448 ng/mL). These exposures are higher than those expected in UGT1A1*28 and UGT1A1*6 carriers following administration of EVG 150 mg QD. In terms of treatment-related adverse events, the safety profile of EVG plus ATV/r was similar to that of ATV/r alone (the most common treatment-related adverse events were hepatobiliary disorders, which are associated with atazanavir use). Therefore, exposures in UGT1A1*28 or UGT1A1*6 carriers following administration of EVG 150 mg are expected to be reasonably safe and well-tolerated.

#### 2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

The inhibitory potential of EVG at concentrations of up to 30 ug/mL on CYP1A, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 were investigated using human liver microsomes (Study JTK303-AD-027). The $IC_{50}$ values for all of the CYP isoforms evaluated was greater than 30 ug/mL, with the exception of CYP3A4, which had an $IC_{50}$ of 28.32 ug/mL. Inhibition of CYP3A4 by EVG is not expected to have a clinical impact, since the steady-state

mean EVG $C_{max}$ is approximately 1.4 ug/mL following oral administration in the presence of RTV, which itself is a potent CYP3A4 inhibitor.

The induction potential of EVG at concentrations of up to 10 ug/mL on CYP1A2, CYP2C9, CYP2C19, and CYP3A4 were investigated using primary cultured human hepatocytes (Study JTK303-AD-023). At the highest concentration evaluated, EVG is a weak inducer of CYP3A4 (10.6 to 19.1-fold increase in CYP3A activity relative to vehicle control). This inductive effect will most likely be overcome by the inhibitory effect of RTV when EVG is coadministered with a RTV-boosted PI per the proposed indication.

### 2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

EVG is a substrate of P-glycoprotein (P-gp). *In vitro* studies demonstrated transport across LLC-PK1 cells transfected with the MDR1 gene in a polarized manner (B:A/A:B ratios ≥13.6; Table 16 and Study JTK303-AD-026). Please refer to Section 2.2.5.3 of this review for further details.

**Table 16. Transport of EVG and control compounds across LLC-PK1 monolayers transfected with control vector or human MDR1**

| Compound | Time (h) | Cleared Volume (µL/mg Cellular Protein) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Control Cells | | | MDR1-Expressing Cells | | |
| | | A-B | B-A | Ratio | A-B | B-A | Ratio |
| EVG | 1 | 179.2 ± 16.7 | 207.8 ± 11.2 | 1.2 | 64.1 ± 17.3 | 961.9 ± 75.8 | 15.0 |
| | 2 | 412.7 ± 20.0 | 512.8 ± 34.4 | 1.2 | 139.4 ± 25.2 | 1891.6 ± 126.1 | 13.6 |
| | 4 | 606.4 ± 18.7 | 912.6 ± 62.9 | 1.5 | 212.1 ± 34.7 | 3085.4 ± 65.7 | 14.5 |
| Digoxin | 1 | 21.6 ± 1.1 | 44.6 ± 10.3 | 2.1 | 25.3 ± 9.0 | 245.8 ± 27.0 | 9.7 |
| | 2 | 48.6 ± 9.5 | 96.7 ± 16.1 | 2 | 54.9 ± 5.1 | 498.1 ± 69.8 | 9.1 |
| | 4 | 103.0 ± 20.1 | 229.8 ± 27.4 | 2.2 | 97.4 ± 12.3 | 1000.2 ± 125.8 | 10.3 |
| Mannitol | 1 | 24.1 ± 12.8 | 16.2 ± 1.2 | 0.7 | 53.9 ± 36.4 | 42.9 ± 18.2 | 0.8 |
| | 2 | 36.6 ± 10.4 | 35.7 ± 4.0 | 1 | 97.0 ± 63.6 | 83.6 ± 27.4 | 0.9 |
| | 4 | 89.9 ± 14.4 | 73.5 ± 6.3 | 0.8 | 176.9 ± 100.2 | 131.7 ± 33.8 | 0.7 |

A-B = apical to basal; B-A = basal to apical; EVG = elvitegravir; MDR1 = P-glycoprotein

The inhibitory potential of EVG on P-gp was also evaluated in LLC-PK1 cells (Study JTK303-AD-026). EVG did not inhibit P-gp at pharmacologically relevant concentrations ($IC_{50}$ >30 uM [13.4 ug/mL]).

### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The inhibitory potential of EVG at concentrations of up to 2 uM (896 ng/mL) on OATP1B1 and OATP1B3 was evaluated in transfected CHO cells (Study AD-183-2030). EVG inhibited OATP1B1 by 40% at the highest concentration tested, with an $IC_{50}$ value >2 uM. The $IC_{50}$ for OATP1B3 was 0.44 uM (197 ng/mL).

The $[I]_1/IC_{50}$ values for both OATP1B1 and OATP1B3 indicated the need for an *in vivo* drug-drug interaction trial using a probe drug such as rosuvastatin.

Please refer to Section 2.4.2.2 above for more information on the role of UGT1A1 in EVG biotransformation.

**2.4.2.6 Does the label specify coadministration of another drug (e.g. combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?**

The label specifies that EVG should be coadministered with a RTV-boosted PI in an ARV background regimen. The pharmacokinetics of EVG/r have been extensively characterized (refer to Section 2.2.5.1). The pharmacokinetics of EVG coadministered with DRV/r, FPV/r, TPV/r, LPV/r, and ATV/r have been evaluated in dedicated drug-drug interaction trials (GS-US-183-0120, GS-US-183-0123, GS-US-183-0110, GS-US-183-0116, and GS-US-183-0147, respectively) as well as in the pivotal Phase 3 trial (GS-US-183-0145). The results of these trials demonstrated that EVG should be dose-reduced to 85 mg QD when coadministered with LPV/r and ATV/r due to protease inhibitor-mediated inhibition of UGT1A1.

**2.4.2.7 What other comedications are likely to be administered to the target patient population?**

People with HIV-1 infection may be receiving a number of concurrent medications to treat or prevent comorbidities, including antihyperlipidemic drugs, selective serotonin reuptake inhibitors (SSRIs), antibacterial drugs, phosphodiesterase 5 (PDE5) inhibitors, oral contraceptives, or drugs used to treat opioid dependence or tuberculosis.

**2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are coadministered?**

The Applicant conducted drug-drug interactions in several trials using EVG boosted by RTV or Cobi. (Since RTV and Cobi are both mechanism-based inhibitors of CYP3A, the effect of a concomitantly administered drug on EVG exposure following EVG/r administration is expected to be the same as that following administration of EVG/Cobi). Clinical recommendations regarding the administration of EVG and concomitant drugs are based on drug-drug interaction trials conducted as part of this NDA or suspected interactions based on mechanistic information.

The pharmacokinetic results of drug-drug interaction trials submitted with this Application, as well as clinical recommendations regarding dosing of EVG and concomitant drugs, are listed in Tables 17 and 18. All drug-drug interaction trials were conducted in healthy subjects.

**Table 17. Tabulated summary of the results of drug-drug interaction trials conducted to determine the effect of coadministered drugs on EVG PK (actionable clinical recommendations are indicated in bold font)**

| Drug | Study | N | Relevant treatments; Dosage regimens; Duration of treatment | EVG $C_{max}$ GLSM ratio (90% CI) | EVG $C_{tau}$ GLSM ratio (90% CI) | EVG $AUC_{tau}$ GLSM ratio (90% CI) | Clinical recommendation |
|---|---|---|---|---|---|---|---|
| Emtricitabine (FTC) Tenofovir (TDF) | 183-0103 | 26 | • EVG/r 50/100 mg QD (10 days)<br>• FTC/TDF 200/300 mg QD (7 days)<br>• FTC/TDF 200/300 mg + EVG/r 50/100 mg QD (10 days) | 98.4 (90.4, 107.2) | 113.7 (104.3, 123.8) | 102.4 (96.3, 109.0) | EVG/r and FTC/TDF can be coadministered with dose adjustments |
| Antacid | | | • EVG/r 50/100 mg QD (10 days)<br>• EVG/r 50/100 mg + 20 mL $Mg^{2+}/Al^{3+}$-containing antacid suspension QD (1 day) | 53.1 (46.8, 60.2) | 59.1 (52.0, 62.7) | 55.1 (50.4, 60.2) | EVG/r and antacid should not be coadministered simultaneously due to complexation with divalent and trivalent cations in the active site of HIV-1 integrase |
| **Antacid** | 183-0119 | 60 | • EVG/r 50/100 mg (10 days)<br>• EVG/r 50/100 mg 4 h before or after 20 mL Maalox Max (1 day)<br>• EVG/r 50/100 mg 2 h before or after 20 mL Maalox Max (1 day) | 4 h after: 94.75 (83.9, 107.0)<br>4 h before: 98.32 (88.16, 109.65)<br>2 h after: 82.23 (74.10, 91.26)<br>2 h before: 78.86 (70.71, 87.95) | 4 h after: 104.3 (88.29, 103.99)<br>4 h before: 99.98 (90.14, 110.90)<br>2 h after: 90.44 (82.29, 99.39)<br>2 h before: 80.48 (72.90, 88.85) | 4 h after: 95.82 (88.29, 103.99)<br>4 h before: 98.20 (91.26, 105.66)<br>2 h after: 84.76 (79.04, 90.90)<br>2 h before: 80.30 (74.63, 86.40) | **EVG/r and antacid coadministration should be staggered by at least 2 hours** |
| Omeprazole | | | • EVG/r 50/100 mg (10 days)<br>• EVG/r 50/100 mg QD 2 h after omeprazole 40 mg (5 days) | 92.64 (82.59, 103.91) | 94.02 (84.71, 104.36) | 98.59 (91.27, 106.50) | EVG/r and omeprazole can be coadministered without dose adjustments |
| Famotidine | 216-0120 | 33 | • EVG/co 150/150 mg QD with food (8 days)<br>• EVG/co 150/150 mg QD with food + famotidine 40 mg with food 12 h after EVG/co (8 days) | 102.31 (89.42, 117.06) | 117.90 (105.13, 132.23) | 103.39 (94.87, 112.68) | EVG/r and famotidine can be coadministered without dose adjustments |
| Zidovudine (ZDV) | 183-0104 | 28 | • ZDV 300 mg BID (7 days)<br>• EVG/r 200/100 mg QD (10 days)<br>• ZDV 300 mg BID + EVG/r 200/100 mg QD (10 days) | 105.0 (98.3, 112.9) | 114.5 (104.4, 125.7) | 105.1 (99.3, 111.3) | EVG/r and ZDV can be coadministered without dose adjustments |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Atazanavir/ ritonavir (ATV/r)** | 183-0106 | 19 | • EVG/r 150/100 mg QD (10 days)<br>• ATV/r 300/100 mg QD (10 days)<br>• EVG 85 mg + ATV/r 300/100 mg QD (10 days) | 90.91 (91.38, 101.57) | 138.08 (118.30, 161.16) | 107.16 (95.09, 120.76) | **The dose of EVG should be reduced to 85 mg QD when coadministered with ATV/r 300/100 QD** |
| | 183-0108 | 32 | • EVG/r 200/100 mg QD (14 days)<br>• ATV/r 300/100 mg QD (14 days)<br>• EVG 200 mg + QTV/r 300/100 mg QD (14 days) | 184.92 (168.52, 202.92) | 287.81 (253.26, 327.08) | 199.50 (184.58, 215.62) | |
| | 183-0147[a] | 18 | • EVG/r 300/100 mg QD (10 days)<br>• EVG 300 mg + ATV 400 mg QD (10 days) | 108.35 (99.01, 118.56) | 89.89 (71.43, 113.12) | 106.73 (95.60, 119.17) | |
| Tipranavir/ ritonavir (TPV/r) | 183-0110 | 34 | • EVG/r 200/100 mg QD (14 days)<br>• TPV/r 500/200 mg BID (14 days)<br>• EVG 200 mg QD + TPV/r 500/200 mg BID (14 days) | 106.0 (89.4, 125.7) | 90.4 (69.8, 116.9) | 92.4 (78.7, 108.4) | EVG and TPV/r can be coadministered without dose adjustments |
| Didanosine (ddI) | 183-0111 | 32 | • ddI 400 mg (single dose)<br>• EVG/r 200/100 mg QD (10 days) | 95.02 (89.68, 100.68) | 106.43 (100.72, 112.46) | 96.74 (92.46, 101.21) | EVG/r and ddI can be coadministered without dose adjustments |
| Stavudine (d4T) | | | • d4T 40 mg (single dose)<br>• EVG/r 200/100 mg QD (10 days) | 96.00 (89.92, 102.48) | 124.34 (116.61, 132.58) | 98.73 (93.89, 103.82) | EVG/r and d4T can be coadministered without dose adjustments |
| Etravirine (ETV) | 183-0112 | 34 | • EVG/r 150/100 mg QD (10 days)<br>• EVG/r 150/100 mg QD + ETV 200 mg BID (10 days)<br>• ETV 200 mg BID (10 days)<br>• ETV 200 mg BID + EVG/r 150/100 mg QD (10 days) | 106.7 (100.8, 112.9) | 106.0 (97.0, 115.8) | 106.3 (99.9, 113.2) | EVG/r and ETR can be coadministered without dose adjustments |
| Abacavir (ABC) | 183-0115 | 26 | • ABC 600 mg (single dose)<br>• EVG/r 200/100 mg (10 days)<br>• ABC 600 mg + EVG/r 200/100 mg | 92.15 (83.91, 101.13) | 107.23 (97.67, 117.72) | 98.29 (91.04, 106.12) | EVG/r and ABC can be coadministered without dose adjustments |
| **Lopinavir/ ritonavir (LPV/r)** | 183-0116 | 32 | • EVG/r 125/100 mg QD (14 days)<br>• EVG 125 mg QD + LPV/r 400/100 mg BID (14 days)<br>• LPV/r 400/100 mg BID (14 days) | 151.74 (128.76, 178.82) | 238.06 (180.95, 313.18) | 174.98 (149.67, 204.57) | **The dose of EVG should be reduced when coadministered with ATV/r 300/100 QD** |
| Maraviroc (MVC) | 183-0118 | 36 | • EVG/r 150/100 mg QD (10 days)<br>• MVC 150 mg BID + EVG/r 150/100 mg QD (10 days)<br>• MVC 150 mg BID (10 days) | 101.11 (88.67, 115.31) | 109.25 (94.74, 125.99) | 106.52 (96.44, 117.65) | No EVG dose adjustments need to be made upon coadministration with MVC |
| Darunavir/ ritonavir (DRV/r) | 183-0120 | 33 | • EVG/r 125/100 mg QD (14 days)<br>• DRV/r 600/100 mg BID (14 days)<br>• EVG 125 mg QD + DRV/r 600/100 mg BID (14 days) | 112.89 (102.65, 124.15) | 118.01 (106.01, 131.37) | 109.81 (99.09, 121.69) | EVG and DRV/r can be coadministered without dose adjustments |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fosamprenavir/ ritonavir (FPV/r) | 183-0123 | 32 | • EVG/r 125/100 mg QD (14 days)<br>• EVG 125 mg QD + FPV/r 700/100 mg BID (14 days)<br>• FPV/r 700/100 mg BID (14 days) | 99.87 (90.62, 110.06) | 96.28 (89.83, 103.20) | 93.38 (87.89, 99.21) | EVG and FPV/r can be coadministered without dose adjustments |
| Rifabutin | 183-0125 | 23 | • EVG/r 300/100 mg QD (13 days)<br>• EVG/r 300/100 mg QD + rifabutin 150 mg QOD (13 days)<br>• Rifabutin 300 mg QD (13 days) | 91.94 (84.16, 100.43) | 94.31 (81.94, 108.54) | 95.59 (89.67, 101.90) | No EVG dose adjustments need to be made upon coadministration with rifabutin |
| Ketoconazole (KTZ) | 183-0146 | 18 | • EVG/r 150/100 mg QD (10 days)<br>• EVG/r 150/100 mg QD + KTZ 200 mg (3 days) | 117.3 (103.8, 132.6) | 166.7 (148.2, 187.5) | 148.3 (136.2, 161.6) | EVG/r and ketoconazole can be coadministered without dose adjustments |
| Rosuvastatin | 216-0123 | 34 | • Rosuvastatin 10 mg (single dose)<br>• EVG/co 150/150 mg QD (10 days)<br>• EVG/co 150/150 mg QD + rosuvastatin 10 mg single dose (1 day) | 93.94 (82.61, 106.82) | 98.20 (83.42, 115.60) | 102.17 (91.44, 114.15) | No EVG dose adjustments need to be made upon coadministration with rosuvastatin |

[a] Excluding Subject 2848-1004 (ATV and EVG concentrations are indicative of noncompliance)

**Table 18. Tabulated summary of the results of drug-drug interaction trials conducted to determine the effect of EVG on the PK of coadministered drugs (actionable clinical recommendations are indicated in bold font)**

| **Drug** | **Study** | **N** | **Relevant treatments; Dosage regimens; Duration of treatment** | **$C_{max}$ GLSM ratio (90% CI)** | **$C_{tau}$ GLSM ratio (90% CI)** | **$AUC_{tau}$ GLSM ratio (90% CI)** | **Clinical recommendation** |
|---|---|---|---|---|---|---|---|
| Emtricitabine (FTC) | 183-0103 | 26 | • EVG/r 50/100 mg QD (10 days)<br>• FTC/TDF 200/300 mg QD (7 days)<br>• FTC/TDF 200/300 mg + EVG/r 50/100 mg QD (10 days) | 115.3 (108.9, 122.2) | 104.1 (96.5, 112.2) | 111.1 (107.1, 115.2) | EVG/r and FTC/TDF can be coadministered with dose adjustments |
| Tenofovir (TDF) | | | • EVG/r 50/100 mg QD (10 days)<br>• FTC/TDF 200/300 mg QD (7 days)<br>• FTC/TDF 200/300 mg + EVG/r 50/100 mg QD (10 days) | 101.3 (93.3, 109.9) | 108.3 (102.2, 114.8) | 107.3 (103.2, 111.7) | |
| Zidovudine (ZDV) | 183-0104 | 28 | • ZDV 300 mg BID (7 days)<br>• EVG/r 200/100 mg QD (10 days)<br>• ZDV 300 mg BID + EVG/r 200/100 mg QD (10 days) | 88.1 (76.5, 101.4) | | 86.0 (79.8, 92.6) | EVG/r and ZDV can be coadministered with dose adjustments |
| Atazanavir/ ritonavir (ATV/r) | 183-0106 | 19 | • EVG/r 150/100 mg QD (10 days)<br>• ATV/r 300/100 mg QD (10 days)<br>• EVG 85 mg + ATV/r 300/100 mg QD (10 days) | 96.62 (86.58, 107.82) | 82.93 (72.14, 95.32) | 89.06 (79.98, 99.18) | No ATV/r dose adjustments need to be made upon coadministration with EVG |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 183-0108 | 32 | • EVG/r 200/100 mg QD (14 days)<br>• ATV/r 300/100 mg QD (14 days)<br>• EVG 200 mg + QTV/r 300/100 mg QD (14 days) | 84.31 (78.19, 90.92) | 65.49 (59.08, 7260) | 79.20 (73.57, 85.27) | |
| Tipranavir/ ritonavir (TPV/r) | 183-0110 | 34 | • EVG/r 200/100 mg QD (14 days)<br>• TPV/r 500/200 mg BID (14 days)<br>• EVG 200 mg QD + TPV/r 500/200 mg BID (14 days) | 91.6 (83.8, 100.1) | 88.9 (77.4, 102.0) | 88.9 (80.0, 98.8) | EVG and TPV/r can be coadministered with dose adjustments |
| Didanosine (ddI) | 183-0111 | 32 | • ddI 400 mg (single dose)<br>• EVG/r 200/100 mg QD (10 days) | 84.11 (67.35, 105.03) | | 85.94[a] (74.91, 98.59) | EVG/r and ddI can be coadministered with dose adjustments |
| Stavudine (d4T) | | | • d4T 40 mg (single dose)<br>• EVG/r 200/100 mg QD (10 days) | 99.63 (93.40, 106.28) | | 106.73[a] (105.39, 108.08) | EVG/r and d4T can be coadministered with dose adjustments |
| Etravirine (ETV) | 183-0112 | 34 | • EVG/r 150/100 mg QD (10 days)<br>• EVG/r 150/100 mg QD + ETV 200 mg BID (10 days)<br>• ETV 200 mg BID (10 days)<br>• ETV 200 mg BID + EVG/r 150/100 mg QD (10 days) | 101.6 (85.8, 120.3) | 89.6 (82.7, 97.1) | 97.6 (88.3, 108.0) | EVG/r and ETV can be coadministered with dose adjustments |
| Abacavir (ABC) | 183-0115 | 26 | • ABC 600 mg (single dose)<br>• EVG/r 200/100 mg (10 days)<br>• ABC 600 mg + EVG/r 200/100 mg | 87.63 (82.04, 93.60) | | 83.51[a] (80.69, 86.44) | EVG/r and ABC can be coadministered with dose adjustments |
| Lopinavir/ ritonavir (LPV/r) | 183-0116 | 32 | • EVG/r 125/100 mg QD (14 days)<br>• EVG 125 mg QD + LPV/r 400/100 mg BID (14 days)<br>• LPV/r 400/100 mg BID (14 days) | 99.21 (87.99, 111.85) | 82.34 (78.73, 108.32) | 96.56 (85.32, 109.29) | No LPV/r dose adjustments need to be made upon coadministration with EVG |
| **Maraviroc (MVC)** | 183-0118 | 36 | • EVG/r 150/100 mg QD (10 days)<br>• MVC 150 mg BID + EVG/r 150/100 mg QD (10 days)<br>• MVC 150 mg BID (10 days) | 214.84 (171.43, 269.26) | 423.33 (347.21, 516.13) | 286.03 (232.93, 351.23) | The dose of MVC should be reduced to 150 mg BID when coadministered with EVG/r **(consult label of coadministered RTV-boosted PI)** |
| Darunavir/ ritonavir (DRV/r) | 183-0120 | 33 | • EVG/r 125/100 mg QD (14 days)<br>• DRV/r 600/100 mg BID (14 days)<br>• EVG 125 mg QD + DRV/r 600/100 mg BID (14 days) | 89.43 (84.96, 94.14) | 82.77 (73.74, 92.90) | 88.73 (82.34, 95.63) | EVG and DRV/r can be coadministered with dose adjustments |
| Fosamprenavir/ ritonavir (FPV/r) | 183-0123 | 32 | • EVG/r 125/100 mg QD (14 days)<br>• EVG 125 mg QD + FPV/r 700/100 mg BID (14 days)<br>• FPV/r 700/100 mg BID (14 days) | 97.90[b] (90.51, 105.88) | 101.17[b] (85.33, 119.96) | 99.05[b] (90.60, 108.29) | EVG and FPV/r can be coadministered with dose adjustments |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Rifabutin** | 183-0125 | 23 | • EVG/r 300/100 mg QD (13 days)<br>• EVG/r 300/100 mg QD + rifabutin 150 mg QOD (13 days)<br>• Rifabutin 300 mg QD (13 days) | rifabutin: 91.67 (82.69, 101.61)<br><br>25-O-desacetyl rifabutin: 539.7 (466.11, 624.82) | rifabutin: 115.9 (102.33, 131.26)<br><br>25-O-desacetyl rifabutin: 1936 (1584.52, 2365.32) | rifabutin: 93.70 (85.62, 102.55)<br><br>25-O-desacetyl rifabutin: 951.1 (809.49, 1117.54) | The dose of rifabutin should be reduced to 150 mg QOD when coadministered with EVG/r **(consult label of coadministered RTV-boosted PI)** |
| **Rosuvastatin** | 216-0123 | 34 | • Rosuvastatin 10 mg (single dose)<br>• EVG/co 150/150 mg QD (10 days)<br>• EVG/co 150/150 mg QD + rosuvastatin 10 mg single dose (1 day) | 189.31 (148.19, 241.84) | 143.10[c] (108.22, 189.22) | 137.98 (113.83, 167.25) | Rosuvastatin should be initiated at the lowest starting dose and titrated while monitoring for safety **(consult label of coadministered RTV-boosted PI)** |

[a] Values correspond to $AUC_{inf}$

[b] Values correspond to amprenavir PK parameters

[c] Values correspond to $C_{last}$

A large number of drug-drug interactions will be due to the inclusion of the potent CYP3A inhibitor RTV in the EVG-containing ARV regimen. There are no specific contraindications for EVG itself. The only actionable dosing recommendations for EVG are for the well-characterized interaction between EVG and ATV/r or LPV/r, for which the 85 mg tablet strength was developed. In all cases of actionable dosing recommendations for the coadministered drug (i.e. maraviroc, statins, and rifabutin), the proposed prescribing information for Vitekta® refers to the prescribing information of coadministered protease inhibitors (which includes Norvir®) for additional information.

General language instructing the reader to consult the prescribing information of coadministered protease inhibitors regarding drug-drug interactions is also included in Sections 5.1 (Drug-Drug Interactions) and 7.2 (Established and Other Potentially Significant Interactions).

In general, the clinical recommendations are appropriate for the drug interactions addressed in Tables 17 and 18.

**Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

There are no known pharmacodynamic drug-drug interactions for EVG.

### 2.4.2.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are two unresolved drug-drug interaction issues, both of which were also addressed during review of NDA 203100 (EVG/Cobi/TDF/FTC fixed-dose combination tablet). The first issue is related to potential DDIs between EVG and methadone or buprenorphine/naloxone and the second is related to potential DDIs with direct-acting agents (DAA) against hepatitis C virus

(HCV). These issues are summarized briefly below. Please refer to Section 2.4.2.10 of the OCP review for NDA 203100 for more information.

I. Coadministration of boosted EVG and methadone or buprenorphine/naloxone. The Applicant conducted a trial to evaluate DDIs using the EVG/Cobi/TDF/FTC fixed-dose combination tablet. Because CYP-mediated metabolism of methadone, buprenorphine, and naloxone occurs through multiple isoforms, potential interactions with RTV should be also be characterized.

II. Coadministration of boosted EVG and HCV DAA. This issue was discussed with the Applicant in the context of the pre-NDA meeting. Due to pharmacokinetic drug-drug interactions observed during trials conducted by the Sponsors of telaprevir and boceprevir, coadministration of the DAA telaprevir is not recommended with DRV/r, FPV/r, or LPV/r and coadministration of the DAA boceprevir is not recommended with DRV/r, ATV/r, or LPV/r. However, there is no recommendation against concomitant administration of telaprevir/r, which resulted in reduced telaprevir exposures and increased ATV exposures. The Applicant has therefore agreed to conduct a drug-drug interaction trial with EVG, ATV/r, and telaprevir.

**2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

There are no unresolved issues related to dose, dosing regimens, or administration.

## 2.5. GENERAL BIOPHARMACEUTICS

**2.5.1. Based on the Biopharmaceutics classification system (BCS) principles, in which class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?**

EVG appears to be a high permeability, low solubility drug, which may classify it as a BCS Class 2 drug. Please refer to the ONDQA review for further details.

**2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?**

The Applicant used the to-be-marketed formulation in the pivotal clinical trial. Therefore, no relative bioavailability study was required.

**2.5.2.1 What data support or do not support a waiver of in vivo BE data?**

Not applicable.

**2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The effect of food on EVG bioavailability was not studied using the to-be-marked formulation of EVG.

Under the proposed indication, EVG will be coadministered with RTV. The package insert for RTV (Norvir®) indicates that RTV should be administered with a meal due to improved tolerability; thus, in the pivotal and supportive clinical trials, EVG was administered in the fed state, as it will be in clinical practice.

Food has variable but minor effects on the absorption of ritonavir, depending on the formulation. The absorption of ritonavir from soft gelatin tablets (used throughout development by the Applicant) was 13% higher under non-fasting conditions. The absorption of ritonavir from tablets (which may have been used in trials in which subjects were responsible for procuring the ARV background regimen, including ritonavir and the boosted PI) decreased by approximately 20% under non-fasting conditions. In both of these situations, ritonavir exposures are expected to provide sufficient CYP3A inhibition to achieve desired EVG exposures based on the ritonavir dose-response relationship characterized in Study GS-US-183-0116.

The effect of food on EVG bioavailability was evaluated using test formulations of unboosted EVG in Studies XAX1-1 and XAX1-2. These studies were not reviewed because the results are not clinically applicable, since EVG will always be administered with a pharmacoenhancer.

**2.5.4. When would a fed BE study be appropriate, and was one conducted?**

Not applicable.

**2.5.5. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?**

Please refer to the ONDQA review.

**2.5.6. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?**

Please refer to the ONDQA review.

## 2.6. ANALYTICAL

**2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and Biopharmaceutics studies?**

The active moieties were identified and measured in the plasma using validated LC-MS/MS assays.

**2.6.2. Which metabolites have been selected for analysis and why?**

The Applicant measured the EVG metabolites GS-9202 (hydroxylation metabolite formed by CYP3A) and GS-9200 (glucuronidation metabolite formed by UGT1A1) in most of the Phase 1 clinical trials in order to fully characterize EVG PK (e.g. the mass balance trial [GS-US-183-0126]), or, in the case of drug-drug interaction trials, to evaluate shifts in the extent of metabolism via specific pathways.

**2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The total concentrations of EVG and its metabolites were measured, as was appropriate. EVG is almost entirely bound to plasma proteins (98-99%, Study JTK303-AD-014).

**2.6.4. What bioanalytical methods are used to assess concentrations?**

Please refer to the individual trial reviews for details on specific bioanalytical methods. Overall, the bioanalytical methods used to assess concentrations were acceptable.

The long-term stability of EVG in plasma stored at -70˚C for 585 days met the acceptance criteria (no more than ±15.0% different from the mean Day 0 concentrations). The long-term stability of EVG in plasma stored at -70˚C for 834 days did not meet the acceptance criteria when compared to the mean Day 0 concentrations, but was acceptable when compared to the nominal concentrations. Overall, the stability data were adequate to cover the sample storage times for the studies reviewed for this Application.

## 3. LABELING RECOMMENDATIONS

Major changes to the sections of the prescribing information that are relevant to clinical pharmacology are highlighted in blue. Note that references to the cobicistat-boosted treatment-naïve indication were removed throughout the prescribing information.

### HIGHLIGHTS OF PRESCRIBING INFORMATION

**----------CONTRAINDICATIONS----------**

(b) (4)

### 1 INDICATIONS AND USAGE

VITEKTA, coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

(b) (4)

## 4 CONTRAINDICATIONS

(b) (4)

## 7 DRUG INTERACTIONS

See also Dosage and Administration (2), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3).

### 7.1 Effect of Concomitant Drugs on the Pharmacokinetics of Elvitegravir

Elvitegravir is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of elvitegravir, as well as ritonavir. This may result in decreased plasma concentrations of elvitegravir and/or protease inhibitor and lead to loss of therapeutic effect and to possible resistance.

### 7.2 Established and Other Potentially Significant Interactions

Table 4 provides dosing recommendations as a result of drug interactions with VITEKTA. These recommendations are based on either drug interactions studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of therapeutic effect.

For additional drug-drug interactions related to protease inhibitors coadministered with ritonavir, consult the prescribing information of the coadministered protease inhibitor and ritonavir.

The table is not all-inclusive (see also Clinical Pharmacology (12.3), Tables 5-6).

**Table 4 Established and Other Potentially Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

| Concomitant Drug Class: Drug Name | Effect on Concentration[b] | Clinical Comment |
|---|---|---|
| **Antiretroviral Agents: Protease Inhibitors (PI)[c]** | | |

| | | |
|---|---|---|
| Atazanavir* | ↔ atazanavir<br>↑ elvitegravir | Atazanavir/ritonavir has been shown to significantly increase the plasma concentrations of VITEKTA. (b) (4) he recommended dose of atazanavir/ritonavir is 300/100 mg once daily.<br>There are no data available to make dosing recommendations for coadministration with other doses of atazanavir. |
| (b) (4) | | |
| Lopinavir/ritonavir* | ↔ lopinavir<br>↑ elvitegravir | Lopinavir/ritonavir has been shown to significantly increase the plasma concentrations of elvitegravir. (b) (4) The recommended dose of lopinavir/ritonavir is 400/100 mg twice daily.<br>There are no data available to make dosing recommendations for coadministration with other doses of lopinavir/ritonavir. |
| (b) (4) | | |
| Other Protease Inhibitors (with or without ritonavir) | Effect is unknown | There are no data available to make dosing recommendations for coadministration with other protease inhibitors. |
| **Antiretroviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** | | |
| Didanosine* | ↔ didanosine<br>↔ elvitegravir | As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after VITEKTA (which is administered with food). |
| (b) (4) | | |
| **Antiretroviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | | |
| Efavirenz | ↓ elvitegravir | Coadministration of efavirenz and VITEKTA is expected to decrease elvitegravir plasma concentration which may result |

| | | |
|---|---|---|
| | | in loss of therapeutic effect and in development of resistance. Such coadministration is not recommended. |
| [redacted] (b) (4) | | |
| Nevirapine | ↓ elvitegravir | Coadministration of nevirapine and VITEKTA is expected to decrease elvitegravir plasma concentration, which may result in loss of therapeutic effect and development of resistance. Such coadministration is not recommended. |
| [redacted] (b) (4) | | |
| **Other Agents:** | | |
| **Acid Reducing Agents:**<br>antacids*<br>[redacted] (b) (4) | ↓ elvitegravir | Elvitegravir plasma concentrations are lower with antacids due to the formation of ionic complexes in the GI tract and not to changes in gastric pH. It is recommended to separate VITEKTA and antacid administration by at least 2 hours. |
| **Anticonvulsants:**<br>carbamazepine<br>oxcarbazepine<br>phenobarbital<br>phenytoin | ↓ elvitegravir | Coadministration of phenobarbital, phenytoin, carbamazepine, or oxcarbazepine (CYP3A inducers) with VITEKTA may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and in development of resistance. Alternative anticonvulsants should be considered. |
| **Antifungals**:<br>ketoconazole* | ↑ elvitegravir<br>↑ ketoconazole | No dose adjustment of VITEKTA is required when coadministered with ketoconazole.<br>Concentrations of ketoconazole may increase when used concomitantly with VITEKTA in combination with protease inhibitors/ritonavir, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Consult the prescribing information of coadministered protease inhibitors for any additional dosing recommendation for ketoconazole. |
| **Antimycobacterial:** | ↓ elvitegravir | Coadministration of rifampin or rifapentine, both potent CYP3A inducers, with VITEKTA may lead to decreased |

| | | |
|---|---|---|
| rifampin<br>rifapentine | | elvitegravir exposures, which may result in loss of therapeutic effect and in development of resistance. Coadministration is not recommended. |
| rifabutin* | ↑ rifabutin<br>↑ 25-*O*-desacetylrifabutin<br>↓ elvitegravir | When rifabutin, a potent CYP3A inducer, is used concomitantly with VITEKTA in combination with a protease inhibitor/ritonavir, dose reduction of rifabutin by at least 75% of the usual dose of 300 mg/day (e.g., 150 mg every other day or 3 times per week) is recommended. Increased monitoring for rifabutin-associated adverse events is warranted. Consult the prescribing information of coadministered protease inhibitors for any additional dosing recommendation for rifabutin.<br>No dose adjustment of VITEKTA is required when coadministered with the reduced dose of rifabutin. |
| **Systemic Corticosteroids:**<br>dexamethasone | ↓ elvitegravir | Systemic dexamethasone, a CYP3A inducer, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered. |
| **Endothelin Receptor Antagonists:**<br>bosentan | ↑ bosentan<br>↓ elvitegravir | Coadministration of bosentan in patients on VITEKTA:<br>In patients who have been receiving VITEKTA for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.<br>Coadministration of VITEKTA in patients on bosentan:<br>Discontinue use of bosentan at least 36 hours prior to initiation of VITEKTA. After at least 10 days following the initiation of VITEKTA, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. |
| [redacted] | | (b) (4) |

| | | |
|---|---|---|
| **HCV Protease Inhibitors:**<br><br>boceprevir<br>telaprevir | ↓ boceprevir<br>↓ telaprevir<br>↑ or ↓ HIV protease inhibitors | Coadministration of boceprevir or telaprevir with HIV protease inhibitors/ritonavir resulted in reduced plasma concentrations of the HCV medication, and may increase or decrease the plasma concentrations of the protease inhibitor. This may result in loss of therapeutic effect and in development of resistance. Because VITEKTA must be administered with a protease inhibitor/ritonavir, coadministration with telaprevir or boceprevir is not recommended. |
| (b) (4) | | |
| **Herbal Products:**<br>St. John's wort (*Hypericum perforatum*) | ↓ elvitegravir | Coadministration of St. John's wort, a potent CYP3A inducer, may decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and in development of resistance.<br>VITEKTA should not be coadministered with St. John's wort. |
| **Hormonal Contraceptives:**<br>norgestimate/ethinyl estradiol | ↑ norgestimate<br>↓ ethinyl estradiol<br>↔ elvitegravir | Plasma concentration of ethinyl estradiol may be decreased when used concomitantly with VITEKTA in combination with a protease inhibitor/ritonavir. Alternative methods of non-hormonal contraception are recommended. |
| (b) (4) | | |

* Indicates that a drug-drug interaction trial was conducted.
a. This table is not all inclusive.
b. ↑ = Increase, ↓ = Decrease, ↔ = No change
c. Protease inhibitors were coadministered with ritonavir.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

VITEKTA is an HIV-1 antiviral drug [See Microbiology (12.4)].

### 12.2 Pharmacodynamics

Effects on Electrocardiogram

The effect of multiple doses of elvitegravir 125 and 250 mg (coadministered with 100 mg ritonavir) on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel group thorough QT study in 126 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 250 mg elvitegravir (with 100 mg ritonavir) is expected to cover the high exposure clinical scenario.

## 12.3. Pharmacokinetics

Absorption

Following oral administration of VITEKTA/ritonavir with food, in HIV-1 infected subjects, peak plasma concentrations were observed 4 hours post-dose for elvitegravir. The steady-state mean elvitegravir (b) (4)

Elvitegravir plasma exposures increased in a less than dose proportional manner, likely due to solubility-limited absorption.

(b) (4)

VITEKTA should be taken with food.

Distribution

Elvitegravir is 98-99% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma–to-blood drug concentration ratio is 1.37.

Metabolism and Elimination

Elvitegravir undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of [$^{14}$C]elvitegravir/ritonavir, elvitegravir was the predominant species in plasma, representing ~94% of the circulating radioactivity. Aromatic and aliphatic hydroxylation or glucuronidation metabolites were present in very low levels, displayed considerably lower anti-HIV activity and did not contribute to the overall antiviral activity of elvitegravir.

Following oral administration of [$^{14}$C]elvitegravir/ritonavir, 94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of elvitegravir; 6.7% of the administered dose was recovered in urine as metabolites. The median terminal plasma half-life of elvitegravir following administration of VITEKTA/ritonavir was approximately 8.7 hours.

*Special Populations*

Race

Population pharmacokinetics analysis of elvitegravir in HIV-1 infected subjects indicated that race had no clinically relevant effect on the exposure of elvitegravir/ritonavir.

Gender

No clinically relevant pharmacokinetic differences have been observed between men and women for elvitegravir/ritonavir.

Pediatric Patients

The pharmacokinetics of elvitegravir in pediatric patients less than 12 years of age have not been established *[See Use in Specific Populations (8.4)].* The steady-state mean elvitegravir $C_{max}$, $AUC_{tau}$, and $C_{trough}$ (mean ± SD) following multiple doses of boosted VITEKTA in HIV-1 infected adolescents were 2.1 ± 0.96 µg/mL, 25 ± 11 µg•hr/mL, and 0.63 ± 0.43 µg/mL, respectively, for the 85 mg dose, and 2.1 ± 0.74 µg/mL, 21 ± 7.6 µg•hr/mL, and 0.32 ± 0.24 µg/mL, respectively, for the 150 mg dose of elvitegravir, with inhibitory quotients of ~ 14 and ~ 7.1 (ratio of $C_{trough}$: protein binding-adjusted $EC_{95}$ for wild-type HIV-1 virus for the 85 mg and 150 mg doses, respectively).

Geriatric Patients

Pharmacokinetics of elvitegravir have not been fully evaluated in the elderly (65 years of age and older) *[See Use in Specific Populations (8.5)].*

Patients with Renal Impairment

(b) (4)

No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects. No dose adjustment of VITEKTA is required for patients with renal impairment. *[See Use in Specific Populations (8.6)].*

Patients with Hepatic Impairment

Elvitegravir is primarily metabolized and eliminated by the liver. (b) (4) No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. (b) (4) The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of elvitegravir has not been studied *[See Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Co-infection

Limited data from population pharmacokinetic analysis (N=56) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of elvitegravir/ritonavir.

Assessment of Drug Interactions

The drug interaction studies described were conducted with VITEKTA coadministered with ritonavir.

Elvitegravir is primarily metabolized by cytochrome CYP3A. Coadministration of VITEKTA with drugs that induce CYP3A may result in decreased plasma concentrations of elvitegravir, (b) (4).

In drug interaction studies conducted with elvitegravir/ritonavir, there was no clinically significant interaction observed between elvitegravir and abacavir, emtricitabine, etravirine, famotidine, omeprazole, stavudine, tenofovir disoproxil fumarate, or zidovudine. The effects of coadministered drugs on the exposure of elvitegravir/ritonavir are shown in Table 5. The effects of elvitegravir/ritonavir on the exposure of coadministered drugs are shown in Table 6.

**Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir/ritonavir in the Presence of the Coadministered Drug[a]**

| Coadministered Drug | Dose of Coadministered Drug (mg) | Elvitegravir Dose (mg) | Ritonavir Dose (mg) | N | Mean Ratio of Elvitegravir/ritonavir Pharmacokinetic Parameters[b] (90% CI); No Effect = 1.00 | | |
|---|---|---|---|---|---|---|---|
| | | | | | $C_{max}$ | AUC | $C_{min}$ |
| Antacids | 20 mL single dose given 4 hours before elvitegravir | 50 once daily | 100 once daily | 8 | 0.95 (0.84,1.07) | 0.96 (0.88,1.04) | 1.04 (0.93,1.17) |
| | 20 mL single dose given 4 hours after elvitegravir | | | 10 | 0.98 (0.88,1.10) | 0.98 (0.91,1.06) | 1.00 (0.90,1.11) |
| | 20 mL single dose given 2 | | | 11 | 0.82 (0.74,0.91) | 0.85 (0.79,0.91) | 0.90 (0.82,0.99) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | hours before elvitegravir | | | | | | |
| | 20 mL single dose given 2 hours after elvitegravir | | | 10 | 0.79 (0.71,0.88) | 0.80 (0.75,0.86) | 0.80 (0.73,0.89) |
| Atazanavir | 300 once daily | 200 once daily | 100 once daily | 33 | 1.85 (1.69 to 2.03) | 2.00 (1.85 to 2.16) | 2.88 (2.53 to 3.27) |
| | 300 once daily | 85 once daily | 100 once daily | 20 | 0.91 (0.81 to 1.02)[c] | 1.07 (0.95 to 1.21)[c] | 1.38 (1.18 to 1.61)[c] |
| Darunavir | 600 twice daily | 125 once daily | 100 twice daily | 21 | 1.13 (1.03, 1.24) | 1.10 (0.99, 1.22) | 1.18 (1.06, 1.31) |
| Didanosine | 400 single dose | 200 once daily | 100 once daily | 32 | 0.95 (0.90, 1.01) | 0.97 (0.92, 1.01) | 1.06 (1.01, 1.12) |
| Ketoconazole | 200 twice daily | 150 once daily | 100 once daily | 18 | 1.17 (1.04, 1.33) | 1.48 (1.36, 1.62) | 1.67 (1.48, 1.88) |
| Lopinavir/ ritonavir | 400 twice daily | 125 once daily | 100 twice daily | 14 | 1.52 (1.29, 1.79) | 1.75 (1.50, 2.05) | 2.38 (1.81, 3.13) |
| Maraviroc | 150 twice daily | 150 once daily | 100 once daily | 17 | 1.01 (0.89, 1.15) | 1.07 (0.96, 1.18) | 1.09 (0.95, 1.26) |
| Rifabutin | 150 once every other day | 300 once daily | 100 once daily | 19 | 0.92 (0.84, 1.00) | 0.96 (0.90, 1.02) | 0.94 (0.82, 1.09) |
| Rosuvastatin | 10 single dose | 150 single dose | NA[d] | 10 | 0.94 (0.83, 1.07)[e] | 1.02 (0.91, 1.14)[e] | 0.98 (0.83, 1.16)[e] |
| Tipranavir | 500 twice daily | 200 once daily | 200 twice daily | 26 | 1.06 (0.89, 1.26)[e] | 0.92 (0.79, 1.08)[e] | 0.90 (0.70, 1.17)[e] |

a. All interaction studies conducted in healthy volunteers
b. The pharmacokinetic parameters of elvitegravir were compared with elvitegravir coadministered with ritonavir 100 mg once daily unless specified otherwise.
c. Comparison based on elvitegravir/ritonavir 150/100 mg once daily.
d. Study was conducted in the presence of 150 mg cobicistat.
e. Comparison based on elvitegravir/cobicistat 150/150 mg once daily.

**Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Elvitegravir/ritonavir[a]**

| Coadministered Drug | Dose of Coadministered | Elvitegravir Dose (mg) | Ritonavir-Dose (mg) | N | Mean Ratio of Coadministered Drug Pharmacokinetic Parameters[b,] (90% CI); No Effect = 1.00 |
|---|---|---|---|---|---|

| | | | | | $C_{max}$ | AUC | $C_{min}$ |
|---|---|---|---|---|---|---|---|
| Atazanavir | 300 once daily | 200 once daily | 100 once daily | 33 | 0.84 (0.78, 0.91) | 0.79 (0.74, 0.85) | 0.65 (0.59, 0.73) |
| | 300 once daily | 85 once daily | 100 once daily | 20 | 0.97 (0.87, 1.08) | 0.89 (0.80, 0.99) | 0.83 (0.72, 0.95) |
| Darunavir | 600 twice daily | 125 once daily | 100 twice daily | 22 | 0.89 (0.85, 0.94) | 0.89 (0.82, 0.96) | 0.83 (0.74, 0.93) |
| Didanosine | 400 single dose | 200 once daily | 100 once daily | 32 | 0.84 (0.67, 1.05) | 0.86 (0.75, 0.99) | NC |
| Lopinavir/ ritonavir | 400 twice daily | 125 once daily | 100 twice daily | 13 | 0.99 (0.88, 1.12) | 0.97 (0.85, 1.09) | 0.92 (0.79, 1.08) |
| Maraviroc | 150 twice daily | 150 once daily | 100 once daily | 11 | 2.15 (1.71, 2.69) | 2.86 (2.33, 3.51) | 4.23 (3.47, 5.16) |
| Rifabutin | 150 once every other day | 300 once daily | 100 once daily | 18 | 0.92 (0.83, 1.02)[c] | 0.94 (0.86, 1.03)[c] | 1.16 (1.02, 1.31)[c] |
| 25-O-desacetyl-rifabutin | | | | | 5.40[c] (4.66, 6.25) | 9.51[c] (8.09, 11.18) | 19.36[c] (15.85, 23.65) |
| Rosuvastatin | 10 single dose | 150 single dose | NA[d] | 10 | 1.89 (1.48, 2.42) | 1.38 (1.14, 1.67) | 1.43 (1.08, 1.89) |
| Tipranavir | 500 twice daily | 200 once daily | 200 twice daily | 26 | 0.92 (0.84, 1.00) | 0.89 (0.80, 0.99) | 0.89 (0.77, 1.02) |

a. All interaction studies conducted in healthy volunteers
b. The pharmacokinetic parameters of the protease inhibitors presented in this table were assessed in the presence of ritonavir.
c. Comparison based on rifabutin 300 mg once daily. Total antimycobacterial activity was increased by 50%.
d. Study was conducted in the presence of 150 mg cobicistat.

# 4. APPENDICES

## 4.1. PHARMACOMETRICS REVIEW

The Pharmacometrics review of NDA 203093 begins on page 51 of this review.

## 4.2. INDIVIDUAL TRIAL REVIEWS

Reviews of the following in vivo trials are appended to the current review. Please see the Table of Contents for the relevant page numbers.

GS-US-183-0103
GS-US-183-0104
GS-US-183-0106
GS-US-183-0108
GS-US-183-0110
GS-US-183-0111
GS-US-183-0112
GS-US-183-0115
GS-US-183-0116
GS-US-183-0118
GS-US-183-0120
GS-US-183-0123
GS-US-183-0125
GS-US-183-0145
GS-US-183-0147
GS-US-183-0152

Reviews of the following studies may be found in the appendix to the Clinical Pharmacology review of NDA 203100 (Stribild®):

<u>In vitro studies pertinent to distribution in blood and plasma</u>
JTK-303-AD-014
JTK-303-AD-013

<u>In vitro studies pertinent to hepatic metabolism</u>
JTK-303-AD-015
JTK-303-AD-016
JTK-303-AD-017
JTK-303-AD-018
JTK-303-AD-024

In vitro studies pertaining to potential drug interactions
JTK-303-AD-025
JTK-303-AD-027
JTK-303-AD-023
AD-183-2028
AD-183-2034
JTK-303-AD-026
AD-183-2030

In vivo studies
GS-US-183-0101
GS-US-183-0102
GS-US-183-0105
GS-US-183-0113
GS-US-183-0119
GS-US-183-0126
GS-US-183-0128
GS-US-183-0133
GS-US-183-0140
GS-US-183-0146
GS-US-216-0116
GS-US-216-0120
GS-US-216-0123
GS-US-216-0124

# OFFICE OF CLINICAL PHARMACOLOGY:
# PHARMACOMETRIC REVIEW

| | |
|---|---|
| **Application Number** | NDA 203093 |
| **Compound** | Elvitegravir (Vitekta®); 85 and 150 mg IR Tablets |
| **Indication** | Treatment of HIV-1 infection in ARV treatment-experienced patients, in combination with a ritonavir-boosted protease inhibitor and other ARV agents |
| **Submission Date** | 27 Jun 2012 |
| **Sponsor** | Gilead Sciences, Inc. |
| **PM Reviewer** | Dhananjay D. Marathe, PhD |
| **PM Secondary Reviewer** | Jeffry Florian, PhD |
| **Related IND** | IND 72177 |

# 1 SUMMARY OF FINDINGS

## 1.1 Key Review Questions

The purpose of this review is to address the following key questions:

### 1.1.1 Dose the exposure-response (E-R) relationship for elvitegravir (EVG) for virologic response support the selected dose?

EVG has a flat E-R relationship for pure virologic response (PVR, with plasma viral load <50 HIV-1 RNA copies/mL) with no clear relationship between virologic response or virologic failure for the EVG exposure range observed when EVG was administered with a ritonavir-(RTV) boosted protease inhibitory (PI) in the applicant's Phase 3 trial (GS-US-183-0145) (Figure 1, Figure 2).

The EVG dosing in the Phase 3 trial was either 150 mg q.d. when administered with darunavir (DRV), fosamprenavir (FPV) or tipranavir (TPV) as the background PI, or 85 mg q.d. when administered with atazanavir (ATV) or lopinavir (LPV) as the background PI. The appropriateness of this dosing based on administered background PI is discussed in detail in 1.1.4. An E-R relationship for PVR was evaluated based on the PK/PD analysis set in Phase 3 population (n=332, both doses combined; 2 subjects excluded from this set because of empty

fields for virologic response). Separate E-R efficacy relationships for PVR were also evaluated for the 85 mg q.d. and 150 mg q.d. EVG dose groups (n = 123 and 209, respectively). For all three scenarios a flat E-R relationship was identified between EVG $C_{tau}$ and PVR. The PVR was 66% in the first exposure quartile, which is within the range of PVR values observed in 2nd to 4th exposure quartiles (70-63%). Similarly, a flat E-R relationship was observed between EVG $C_{tau}$ and virologic failure in the applicant's Phase 3 trial (combined results shown in Figure 2; E-R virologic failure results for 85 mg q.d. and 150 mg q.d. as separate analyses are not shown, but were similarly flat). Analysis with AUC as exposure metric (instead of $C_{tau}$) also confirmed the flat exposure-response relationship for PVR (data not shown). Overall, the lack of a discernible E-R relationship for the overall population or either of the selected EVG doses within the respective subgroups (i.e., 85 mg q.d. and 150 mg q.d.) supports the selected EVG doses for a treatment-experienced population administered a RTV-boosted PI.

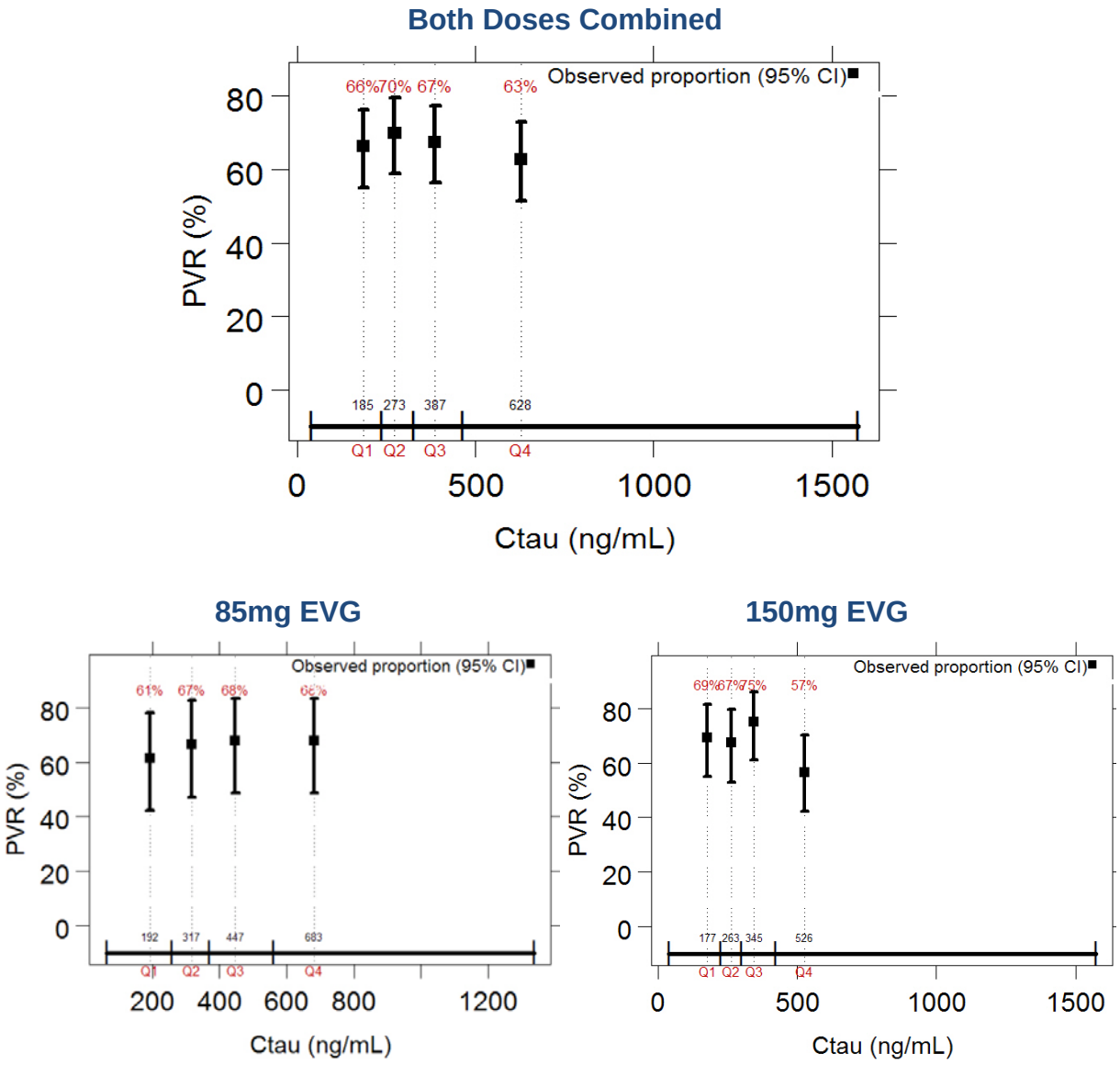



**Figure 1: Percentage of patients achieving Pure Virologic Response (<50 HIV-1 RNA copies/mL, week 48) versus elvitegravir $C_{tau}$ with both elvitegravir doses combined or in**

**separate dosing groups (85 mg and 150 mg q.d.)** (EVG $C_{tau}$ values [derived from the applicant's population PK analysis] are represented as quartiles)

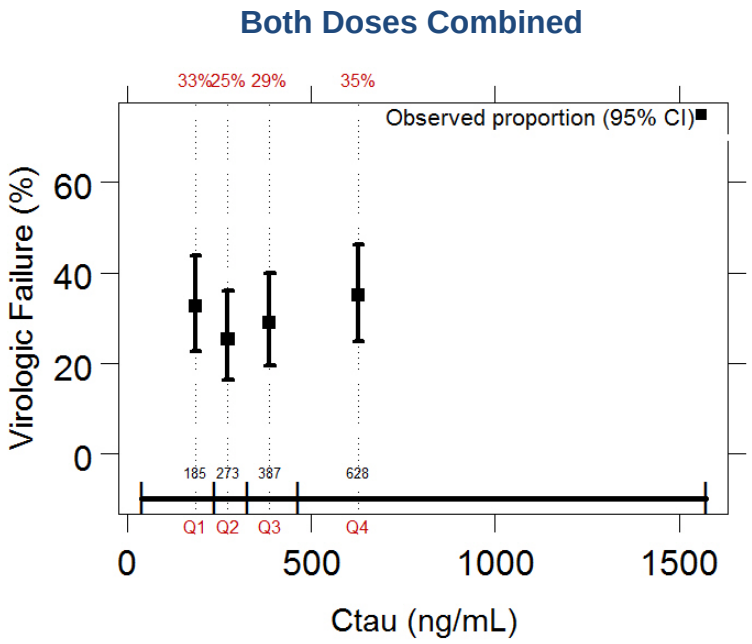


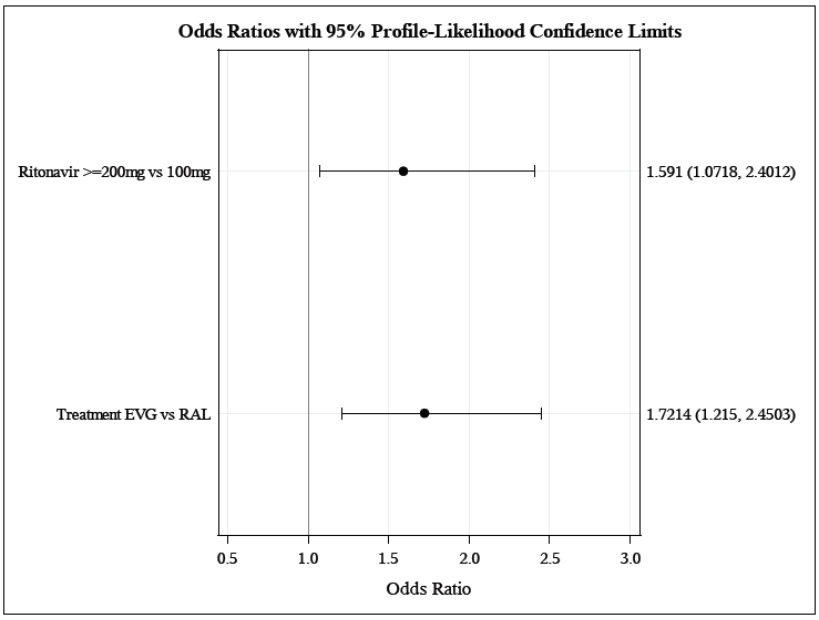

**Figure 2: Percentage of patients with confirmed virologic failure (>50 HIV-1 RNA copies/mL, week 48) versus elvitegravir $C_{tau}$ with both elvitegravir doses combined (85 mg and 150 mg)** (EVG $C_{tau}$ values [derived from the applicant's population PK analysis] are represented as quartiles)

### 1.1.2 Is there evidence of either a dose- or exposure-safety relationship for EVG (exposure) or RTV (dose) and adverse events of interest (diarrhea)?

Yes, there were increased odds of occurrence for diarrhea based on administration of EVG compared to raltegravir (RAL); however, an E-R relationship could not be identified between EVG exposure and diarrhea. In addition, RTV was identified as a separate and primary contributor to diarrhea occurrence in the Phase 3 trial. A dose-response relationship for RTV was identified for odds of occurrence for diarrhea based on RTV doses ≥200 mg compared to RTV doses of 100 mg (Figure 3).

Diarrhea was the most frequently reported study drug-related adverse event in treatment-experienced HIV-1 infected subjects from the pivotal Phase 3 trial. Once-daily EVG had no exposure-response relationship for any of the safety adverse events of interest (diarrhea; analyses not shown). However, diarrhea events were more common in the EVG arm (n=335) compared to the RAL arm (n=338) with 72% increased odds of occurrence. This increase in odds of occurrence was present even after accounting for RTV dose, which was identified as the primary contributor to diarrhea and exhibited a dose-response relationship. For diarrhea, a difference in RTV doses in the background anti-retroviral (ARV) regimens across both treatment arms was responsible for 59% increased odds of diarrhea (all grades) occurrence for subjects receiving ≥200 mg RTV total daily dose (n=481) compared to 100 mg RTV total daily dose (n=198). A similar relationship of increased odds of diarrhea with increasing RTV dose or EVG treatment compared to RAL treatment was observed for Grades≥2 diarrhea (analyses not shown).

**A.**




**B.**

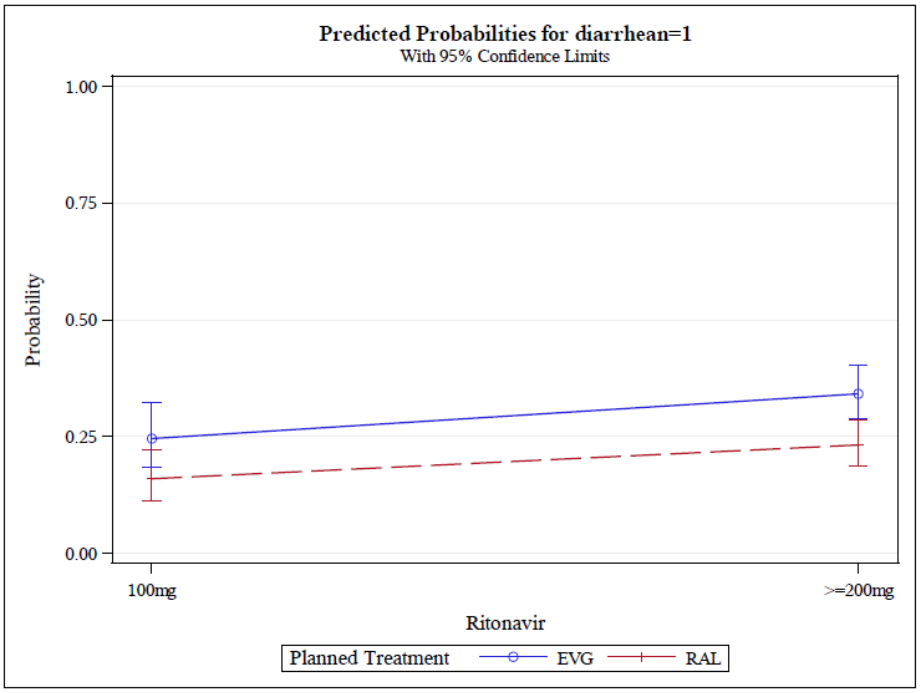



**Figure 3: Dose/exposure-response relationship for EVG treatment or ritonavir (RTV) dose on diarrhea adverse events (All Grades diarrhea):** A) Odds ratio of diarrhea occurrence for ≥200 mg RTV as compared to 100 mg RTV total daily dose in background regimen and for EVG treatment as compared to RAL treatment arm. B) Percentage of patients with any grade diarrhea versus RTV dose, grouped by treatment arm (EVG versus RAL). A similar relationship of increased odds of diarrhea with increasing RTV dose or EVG treatment compared to RAL treatment was observed for Grades≥2 diarrhea (analyses not shown).

### 1.1.3 Is the selected EVG dose of 85 mg q.d. for background ARV regimen (BR) involving ATV or LPV appropriate based on achieving similar exposures to EVG 150 mg. q.d. with DRV, FPV, TPV and available E-R efficacy relationships?

The selected EVG dose of 85 mg q.d. for BR involving ATV or LPV is appropriate based on PK and efficacy perspective. The exposures ($C_{tau}$ Figure 4; AUC was also similar, analyses not shown) achieved in subjects with EVG 85 mg q.d. administered with a RTV-boosted PI (ATV or LPV as BR) were similar to EVG 150 mg administered with a RTV-boosted PI (DRV, FPV or TPV as BR). In addition, the overall efficacy (Figure 4, B) was similar for both EVG dose groups, and the E-R relationship for PVR and virologic failure for both doses was flat based on the analysis presented above in 1.1.1..

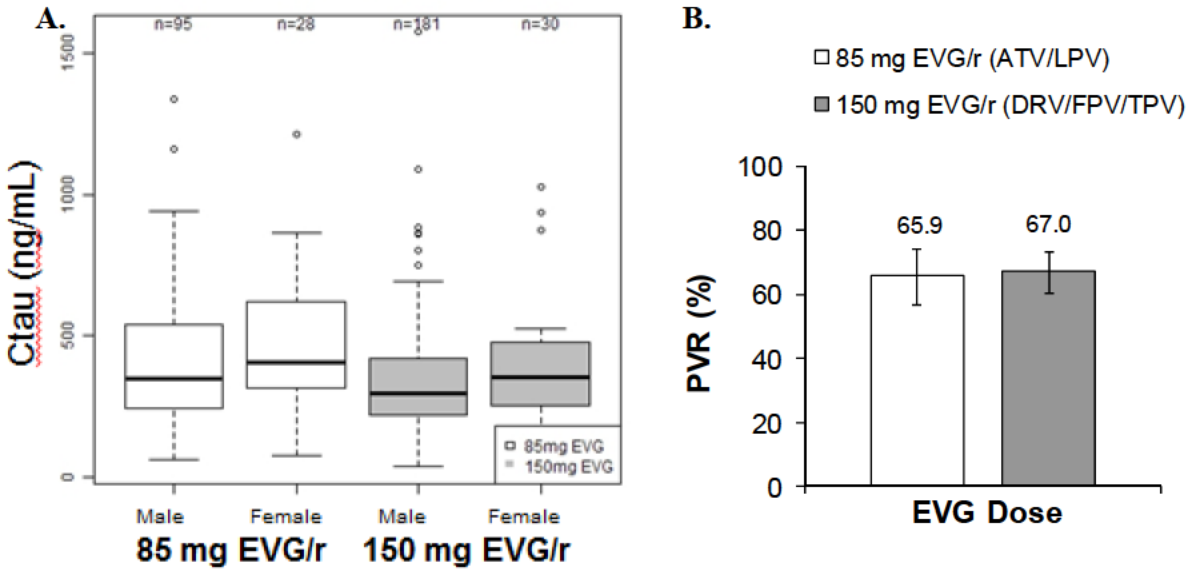



**Figure 4: Plots for A) exposures (Ctau) and B) pure virologic response (PVR) in 85 mg and 150 mg RTV boosted EVG (EVG/r) subgroups.**

### 1.1.4 Are the pop-PK based claims for effect of intrinsic factors (race, gender, hepatitis B/C virus co-infections) on exposures appropriate?

The pop-PK based claims for intrinsic factors of race, gender and hepatitis B/C virus co-infections) on exposures are appropriate from PK perspective with no clinically significant change in PK with any of these intrinsic factors.

### 1.1.5 Is the EVG PK comparable between adults administered EVG regimens described above and adolescents administered with same EVG regimens (150 mg q.d. or 85 mg q.d. depending on the RTV-boosted PI in the BR)?

Yes, EVG exposures ($C_{tau}$) were similar between adolescents (age 12 to less than 18 years and weight >40 kg) administered EVG 85 or 150 mg q.d. depending on the RTV-boosted PI in the BR (GS-US-183-0152), and adults from the Phase 3 trial described above (GS-US-183-0145, same dosing regimen as that used in adolescents) (Figure 5).

There was limited efficacy data available from the open label extension phase of adolescent study (n=9). Of these adolescents, the PVR (HIV-1 RNA <50 copies/mL) was 22.2% (n/N=2/9) at 48 weeks, which was lower than ~59.8% PVR achieved in adults. This lower efficacy in adolescents may be attributable to poor adherence as assessed by the number of subjects with one or more concentration measurements below the limit of quantification (BLQ).

Of the 9 subjects in the open-label extension, 8 subjects had multiple BLQ measurements through 48 weeks. The subject with no BLQ measurements on treatment achieved PVR as did one of the subjects with 4 BLQ measurements (Figure 6).

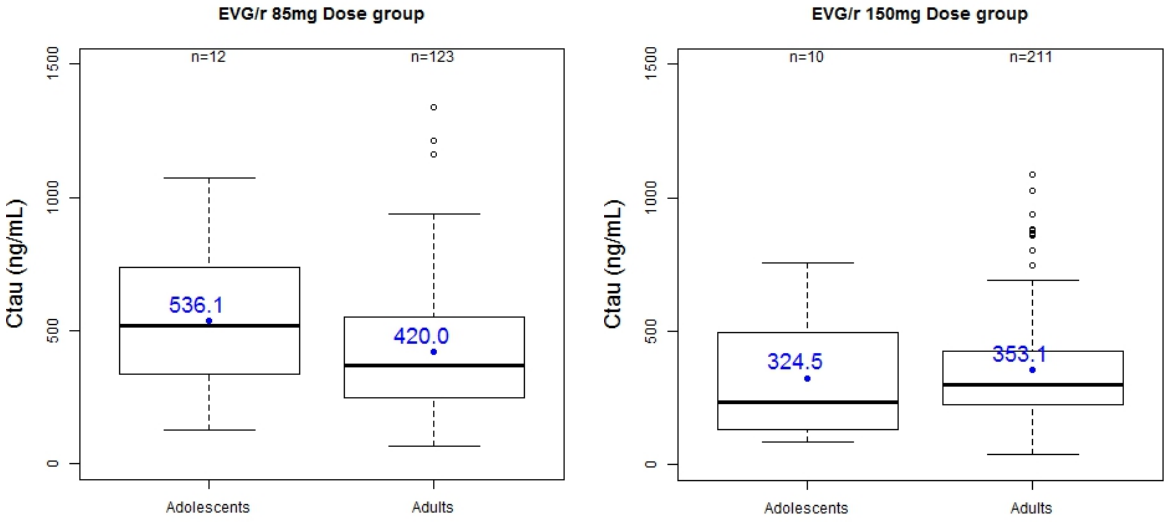



**Figure 5: Comparison of EVG exposures ($C_{tau}$) in adolescents (Trial GS-US-183-0152*) and adults (Phase 3 Trial GS-US-183-0145)**

* A very high concentration outlier is excluded in this analysis

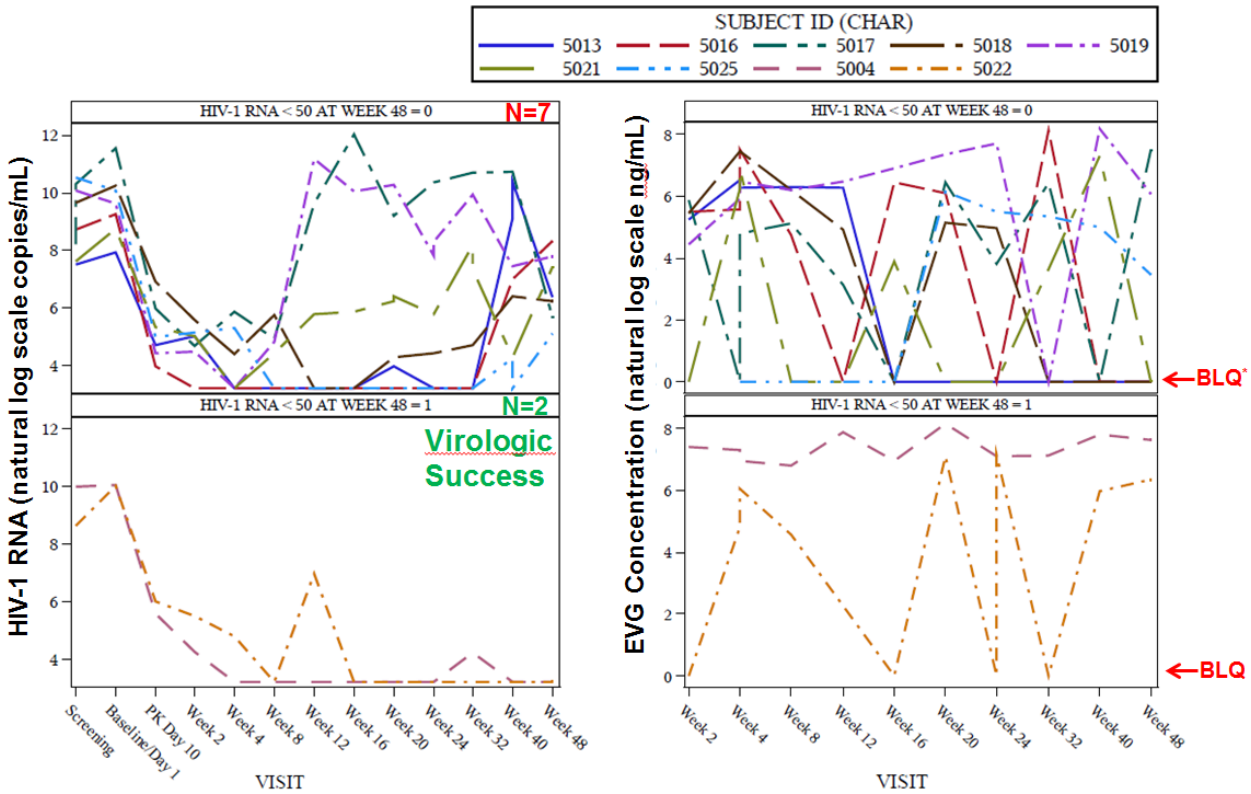



**Figure 6: Measurements of HIV-1 RNA** and EVG concentrations* in adolescents in planned measurement visits through week 48 (Trial GS-US-183-0152).** The lower panels

show subjects with virologic success (HIV-1 RNA <50 at week 48) and the upper panels show subjects without virologic success.

*BLQ measurements of concentration are set to 0, and **HIV-1 RNA measurements < 50 are set to 25 [ln(25)=3.22] for depiction purposes in the plot.

### 1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective.

### 1.3 Label Statements

Please refer to Section 3, Labeling Recommendations in Clinical Pharmacology Review.

## 2 PERTINENT REGULATORY BACKGROUND

Please refer to Section 1, Executive Summary in Clinical Pharmacology Review.

The following clinical study from the EVG submission was evaluated in the Pharmacometric's review:

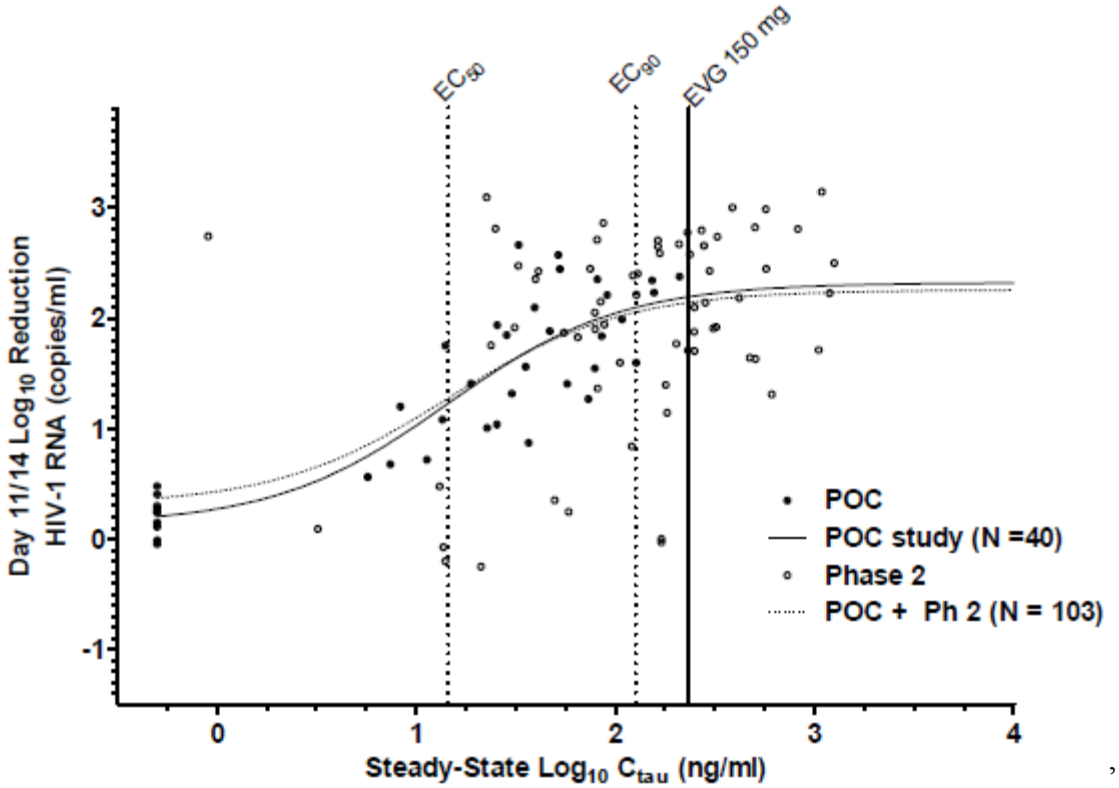
1. a pivotal Phase 3 randomized, double-blind, non-inferiority trial with an EVG treatment arm and a raltegravir (RAL) treatment arm used as an active control. Both EVG and RAL were administered in combination with a RTV-boosted PI background regimen in treatment-experienced HIV-1 infected adults.

With this submission, the sponsor provided a population PK model report and a PKPD supplemental document that evaluated Phase 3 efficacy and safety data with various exposure metrics.

## 3 RESULTS OF SPONSOR'S ANALYSIS

### 3.1 Dose Selection

The EVG dose was selected based on a Phase 1 monotherapy study (with EVG and RTV-boosted EVG dosing) followed by a phase 2 dose finding trial with 20, 50 and 125 mg of EVG boosted by 100 mg RTV. In the Phase 2 dose-finding trial, EVG/RTV 125/100 mg demonstrated greater antiviral activity (i.e. decreases in HIV-1 RNA at Week 24) compared to EVG/RTV 50/100 mg or 20/100 mg. The exposure-response analysis for reduction in $Log_{10}$ HIV-1 RNA with EVG exposures ($C_{tau}$) showed an Emax relationship with 125/100 mg EVG/RTV achieving the mean $C_{tau}$ values ~6-fold of protein binding adjusted in vitro $IC_{95}$ value of 45 ng/ml (Figure 7). A subsequent relative bioavailability trial demonstrated that exposures of EVG were similar following administration of EVG/RTV 150/100 mg (Phase 3 EVG formulation) compared to EVG/RTV 125/100 mg (Phase 2 EVG formulation). The EVG 85 mg dose was selected for ATV/RTV or LPV/RTV BR based on drug-drug interaction studies, to match the exposures attained with RTV-boosted 150 mg EVG.

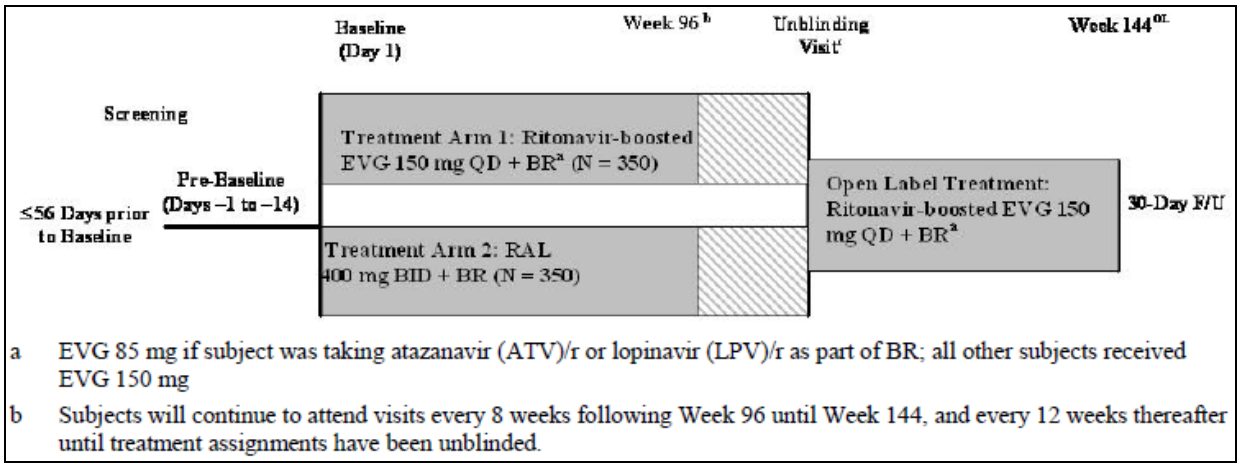



Ph 2, Phase 2 Study GS-US-183-0105; POC, proof-of-concept Study GS-US-183-0101

**Figure 7: EVG Dose-Response Model Based on Monotherapy and Phase 2 Dose-Ranging Study** *Source: Sponsor's Clinical Overview Report, Figure 1, Page 39*

### 3.2 Phase 3 Pivotal Trial

A brief description of Phase 3 pivotal trial is given in Figure 8.




a EVG 85 mg if subject was taking atazanavir (ATV)/r or lopinavir (LPV)/r as part of BR; all other subjects received EVG 150 mg

b Subjects will continue to attend visits every 8 weeks following Week 96 until Week 144, and every 12 weeks thereafter until treatment assignments have been unblinded.

**Figure 8: Overview for Phase 3 Pivotal Trial**. *Source: Sponsor's Week 96 Interim Clinical Study Report, Figure 7-1, Page 36*

### 3.3 Population Pharmacokinetic Analysis

The sponsor performed population pharmacokinetic (PPK) analyses to:

1. Characterize PK of ritonavir-boosted-EVG,
2. Evaluate the effect of RTV exposure on RTV-boosted EVG PK, and
3. Assess the effect of demographics, intrinsic factors and formulation (phase 2 formulation vs. phase 3 formulation) on EVG PK.

### 3.3.1 Methods

The PK dataset consisting of 13006 EVG concentration data from 876 subjects (485 healthy and 391 patients) across 22 different studies (19 in healthy and 3 in patients) was used for pop-PK model development. In pivotal phase 3 study intensive PK sampling was done on a subset of patients at 2 weeks from start of first dose while multiple trough samples were collected from all subjects upto 48 weeks. Also at Week 4, additional PK samples were planned to be collected from all subjects at pre-dose (trough) and at 1 hour and 24 hours post-dose, as well as optional blood sampling at 2, 3, and/or 4 hours post-dose. In the adolescent study with 10-day PK phase followed by an optional open label 48-week treatment phase, the PK samples were collected at 0 (pre-dose), 2, 4, 4.5, 5, 8, 10-12 hours post-dose on day 10. Also, a plasma PK sample was collected for all adolescent subjects participating in the open-label phase at the Week 2, Week 4 and all subsequent visits through Week 48.

### 3.3.2 Results

The final Pop-PK model consisted of two-compartment mammillary PK model with first-order absorption and an absorption lag time. The final model consisted of BSA covariate on drug clearance and intercompartmental clearance (CL and Q), an effect of RTV exposure (RAUC) on the bioavailability (F) of EVG, and an effect of co-administration of ATV/r or LPV/r on EVG clearance (CL). In the absence of concentration data for ATV and LPV, these effects were modeled with 85 mg dose as a covariate. Final parameter estimates for the population PK model are summarized in Table 1. The goodness of fit (Observed vs individual predicted concentrations etc.) plots are provided in Figure 9.

**Table 1: Pharmacokinetic and covariate parameter estimates of the final model**

| Parameter | Population Mean | | IIV | |
|---|---|---|---|---|
| | Estimate | RSE (% CV) | Estimate | RSE (% CV) |
| CL/F (L/h) | 7.10 | 0.9 | 39.1 | 5.7 |
| CL~BSA | 1.30 | 9.9 | - | - |
| CL~DOSE=85 | -0.335 | 12.5 | - | - |
| Vc/F (L) | 18.9 | 1.2 | 37.5 | 14.4 |
| Q/F (L/h) | 5.21 | 1.9 | 32.6 | 17.3 |
| Q~BSA | 2.47 | 8.3 | - | - |
| Vp/F (L) | 179 | 1.8 | 128 | 9.1 |
| $K_a$ (1/h) | 0.176 | 1.3 | 17.0 | 21.2 |
| $T_{lag}$ (h) | 1.15 | 25.8 | 80.5 | 5.9 |
| F~RAUC | 0.14 | 2.5 | - | - |
| σ1 (proportional, %) | 28.1 | 11.5 | 75.9 | 8.1 |

*Source: Sponsor's Population PK Study Report, Table 8-4, Page 25*

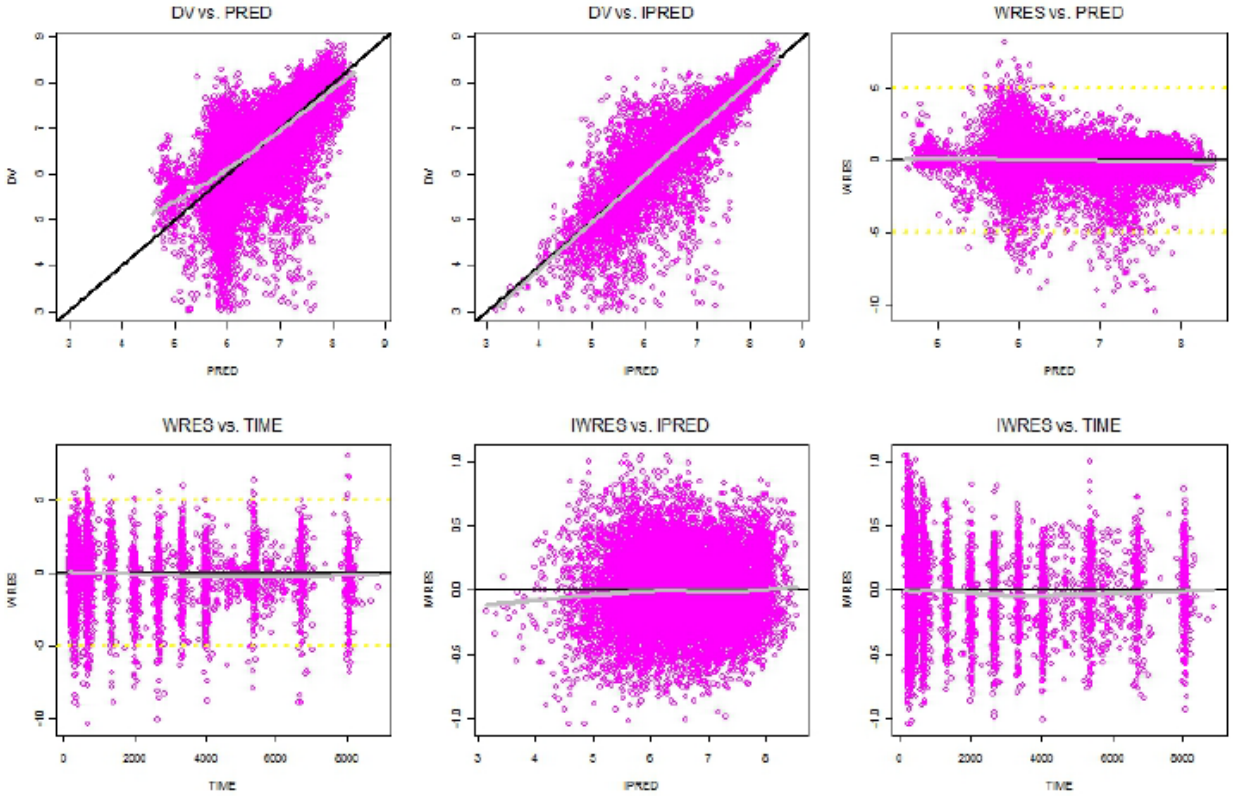



**Figure 9: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model** *Source: Sponsor's Population PK Study Report, Figure 8-6, Page 26*

### 3.3.3 Covariate effects

The final Pop PK model was used to assess the effects of the covariates.

- Relative to the median BSA (1.87 $m^2$) in the study population the range of observed BSA of (1.52 $m^2$ and 2.25 $m^2$ representing 5th and 95th percentile) resulted in differences of -24% and +27% in EVG clearance, respectively. Correspondingly the median EVG $C_{tau}$ within the bottom 5th and the upper 95th percentile of BSA was 519 ng/ml and 327 ng/ml, respectively, as compared to the population median of 381 ng/ml. These values were several-fold above the protein-binding adjusted $IC_{95}$ of 45 ng/ml. Thus the BSA effect was not considered to be clinically relevant for any dose adjustment.
- Subjects receiving 85 mg EVG in combination with ATV/RTV or LPV/RTV had a 28% lower EVG clearance (and comparable $AUC_{tau}$, $C_{max}$, but higher $C_{tau}$) compared to those receiving EVG 150 mg with other three types of protease inhibitor/ritonavir combinations. This justifies the reduction of dose from 150 to 85 mg for these background ARVs.
- Relative to the median RTV AUC value of 5595 ng*h/ml in the dataset, the range of observed RTV AUC of 1729 – 12672 ng*h/ml ($5^{th}$ to $95^{th}$ percentile) corresponded to differences of only -15% and 12% in bioavailability, respectively. Hence, the RAUC at the clinically relevant ritonavir dose was not found to have any clinically meaningful effect on the bioavailability of EVG.

*Reviewer's comments:*

1. *The sponsor's Pop-PK model provides reasonable description of EVG concentrations for individual predictions (observed vs. individual predicted concentrations in Figure 9). There appears to be some over-estimation at lower observed concentrations for a limited number of observations.*
2. *Among the list of covariates for clearance, effect of BSA and 85 mg EVG dose in combination with ATV/RTV or LPV/RTV were the most significant covariates. However, the magnitudes of covariate effects on exposure ($C_{tau}$) are not clinically relevant and there is no need for dose adjustment based on any of these covariates (lack of E-R for safety justifies allowing somewhat higher exposure ($C_{tau}$) observed with the covariate of 85mg dose).*

## 3.4 Exposure-Response Analysis

### 3.4.1 Objective

The sponsor conducted the exposure-response (E-R) analysis to evaluate the relationship of EVG exposures to efficacy and safety parameters.

### 3.4.2 Exposure Parameters

The exposure parameters for each individual in GS-US-183-0145 were derived from noncompartmental analysis of simulated EVG concentrations that were generated using the final pop-pk model. AUCtau, Cmax and Ctau were the exposure metrics used for E-R analysis.

### 3.4.3 Methods

The EVG exposure-efficacy relationship was evaluated for treatment-experienced HIV-1 infected subjects in Phase 3 based on PVR (sustained virologic suppression and no rebound in HIV-1 RNA) of < 50 copies/mL of HIV-1 RNA at Week 48. PVR is the most appropriate metric assessing virologic response pharmacologically as it is unaffected by nonvirologic factors such as discontinuation for various reasons. Similar E-R analyses were also conducted with other efficacy (Snapshot, TLOVR with HIV-1 RNA<50 copies/mL and <400 copies/mL at 48 weeks, change from baseline in HIV-1 RNA at Week 2) and safety parameters. The safety parameters included commonly observed AEs, namely diarrhea, headache, nausea, and upper respiratory tract infections. The E-R for safety was performed using EVG AUCtau and Cmax as exposure metrics.

### 3.4.4 Results

***Exposure-efficacy Results***

In the analysis using EVG $C_{tau}$ vs PVR, PVR rate was ~65% with no relevant trends in E-R relationship across $C_{tau}$ quartiles (Table 2).

**Table 2: Percentage of Pure Virologic Responders (PVR, HIV-1 RNA< 50 copies/mL) at Week 48 Across Quartiles of EVG Exposure**

| EVG Overall (N = 334) | | EVG 85 mg (N = 125) | | EVG 150 mg (N = 209) | |
|---|---|---|---|---|---|
| EVG $C_{tau}$ (ng/mL) | PVR (%) | EVG $C_{tau}$ (ng/mL) | PVR (%) | EVG $C_{tau}$ (ng/mL) | PVR (%) |
| Quartiles | | | | | |
| n = 82 to 84 | | n = 29 to 32 | | n = 52 to 53 | |
| 38 to < 236 | 66 | 64 to < 247 | 62 | 38 to < 224 | 69 |
| 236 to < 325 | 70 | 247 to < 367 | 65 | 224 to < 298 | 67 |
| 325 to < 461 | 68 | 367 to < 554 | 68 | 298 to < 421.6 | 75 |
| 461 to 1573 | 63 | 554 to 1337 | 69 | 421.6 to 1573 | 57 |

*Source: Sponsor's Summary of Clinical Pharmacology Report, Table 62, Page 193*

***Exposure-safety Results***

The E-R analysis using $C_{max}$ or $AUC_{tau}$ and selected safety parameters did not show any trends in the exposure-safety relationships. The Figure 10 below shows a representative result and the rest of the results can be found in sponsor's Summary of Clinical Pharmacology Report (Page 194-200).

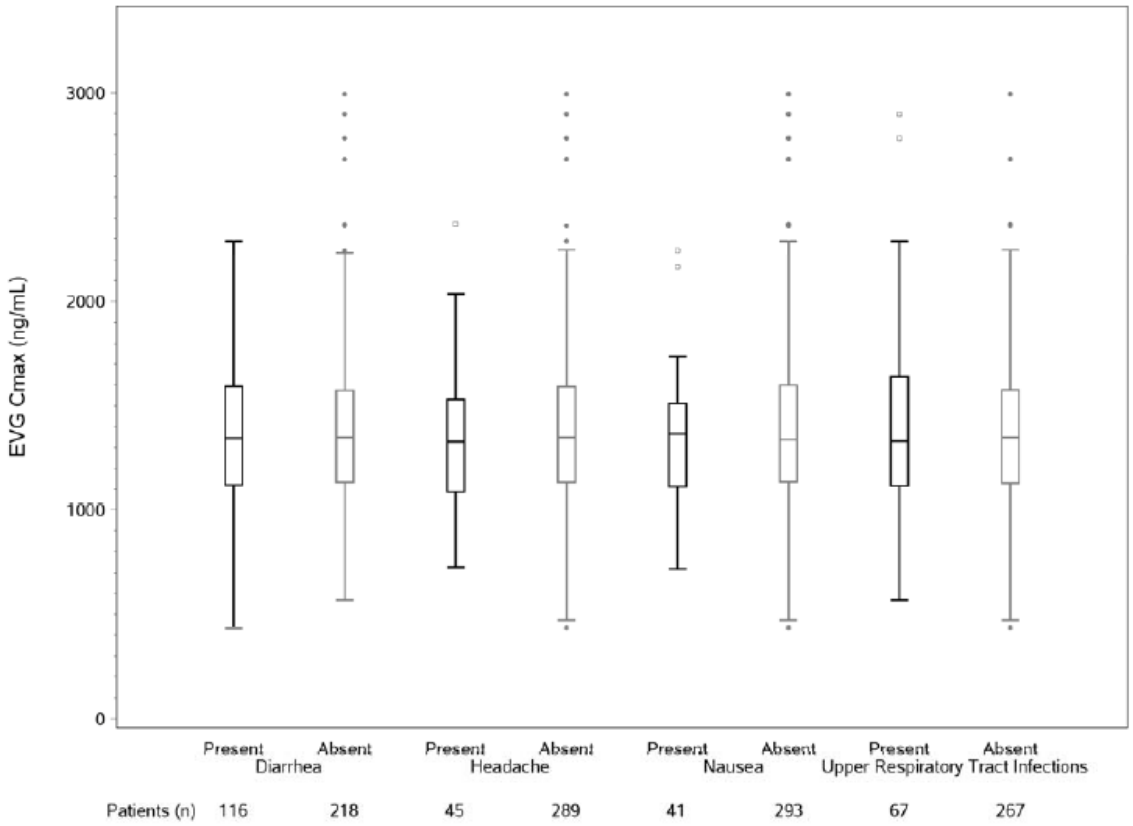



**Figure 10: Box Plot of EVG Cmax (ng/mL) Versus Incidence of Selected Adverse Events**
*Source: Sponsor's Summary of Clinical Pharmacology Report, Figure 6, Page 198*

*Reviewer's comments:*

1. *The sponsor's E-R analysis gives evidence that there are no trends in exposure-response relationship for both efficacy and safety within the exposures achieved with 150 mg (or 85 mg in case of ATV or LPV BR) EVG dose in phase 3 study.*

## 4 RESULTS OF REVIEWER'S ANALYSIS

### 4.1 Objectives

Analysis objectives are to:

1. Evaluate characteristics of the dose/exposure-response relationships for efficacy and safety for RTV boosted EVG
2. Evaluate the POPPK based claims for intrinsic factors (gender, race, hepatitis B/C co-infection).
3. Evaluate adolescent PK for potential extension of currently proposed adult indication to adolescents.

### 4.2 Methods

### 4.2.1 Datasets

Datasets used for the analysis and the link to EDR is provided in Table 3 below.

### 4.2.2 Software

The SAS software (v9.3), TIBCO Spotfire S-plus 8.1 and Rstudio/R 2.14.0 were used for data manipulation and analysis.

## 4.3 Results

### 4.3.1 Characteristics of the dose/exposure-response relationships for efficacy and safety for RTV boosted EVG

***Efficacy***

Please refer to Section 1.1.1, Summary of Findings for a description of the efficacy analyses performed by the reviewer. Visual plots of the E-R relationship between $C_{tau}$ and PVR and virologic failure are shown in Figure 1 and Figure 2, respectively.

***Safety***

Please refer to Section 1.1.2, Summary of Findings for a description of the safety analyses performed by the reviewer. Visual plots of the E-R relationship between RTV dose and treatment arm are shown in Figure 3.

### 4.3.2 Appropriateness of EVG dose reduction from 150 mg to 85 mg for BR involving ATV or LPV

Please refer to Section **1.1.3**, Summary of Findings for a description of the analyses used to assess selection of the EVG 85 mg q.d. dose. A comparison plot of exposures and efficacy for the EVG 150 mg q.d. and 85 mg q.d. doses are shown in Figure 4.

### 4.3.3 Pop-PK based evaluation of effect of intrinsic factors on RTV boosted EVG PK

***Gender***

Based on population PK analysis of pooled data across 22 studies, females had approximately 21% lower clearance compared to males. In phase 3 study with treatment experienced HIV-1 patients, females (n=58) had ~17% higher EVG exposures ($C_{tau}$) than males (n=276) based on individual predicted exposures using POP-PK analysis. However, this higher exposure did not result in any corresponding higher virologic response (PVR) for females (Figure 11). In fact the PVR were 11-18% lower in females compared to males in this Phase 3 study across the two dose subgroups (Figure 11). The analysis with actual concentrations measured through 48 weeks for each individual showed that there were 54.4% female subjects who had one or more BLQ (below level of quantitation) concentrations compared to 41.5% of males. Thus the lower efficacy (PVR) in females can be partially attributable to lower adherence to dosing regimen observed in females compared to males. Since gender differences did not have a clinically significant effect on EVG exposures and EVG exposures did not contribute to difference in efficacy responses across genders, it does not warrant dose adjustment.

A. B.

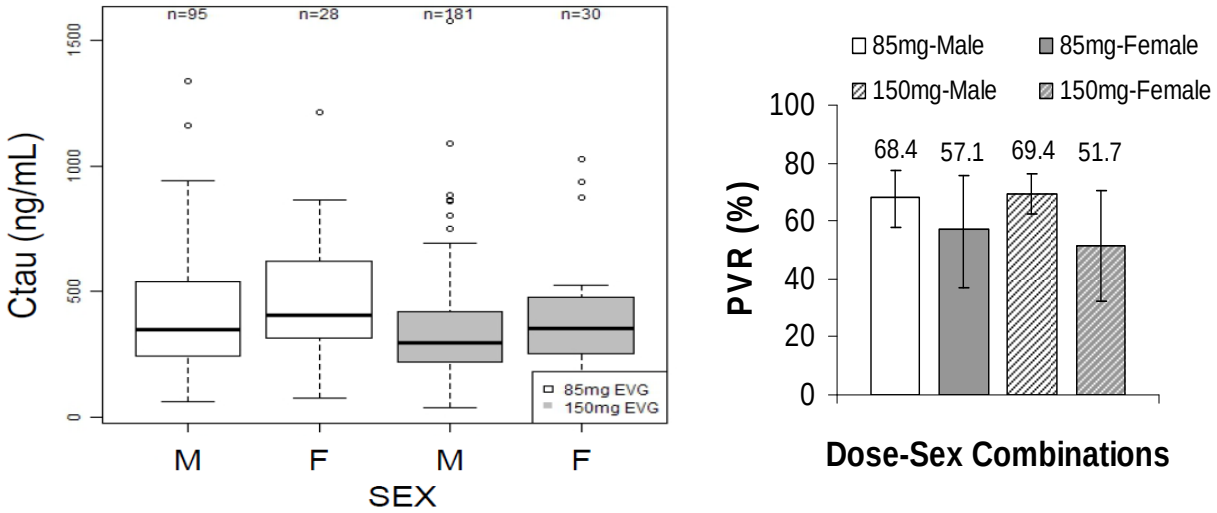



**Figure 11: A) EVG $C_{tau}$ derived from pop-PK analysis vs. gender and B) percentage PVR vs. gender relationship in different dose subgroups in Phase 3 data.**

***Race***

Population PK analysis of pooled data from 22 studies (n=609, 227 and 46 for White, Black and Others) showed no difference in EVG clearance based on race (analyses not shown). The analysis with actual EVG concentrations measured through 48 weeks for each individual (who had measured concentrations) in Phase 3 showed that there were 51.7% Black (or African American) subjects who had one or more BLQ (below level of quantitation) concentrations compared to 39.8% of White and 22.2% Asian subjects. Thus, there was lower adherence to dosing regimen (based on observed BLQ concentrations) in Black (or African American) race as compared to White or Asian race.

***Hepatitis B/C co-infection***

Population PK analysis showed no difference in EVG clearance and thus no clinically relevant changes in EVG PK for subjects with Hepatitis B (n=16) or Hepatitis C (n=41) virus co-infection (analyses not shown)

### 4.3.4 Evaluation of adolescent PK from an adolescent PK-safety-tolerability study

Study GS-US-183-0152 in HIV-1 infected adolescents (aged 12 to <18 years old) involved rich PK collection at day 10 of EVG treatment (N=23 subjects) followed by an optional open label extension phase that continued EVG treatment through 48 weeks (N=9 subjects) to evaluate safety and efficacy. The EVG dose and associated ARV BR were identical to those evaluated in adults in Phase 3 study. The results of this study showed that EVG exposures in both the 85 mg and 150 mg dose groups were comparable between adolescents and adults (Figure 5).

There was no specific trend in exposure ($C_{tau}$) with age amongst the adolescents. There was a slight increasing trend in EVG clearance with body weight, but the extent of increase is not clinically significant within normal body weight range of adolescents (analysis not shown). Thus dose adjustment is not warranted in adolescents with body weight >40 kg.

In the open label extension study, only 2 out of 9 enrolled adolescent subjects achieved pure virologic response (PVR=22.2%, HIV-1 RNA <50 copies/mL) at 48 weeks, which was lower than ~65% PVR achieved in adults. An analysis of PK concentration data collected through 48

weeks showed multiple BLQ concentrations for 8 out of 9 subjects. Thus the lower efficacy observed in adolescents may be attributable to poor adherence in the adolescents who enrolled in the open-label extension.

## 5 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

**Table 3: Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| GS-US-183-0145 | adae.xpt<br>(Adverse events)<br>adpkpd.xpt<br>(PKPD ER parameters)<br>adpc.xpt<br>(Plasma Concentrations)<br>adsl.xpt<br>(Subject-Level Analysis)<br><br>evgex.xpt<br>(EVG exposure estimates)<br>sparse2.csv<br>(POPPK input file)<br>sdtab116, patab116, cotab116, catab116<br>(POPPK output files from final model run) | \\cdsesub1\EVSPROD\NDA203093\\0005\m5\datasets\gs-us-183-0145\analysis\adam\datasets\48-wk\<br><br>\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Elvitegravir_NDA203093_DDM\PPK Analyses\datasets\run116\ |
| GS-US-183-0152 | adpkparm.xpt<br>(PK parameters)<br>adsl.xpt<br>(Subject Level Analysis)<br>adeff.xpt<br>(Efficacy Analysis)<br>(b) (4) lab.xpt<br>(lab measurements) | \\cdsesub1\EVSPROD\NDA203093\0000\m5\datasets\gs-us-183-0152\analysis\datasets\<br><br>\\cdsesub1\evsprod\NDA203093\0000\m5\datasets\gs-us-183-0152\tabulations\legacy\ |

**Table 4: Codes and Output Files**

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| PK_analysis_plotting.R<br>EVG_exposure_sex_difference.sas | Subgroup analysis of CL and exposures for POP-PK results<br>Analysis of sex related differences in PK and BLQ values | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Elvitegravir_NDA203093_DDM\PPK Analyses\ |

| | | |
|---|---|---|
| peds_adults_pk_comparison r | Comparison of adults and adolescents PK | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Elvitegravir_NDA203093_DDM\ER Analyses\peds\ |
| EVG_peds_efficacy.sas | Efficacy (RNA measurements) in open label treatment in adolescents | |
| diarrhea_toxic_final.sas | E-R analysis for diarrhea | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Elvitegravir_NDA203093_DDM\ER Analyses\ |
| Efficacy_Conc_Quartiles_final_PVR.ssc | E-R analysis for PVR | |
| Efficacy_Conc_Quartiles_final_PVF.ssc | E-R analysis for PVF | |

**Trial GS-US-183-0103**
**A Phase 1, Open Label, Multiple-Dose, Pharmacokinetic Drug Interaction Study of GS-9137 and Fixed-Dose Combination of Emtricitabine/Tenofovir Disoproxil Fumarate**

**Trial Period**
12 Oct to 8 Dec 2005
Final report date: 5 Sept 2006 (submitted to IND 72,177)

**Trial Site**
MDS Pharma Services, Phoenix, Arizona, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). Coadministration of GS-9137 with the HIV PI ritonavir (RTV; GS-9137/r) results in a 20-fold increase in GS-9137 exposures due to the inhibition of CYP3A activity by RTV. In clinical practice, GS-9137/r may be coadministered with the N(t)RTIs tenofovir DF and emtricitabine (fixed-dose combination trade name: Truvada®). This study was conducted to determine whether the pharmacokinetics of GS-9137, tenofovir, and emtricitabine were affected by concomitant administration.

**Trial Objectives**
The primary objective of the trial was to:

- evaluate whether the pharmacokinetic parameters of GS-9137, emtricitabine, or tenofovir are affected after coadministration of GS-9137 boosted with ritonavir and emtricitabine/tenofovir DF fixed-dose combination tablet compared to their administration alone

The secondary objective of the trial was to:

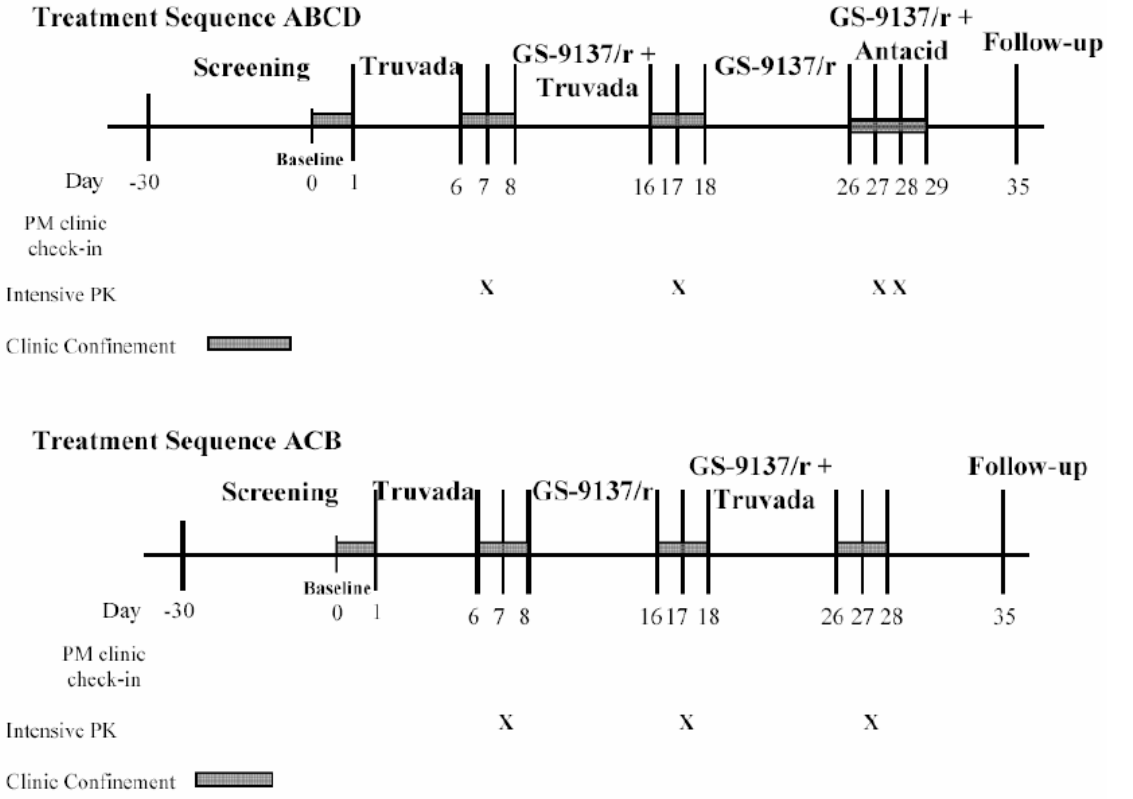
- evaluate the safety of coadministration of GS-9137 boosted with ritonavir and emtricitabine/tenofovir DF fixed-dose combination tablet
- evaluate the effect of an aluminum/magnesium-containing antacid on the pharmacokinetics of GS-9137

**Trial Design**
This was an open-label, multiple-dose, drug interaction study. There were four treatment periods: the first lasted seven days, the second and third lasted 10 days each, and the fourth lasted one day, followed by a 7-day follow-up phase.

| | |
|---|---|
| Treatment A | Emtricitabine/tenofovir DF 200/300 mg QD (Days 1 to 7) |
| Treatment B | GS-9137/r 50/100 mg QD plus emtricitabine/tenofovir DF 200/300 mg QD (Days 8 to 17 or Days 18 to 27) |
| Treatment C | GS-9137/r 50/100 mg QD (Days 18 to 27 or Days 8 to 17) |
| Treatment D | GS-9137/r 50/100 mg plus magnesium/aluminum-containing antacid 20 mL (Day 28) |

Subjects were randomized to Treatment Sequence ABCD or Treatment Sequence ACB. The study schema for both sequences is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




GS-9137 (50 mg); r, 100 mg of ritonavir; Truvada, emtricitabine/tenofovir DF (200/300 mg); antacid, 20 mL Maalox Max

### Drug Administration

All study drugs were administered in the morning with 240 mL of water and within 5 minutes of completing a meal on Days 1 to 27 or 28. The morning meal was standardized (400 kcal and 13 g of fat) on Days 1, 6, 7, 8, 16, 17, 18, 26, 27, and 28. Evening meals that were similar in calorie and fat content were provided on Days 0, 6, 7, 16, 17, 26, 27, and 28. Water was allowed as desired except for 1 h before until 2 h after dosing. On mornings of intensive PK sampling days (Days 7, 17, 27, and 28), subjects fasted after drug administration until after the 4 h postdose blood draw.

### Rationale for Dose Selection

The GS-9137/r dose of 50/100 mg was selected for this study because it was the dose being evaluated in the concurrent Phase 3 study.

The emtricitabine and tenofovir DF doses of 200/300 mg were selected for this study because they are the same doses that are currently marketed in the fixed-dose combination tablet (Truvada®).

The antacid dose of 20 mL (approximately 4 teaspoons) was selected for this study because it is the maximum dose to be given at one time, as indicated by the product directions.

**Investigational Product**

Tablets containing 50 mg of GS-9137 were manufactured by Japan Tobacco, Inc. (Lot 071-4). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 247022E21). Fixed-dose combination tablets containing 200 mg emtricitabine and 300 mg tenofovir DF (Truvada®) were manufactured by Gilead Sciences, Inc. (Foster City, California, USA; Lot V401B1(FP-0521)). Antacid suspension containing aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (Maalox® Advanced Maximum Strength) was manufactured by Novartis Consumer Health, Inc. (Parsippany, NJ, USA; Lot 10009217).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits, fruit and vegetable juices, antacids, and calcium channel blockers was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137 and/or emtricitabine and tenofovir on the specified study days at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 7, 17, 27, and 28 | 0:00 (predose), 0:15, 0:30, 0:45 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |

Urine was collected for the analysis of emtricitabine and tenofovir on the specified study days over the time intervals (in hours post-dose) listed below:

| | |
|---|---|
| Days 7, 17, and 27 | 0 (predose), 0 to 4, 4 to 8, 8 to 12, and 12 to 24 |

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max}$, $T_{max}$, $C_{last}$, $T_{last}$, $C_{tau}$, $\lambda_z$, $AUC_{0\text{-}last}$, $AUC_{tau}$, and $t_{1/2}$ for GS-9137, emtricitabine, and tenofovir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$, and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences between treatments ($C_{max}$, $C_{tau}$, and $AUC_{tau}$) were estimated using a parametric analysis of variance (ANOVA) using a mixed effects model, with sequence, period, and treatment as fixed effects and subject as a random effect. The model was used to generate the point estimate and 90% CI between treatments. GS-9137 PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143%.

## Trial Results

***Bioanalytical methods***

Concentrations of GS-9137 in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16443V4) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Concentrations of emtricitabine and tenofovir in plasma samples were determined using LC-MS/MS (Method M-02-BIO-TP006-02v5 by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 1 Dec and 8 Dec 2005 and analysis was performed between 9 Dec 2005 and 19 Jan 2006. The maximum storage sample time was within the validated long-term frozen stability durations for GS-9137, emtricitabine, and tenofovir.

The GS-9137 calibration standards ranged from 1-1000 ng/mL and the quality control (QC) concentrations were 3.0, 250, and 750 ng/mL. For FTC, the calibration standards ranged from 5-2000 ng/mL and the QC concentrations were 15.0, 500, and 1500 ng/mL. For TFV, the calibration standards ranged from 10-1000 ng/mL and the QC concentrations were 25, 500, and 750 ng/mL. All inter-assay accuracy and precision

estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, FTC, and TFV in human plasma** (source: Study Report Table 5-3)

| | GS-9137 in Plasma | FTC in Plasma | TFV in Plasma |
|---|---|---|---|
| Linear Range (ng/mL) | 1 to 1000 | 5 to 2000 | 10 to 1000 |
| LLQ (ng/mL) | 1 | 5 | 10 |
| Inter-Assay Precision Range[a] | 4.6% to 20.0% | 3.98% to 9.47% | 4.37% to 7.85% |
| Inter-Assay Accuracy Range[b] | –3.3% to 0.8% | –1.7% to 8.0% | –5.2% to 4.0% |
| Stability in Frozen Matrix (days) | 90 | 460 | 460 |

LLQ, lower limit of quantitation; FTC, emtricitabine; TFV, tenofovir

a Relative standard deviation

b Difference from nominal concentrations

Source: Appendix 15

***Trial population***

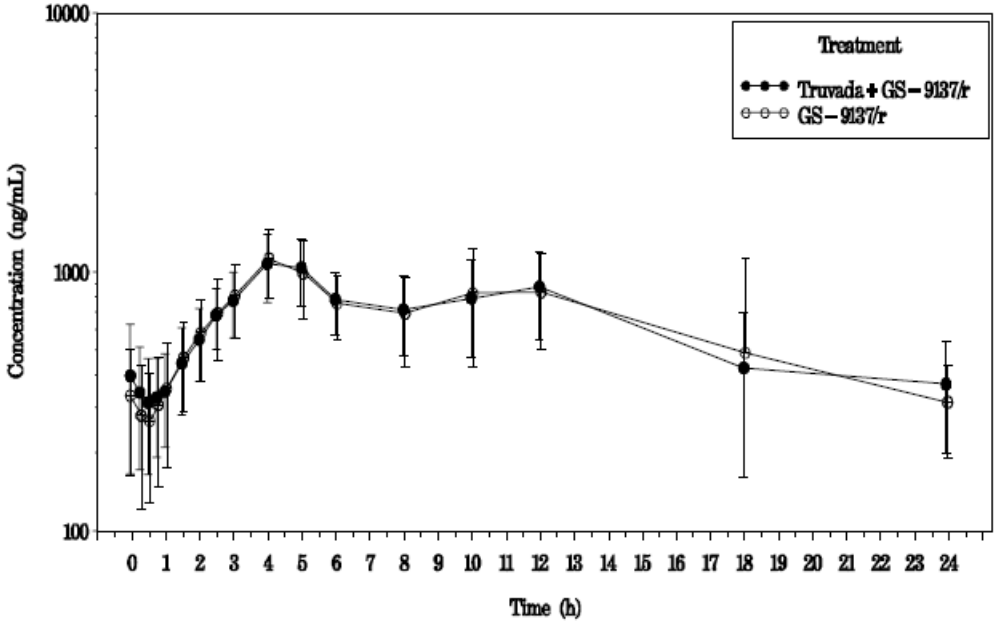
A total of 26 healthy adult subjects were enrolled in the study; 24 subjects completed the study. One subject was withdrawn on Day 17 because of a positive pregnancy test and the other withdrew for a personal reason on Day 17. Both subjects were randomized to Treatment Sequence ACB. Of the safety analysis set (n=26), the majority of subjects were Hispanic (84.6%); 11.5% were white and 3.8% were black. Most of the subjects were female (58.3%). Subjects had a mean age of 30 years (range: 19-44 years).

***Results of pharmacokinetic analyses***

In this study, the effects of coadministration of emtricitabine/tenofovir DF or antacid on GS-9137 pharmacokinetics were evaluated. In addition, the effect of GS-9137 administration on emtricitabine and tenofovir pharmacokinetics were evaluated.

Ten days of emtricitabine/tenofovir DF 200/300 mg QD coadministration with GS-9137/r 50/100 mg QD had no effect on GS-9137 plasma concentrations at all time points (see Figure 2), while a single dose of antacid decreased GS-9137 plasma concentrations (see Figure 3). The PK parameters for GS-9137 alone and with FTC/TDF or antacid are listed in Table 2. When coadministered with FTC/TDF, there were no significant alterations in GS-9137 $AUC_{tau}$ and $C_{tau}$, with 90% CI values within the prespecified bounds of 70-143% (see Table 3). When coadministered with antacid, GS-9137 exposures were significantly lower, with 90% CI values below the prespecified no effect bounds (see Table 3).

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with FTC/TDF** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Values presented as mean ± SD. the pharmacokinetic analysis set excludes Subjects 4 and 24 because they did not have an evaluable pharmacokinetic profile for each treatment pair.

Source: Section 11.1, Figure 1

**Figure 3: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with antacid** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)

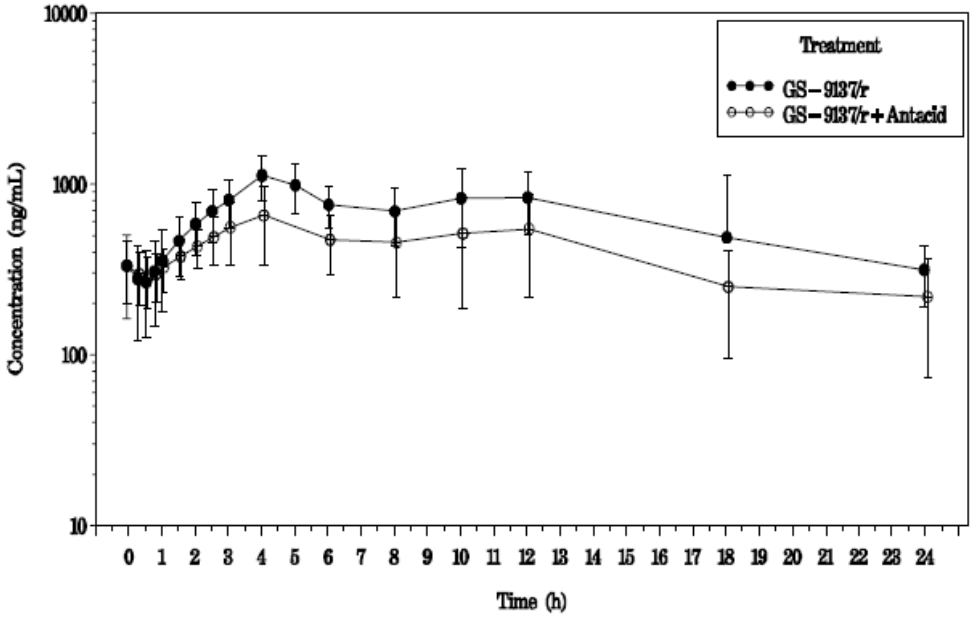


**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with FTC/TDF or antacid** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Steady-State Plasma PK Parameters[a] | GS-9137/r (N = 24) | GS-9137/r + FTC/TDF (N = 24) | GS-9137/r + Antacid (N = 13) |
|---|---|---|---|
| $C_{max}$ (ng/mL) Mean (% CV) | 1223.2 (46.4) | 1155.7 (27.4) | 716.2 (42.2) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 15028.6 (45.0) | 15055.6 (32.9) | 9507.1 (50.4) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 314.1 (39.1) | 369.4 (45.9) | 218.5 (66.0) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.03 (4.00, 5.00) | 4.03 (4.00, 5.00) | 4.00 (4.00, 4.00) |
| $T_{½}$ (hours) Median (Q1, Q3) | 8.78 (7.93, 11.31) | 9.94 (7.49, 13.11) | 11.04 (7.17, 12.13) |

a The pharmacokinetic analysis set excludes Subjects 4 and 24 because they did not have an evaluable pharmacokinetic profile for each treatment pair.

GS-9137/r, 50 mg of GS-9137 + 100 mg of ritonavir; FTC/TDF, fixed-dosed emtricitabine/tenofovir DF (200/300 mg); antacid, 20 mL of Maalox Max; CV, coefficient of variation; Q1, first quartile; Q3, third quartile

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137 alone or with FTC/TDF or antacid** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| FTC/TDF + GS-9137/r vs. GS-9137/r[b] | | | | |
| $C_{max}$ (ng/mL) | 1106.3 | 1123.9 | 98.4 | 90.4, 107.2 |
| $C_{tau}$ (ng/mL) | 324.7 | 285.7 | 113.7 | 104.3, 123.8 |
| $AUC_{tau}$ (ng•h/mL) | 14,149.1 | 13,814.0 | 102.4 | 96.3, 109.0 |
| Antacid + GS-9137/r vs.GS-9137/r[c] | | | | |
| $C_{max}$ (ng/mL) | 664.1 | 1250.6 | 53.1 | 46.8, 60.2 |
| $C_{tau}$ (ng/mL) | 184.4 | 311.8 | 59.1 | 52.0, 67.2 |
| $AUC_{tau}$ (ng•h/mL) | 8561.5 | 15,550.7 | 55.1 | 50.4, 60.2 |

a N = 24/treatment except for antacid + GS-9137/r vs.GS-9137/ritonavir where N = 13/Treatment; the pharmacokinetic analysis set excludes Subjects 4 and 24 because they did not have an evaluable pharmacokinetic profile for each treatment pair.

b Test Treatment = GS-9137/r plus emtricitabine/tenofovir DF, Reference Treatment = GS-9137/r

c Test Treatment = GS-9137/r plus antacid, Reference Treatment = GS-9137/r

GS-9137/r, 50 mg of GS-9137 + 100 mg of ritonavir; FTC/TDF, fixed-dosed emtricitabine/tenofovir DF (200/300 mg); antacid, 20 mL of Maalox Max; CI, confidence interval

Source: Section 11.1, Table 6.1

The steady-state pharmacokinetics of emtricitabine and tenofovir were similar following administration of FTC/TDF with or without GS-9137/r.

Note that GS-9137 exposures were approximately three-fold higher in the current study compared to exposures after administration of the same dose of GS-9137/r in Study GS-US-183-0101. The Applicant is unable to provide an explanation for this phenomenon.

***Results of safety analysis***

Study drugs were generally safe and well-tolerated. Headache was the most common AE and was experienced at similar rates between treatment groups. Coadministration of GS-9137/r and antacid primarily resulted in GI system disorders. There were no serious adverse events, discontinuations due to adverse events, or deaths during this trial.

**Trial Summary**

This study was designed to evaluate the effect of coadministration of GS-9137/r 50/100 mg and the HIV antiretroviral fixed-dose combination emtricitabine/tenofovir DF (FTC/TDF), and to investigate the influence of coadministration of FTC/TDF or antacid on the pharmacokinetics of GS-9137, in healthy subjects.

Coadministration of GS-9137/r and FTC/TDF did not substantially affect the pharmacokinetics of GS-9137, FTC, or tenofovir. However, coadministration of GS-9137/r and antacid led to decreased plasma levels of GS-9137, likely due to the chelation of divalent cations in the antacid by the quinolone moiety of GS-9137. Therefore, the Applicant recommends that administration of GS-9137/r and antacids containing high concentrations of divalent cations be separated by at least four hours. This recommendation is similar to that regarding coadministration of antacids and the quinolone antibiotics, which also chelate multivalent cations, and is supported by the clinical pharmacology information generated by the GS-9137 development program to date.

Note that Trial GS-US-183-0119 was subsequently conducted to investigate the effects of staggered administration of GS-9137/r and antacid; please refer to the clinical pharmacology review of Trial GS-US-183-0119 for details.

**Trial GS-US-183-0104**
**A Phase 1, Open Label, Multiple-Dose, Pharmacokinetic Drug Interaction Study of GS-9137/r and Zidovudine**

**Trial Period**
8 Nov to 20 Dec 2005
Final report date: 24 Aug 2006 (submitted to IND 72,177)

**Trial Site**
MDS Pharma Services, Phoenix, Arizona, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). Coadministration of GS-9137 with the HIV PI ritonavir (RTV; GS-9137/r) results in a 20-fold increase in GS-9137 exposures due to the inhibition of CYP3A activity by RTV. In clinical practice, GS-9137/r may be coadministered with the NRTI zidovudine (trade name Retrovir®). This study was conducted to determine whether the pharmacokinetics of GS-9137, ritonavir, zidovudine, and its metabolite zidovudine glucuronide were affected by concomitant administration.

**Trial Objectives**
The primary objective of the trial was to:

- evaluate whether the pharmacokinetic parameters of GS-9137 or zidovudine are affected after coadministration of GS-9137 boosted with ritonavir and zidovudine compared to their administration alone

The secondary objectives of the trial were to:

- evaluate the safety of coadministration of GS-9137 boosted with ritonavir and zidovudine
- evaluate the pharmacokinetics of ritonavir

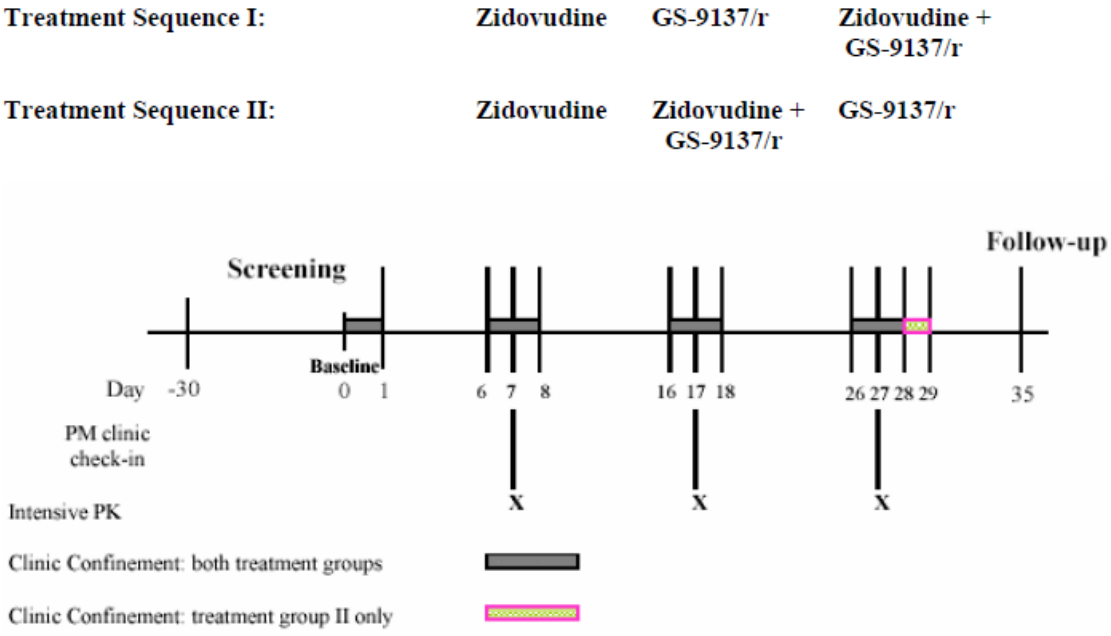
**Trial Design**
This was an open-label, multiple-dose, drug interaction study. There were three treatment periods: the first lasted seven days and the second and third lasted 10 days each. The third treatment period was followed by a 7-day follow-up phase.

Treatment A Zidovudine 300 mg BID (Days 1 to 7)
Treatment B GS-9137/r 200/100 mg QD (Days 8 to 17 or Days 18 to 27)

Treatment C GS-9137/r 200/100 mg QD and zidovudine 300 mg BID (Days 18 to 27 or Days 8 to 17)

Subjects were randomized to Treatment Sequence I (ABC) or II (ACB). The study schema for both sequences is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




## Drug Administration

All study drugs were taken within 5 minutes of consuming a meal. Doses administered at the study center (Days 1, 6 to 8, 16 to 18, and 26 to 28 or 29) were taken with 240 mL of water and within 5 minutes of consuming a standardized meal (400 kcal and 13 g of fat). Evening meals that were similar in calorie and fat content were provided on Days 0, 6, 7, 16, 17, 26, 27, and 28. Water was allowed as desired except for 1 h before until 2 h after dosing. On mornings of intensive PK sampling days (Days 7, 17, and 27), subjects fasted after drug administration until after the 4 h postdose blood draw.

## Rationale for Dose Selection

The GS-9137/r dose of 200/100 mg QD was selected for this study because it was predicted to provide GS-9137 exposures at the upper limit of what is expected in planned clinical trials, thus establishing the maximum potential for a drug-drug interaction.

The zidovudine dose of 300 mg BID was selected for this study because it is the same dose that is currently marketed.

## Investigational Product

Tablets containing 200 mg of GS-9137 were manufactured by Japan Tobacco, Inc. (Lot 401). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by

Abbott Laboratories (Abbott Park, Illinois, USA; Lot 247022E21). Film-coated tablets containing 300 mg of zidovudine (Retrovir®) were manufactured by (b) (4) .

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, ritonavir, zidovudine, and zidovudine glucuronide were collected on the specified study days at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 7, 17, and 27 | 0:00 (predose), 0:15, 0:30, 0:45 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |
| Day 28 (Sequence II) | 28:00, 32:00, 36:00, and 48:00 |

Urine was collected on the specified study days over the time intervals (in hours post-dose) listed below:

| | |
|---|---|
| Days 7, 17, and 27 | 0 (predose), 0 to 4, 4 to 8, and 8 to 12 |

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max}$ and $AUC_{tau}$ for GS-9137, ritonavir, zidovudine, and zidovudine glucuronide, and $C_{tau}$ for GS-9137 and ritonavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences between treatments were estimated using the ESTIMATE statement in the MIXED procedure (SAS®, SAS Institute Inc, Cary, North Carolina, USA). The model was used to generate the point estimate and 90% CI between treatments. GS-9137 PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143%.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137 in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16443V5) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Concentrations of zidovudine (AZT) and zidovudine glucuronide (gAZT) in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16467V1) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 7 Dec 2005 and 4 Jan 2006 and analysis was performed between 13 and 30 Jan 2006. The maximum sample storage time was within the validated long-term frozen stability duration.

Concentrations of ritonavir in plasma samples were determined using LC-MS/MS ((b) (4) Project 42-0316) by (b) (4). Frozen plasma samples were received between 10 Jan and 1 Feb 2006 and analysis was performed between 10 Jan and 6 Feb 2006. The maximum sample storage time was within the validated long-term frozen stability duration.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For AZT, the calibration standards ranged from 5-2000 ng/mL and the QC concentrations were 15.0, 250, and 1500 ng/mL. For gAZT, the calibration standards ranged from 20-8000 ng/mL and the QC concentrations were 60.0, 1000, and 6000 ng/mL. For ritonavir, the calibration standards ranged from 1-1000 ng/mL and the QC concentrations were 1, 3, 9, 200, and 800 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, ritonavir, AZT, and gAZT in human plasma** (source: Study Report Table 5-4)

| | GS-9137 | Ritonavir | Zidovudine | Zidovudine glucuronide |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 1 to 1000 | 5 to 2,000 | 20 to 8,000 |
| LLQ[a] (ng/mL) | 20 | 1 | 5 | 20 |
| Intra-Assay Precision Range[b] (ZDV/gZDV: Varian Matrix SPE) | 1.2% to 9.4% | 6.4 to 7.4 | 5.7% to 7.9% | 1.6% to 8.1% |
| Intra -Assay Precision Range[b] (ZDV/gZDV: Varian 96 SPE) | NA | NA | 7.4% to 13.7% | 2.7% to 6.0% |
| Intra -Assay Accuracy Range[c] (ZDV/gZDV: Varian Matrix SPE) | –4.5% to 1.0% | –7.7 to 1.6 | –12.0% to 6.0% | –3.4% to 4.3% |
| Intra -Assay Accuracy Range[c] (ZDV/gZDV: Varian 96 SPE) | NA | NA | –2.9% to 12.0% | –4.0% to 3.5% |
| Stability in Frozen Matrix (days) | 90 | 343 | 22 | 22 |

a LLQ, lower limit of quantitation
b Relative standard deviation
c Difference from nominal concentrations
Source: Appendix 15

***Trial population***

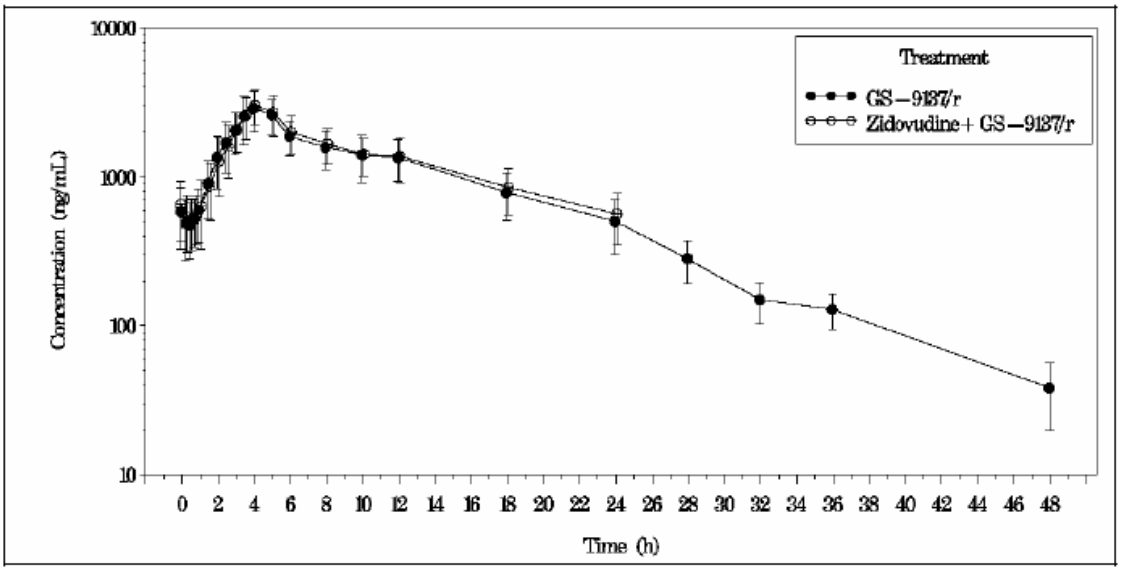
A total of 28 healthy adult subjects were enrolled in the study; 24 subjects completed the study. One subject withdrew consent, one subject was discontinued by the investigator because of a positive urine drug screen, and the other two subjects (both in Treatment Sequence II) discontinued due to adverse events, one on Day 12 (GS-9137/r+ZDV, Grade 1 vomiting) and the other on Day 6 (GS-9137/r+ZDV, Grade 1 abdominal distention). Of the safety analysis set (n=28), the majority of subjects were Hispanic (78.6%); the remainder were white. Half of the subjects were female (50%). Subjects had a mean age of 31 years (range: 20 to 42 years).

***Results of pharmacokinetic analyses***

In this study, the effects of coadministration of ritonavir-boosted GS-9137 and zidovudine on the pharmacokinetics of GS-9137, ritonavir, zidovudine, and zidovudine glucuronide were evaluated.

Ten days of GS-9137/ritonavir 200/100 mg QD coadministration with zidovudine 300 mg BID had no effect on GS-9137 plasma concentrations at all time points (see Figure 2). The PK parameters for GS-9137 alone and with zidovudine are listed in Table 2. When coadministered with zidovudine, there were no significant alterations in GS-9137 $AUC_{tau}$ and $C_{tau}$, with 90% CI values within the prespecified bounds of 70-143% (see Table 3).

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with zidovudine** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Note: Subjects 4, 16, 17, and 28 did not have evaluable PK for each treatment pair and were excluded from PK analysis set and all summary statistics (as predefined in the statistical analysis plan). Plasma concentrations below lower limit of quantification (BLQ) were treated as 0 for determination of summary and order statistics. Plasma concentrations not reported (NR) or not obtained were excluded for determination of summary and order statistics.

Values presented as mean ± SD (semi-logarithmic scale).

Source: Section 11.1, Figure 1

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with zidovudine** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Steady-State PK Parameter | GS-9137/r Alone (N = 24) | GS-9137/r + Zidovudine (N = 24) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 3051.2 (27.2) | 3202.2 (26.1) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 29830.1 (24.1) | 31153.7 (24.4) |
| $C_{tau}$ (ng/mL) Mean (% CV) | 503.4 (40.2) | 565.7 (37.6) |
| $T_{max}$ (h) Median (Q1–Q3) | 4.00 (3.51–5.00) | 4.00 (4.00–4.00) |
| $T_{1/2}$ (h) Median (Q1–Q3) | 7.96 (7.43–8.84) | 9.13 (8.05–10.92) |

Source: Section 11.1, Table 5; Appendix 14, Listing 22

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with zidovudine** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| **Analyte: GS-9137** | | | | |
| $C_{max}$ (ng/mL) | 3080.0 | 2923.7 | 105.0 | 98.3, 112.9 |
| $C_{tau}$ (ng/mL) | 523.6 | 457.2 | 114.5 | 104.4, 125.7 |
| $AUC_{tau}$ (ng•h/mL) | 30100.5 | 28636.6 | 105.1 | 99.3, 111.3 |

a Test vs. Reference = GS-9137/r + Zidovudine vs. GS-9137/r alone. N = 24/treatment; the pharmacokinetic analysis set excludes Subjects 4, 6, 17, and 28 because they do not have an evaluable data from a treatment pair (as predefined in the statistical analysis plan).

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, ZDV = 300 mg

Source: Section 11.1, Table 6

The steady-state pharmacokinetics of ritonavir were similar following administration of GS-9137/r with or without zidovudine. In addition, the steady-state pharmacokinetics of both zidovudine and zidovudine glucuronide were similar following administration of zidovudine with or without GS-9137/r.

***Results of safety analysis***

Study drugs were generally safe and well-tolerated. Nausea, vomiting, dizziness, and headache were the most common AEs. Vomiting was experienced at a higher rate in the GS-9137/r+ZDV treatment group than in the other groups. There were two discontinuations due to study drug-related adverse events (Grade 1 nausea and Grade 1 abdominal distension), both during treatment with GS-9137/r+zidovudine. There were no serious adverse events or deaths during this trial.

**Trial Summary**

This study was designed to evaluate the effect of coadministration of GS-9137/r 200/100 mg and the HIV NRTI zidovudine 300 mg BID on the pharmacokinetics of GS-9137, ritonavir, zidovudine, and zidovudine glucuronide in healthy subjects.

Coadministration of ritonavir-boosted GS-9137 and zidovudine did not substantially affect the pharmacokinetics of GS-9137, ritonavir, zidovudine, or zidovudine glucuronide. No adjustments to the doses of GS-9137, ritonavir, or zidovudine are recommended by the Applicant when GS-9137/r and zidovudine are coadministered; this is supported by the results of this study.

**Trial GS-US-183-0106**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of Atazanavir Sulfate/r and Dose-Reduced GS-9137/r**

**Trial Period**
11 Jan to 22 Mar 2007
Final report date: 6 Dec 2007 (submitted to IND 72,177)

**Trial Site**
Northwest Kinetics, Tacoma, Washington, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). In clinical practice, GS-9137 may be coadministered with the PI atazanavir (trade name Reyataz®) boosted by the HIV PI ritonavir (RTV). GS-9137 and atazanavir are both substrates of CYP3A; when given in combination with ritonavir, exposures are elevated due to the inhibition of CYP3A activity by ritonavir. A previous drug-drug interaction study (GS-US-183-0108) demonstrated altered pharmacokinetics when GS-9137 200 mg was coadministered with atazanavir/r 300/100 mg. This study was conducted to determine whether a lower dose of GS-9137 (85 mg) will obviate previously observed pharmacokinetic alterations when GS-9137 and atazanavir/r 300/100 are coadministered.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetic parameters of GS-9137, atazanavir, or ritonavir are affected following coadministration of atazanavir/r and dose-reduced GS-9137 (85 mg) compared to atazanavir/r or regular-dose GS-9137/r (150 mg) administered alone

The secondary objective of the trial was to:

- evaluate the safety of GS-9137/r or atazanavir/r alone, and the combination of atazanavir/r and dose-reduced GS-9137

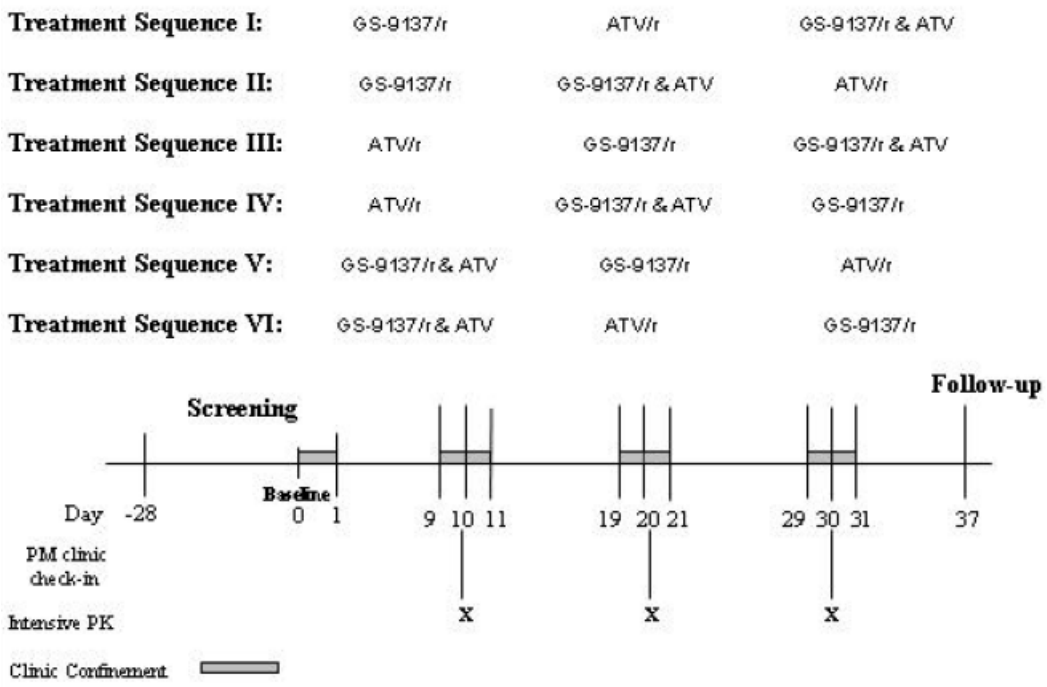
**Trial Design**
This was an open-label, multiple-dose, drug interaction study. There were three treatment periods, each lasting 10 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A GS-9137/r 150/100 mg QD

Treatment B atazanavir/r 300/100 mg QD
Treatment C GS-9137 85 mg plus atazanavir/r 300/100 QD

Subjects were randomized to one of six treatment sequences: ABC, ACB, BAC, BCA, CAB, or CBA. The study schema for all six sequences is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




## Drug Administration

All study drugs were taken with 240 mL of water and within 5 minutes of consuming a meal at approximately the same time every morning. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 5, 10, 11, 15, 20, 21, 25, 30, and 31. Evening meals that were similar in calorie and fat content were provided on Days 0, 9, 10, 19, 20, 29, and 30. On mornings of intensive PK sampling days (Days 10, 20, and 30), water was restricted beginning 1 h before until 2 h after dosing, and subjects fasted after drug administration until after the 4 h postdose blood draw.

## Rationale for Dose Selection

The GS-9137 dose of 150 mg QD was selected for this study because it is the proposed commercial dose and formulation. Note that the GS-9137 formulation used in the previous drug interaction trial with atazanavir/ritonavir (GS-US-183-0108) was a different (nonbioequivalent) formulation.

The GS-9137 dose of 85 mg QD to be given in combination with atazanavir/ritonavir was selected for this study because it was predicted to maintain high GS-9137 trough

concentrations while limiting systemic exposures, based on a model generated using pharmacokinetic data from GS-US-183-0108.

The atazanavir/r dose of 300/100 mg QD was selected for this study because it is the same dose that is currently marketed for treatment-experienced adults infected with HIV-1.

**Investigational Product**

Tablets containing either 85 or 150 mg of GS-9137 were manufactured by (b) (4) Lots AJ0609C1 and AJ0609D1, respectively). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 441432E22). Capsules containing 150 mg of atazanavir (Reyataz®) were manufactured by Bristol-Myers Squibb Co. (New York, New York, USA; Lot 6J3086A).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 19 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, and/or atazanavir were collected on the specified study days at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 10, 20, and 30 | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137 and atazanavir. In addition, $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{1/2}$, $C_{tau}$, and $AUC_{tau}$ were calculated for GS-9137, its metabolite M4, ritonavir, and atazanavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences between treatments (GS-9137 PK parameters between Treatments C and A; atazanavir PK parameters between Treatments C and B; ritonavir PK parameters between Treatments C and A and Treatments C and B) were calculated using a parametric ANOVA using the MIXED procedure (SAS®, SAS Institute Inc, Cary, North Carolina, USA). The model included treatment, sequence, and period and fixed effects and subjects-within-sequence as a random effect. The model was used to generate the point estimate and 90% CI between treatments. GS-9137 and ritonavir PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143%; atazanavir PK parameters were considered unaltered if the 90% CI values were within 70-125%.

## Trial Results

***Bioanalytical methods***

Concentrations of GS-9137, GS-9200. GS-9202, and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16443V6) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 13 Feb and 14 Mar 2007 and stored at -80˚C. Analysis was performed between 8 and 21 Mar 2007. The first day of sample collection was 30 Jan 2007, so the maximum sample storage time was 49 days, which is within the validated long-term frozen stability duration (at -80˚C) of 268 days for GS-9137, GS-9200, GS-9202, and RTV.

Concentrations of atazanavir in plasma samples were determined using LC-MS/MS ((b) (4) 06-204) by (b) (4). Frozen plasma samples were received between 13 Feb and 2 Mar 2007 and stored at -70˚C. Analysis was performed between 7 Mar and 9 Apr 2007. The first day of sample collection was 30 Jan 2007, so the maximum sample storage time was 49 days, which is within the validated long-term frozen stability duration (at -70˚C) of 96 days.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For GS-9200 and GS-9202, the calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50.0, 150, and 750 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For atazanavir, the calibration

standards ranged from 10-5000 ng/mL and the QC concentrations were 30.0, 2000, and 4000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, atazanavir, and ritonavir in human plasma** (source: Study Report Table 5-4)

| Parameter | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Atazanavir | Ritonavir |
|---|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 1,000 | 20 to 1,000 | 10 to 5, 000 | 5 to 5, 000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 10 | 5 |
| Inter-Assay Precision Range[a] | 2.1% to 6.3% | 4.7% to 14.7% | 3.5% to 10.9% | 2.3% to 3.0% | 8.0% to 11.6% |
| Inter-Assay Accuracy Range[b] | −13.0% to −2.4% | −4.5 %to −1.5% | −5.1% to −3.3% | −5.7% to −1.5% | −2.0% to 9.4% |
| Stability in Frozen Matrix (days) | 268 | 268 | 268 | 96 | 268 |

LLQ, lower limit of quantitation

a % coefficient of variation for quality control samples

b %bias (mean percent difference from nominal concentration) for quality control samples

Source: Appendix 10

***Trial population***

A total of 30 healthy adult subjects were enrolled in the study; 19 subjects completed the study. Seven subjects withdrew for safety or tolerability reasons related to study drugs, two were withdrawn because of protocol violations, and the other two subjects withdrew consent. Of the seven subjects who discontinued due to safety or tolerability reasons, four had AEs of moderate dermatitis, and one each had moderate papular rash, moderate insomnia, and moderate toxic myopathy with severe elevated blood CPK (see "Results of safety analysis" section for further details). Of the safety analysis set (n=30), the majority of subjects were white (63.3%); the remainder were black (23.3%), Asian (6.7%), Pacific Islander (3.3%), or classified as "other" (3.3%). Most of the subjects were male (73.3%). Subjects had a mean age of 26 years (range: 19 to 44 years).

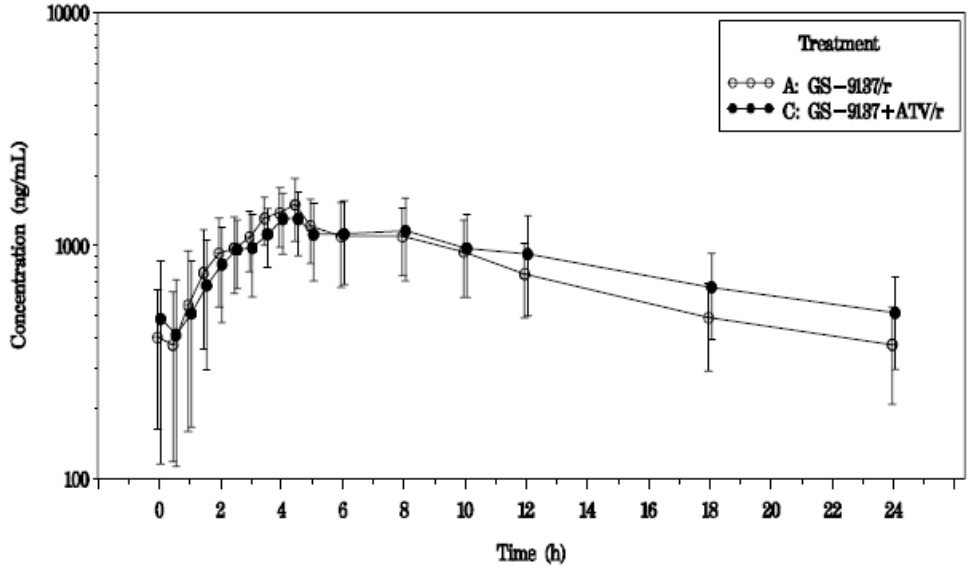
***Results of pharmacokinetic analyses***

In this study, the pharmacokinetics of GS-9137, ritonavir, and atazanavir were compared following coadministration of low-dose GS-9137 (85 mg) and atazanavir/r versus administration of GS-9137 150 mg or atazanavir/r alone.

Following ten days of GS-9137 85 mg QD coadministration with atazanavir/r 300/100 mg QD, the early GS-9137 concentration-time profile (up to 10 h post-dose) was similar to that generated following administration of GS-9137/r 150/100 mg alone, but GS-9137 concentrations were higher thereafter when coadministered with atazanavir/r compared to administration alone (see Figure 2). The PK parameters for GS-9137 alone and with

atazanavir/r are listed in Table 2. When GS-9137 was coadministered at the 85 mg dose with atazanavir/r, its half-life increased from 11.9 to 16.2 h, most likely due to a decrease in GS-9137 clearance due to inhibition of glucuronidation by atazanavir (see Table 2). The 90% CI values for GS-9137 $AUC_{tau}$ and $C_{max}$ were within the prespecified bounds of 70-143%, but the GLSM $C_{tau}$ value was 38% higher compared to that following administration of GS-9137/r 150/100 mg (90% CI 118.30-161.16, see Table 3).

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or at a lower dose with atazanavir/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




GS-9137/r = 150 or 85 mg of GS-9137 + 100 mg of ritonavir once-daily when administered alone or with atazanavir, respectively, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily.

Values presented as mean ± SD. The pharmacokinetic analysis set includes 20 subjects who had evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.1

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or at a lower dose with atazanavir/r** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | 150/100 mg GS-9137/r (N = 20) | 85 mg GS-9137 + Atazanavir/r (N = 20) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 1563.0 (26.8) | 1443.8 (30.7) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 18222.7 (30.0) | 20097.0 (37.2) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 376.8 (44.7) | 515.0 (42.7) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.50 (3.50, 4.50) | 4.00 (4.00, 4.50) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 9.63 (8.12, 12.37) | 13.25 (10.62, 17.61) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.0 (24.0, 24.0) | 24.0 (24.0, 24.0) |

GS-9137/r = 150 or 85 mg of GS-9137 + 100 mg of ritonavir once-daily when administered alone or with atazanavir, respectively, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

a The pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or at a lower dose with atazanavir/r** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **85 mg GS-9137 + Atazanavir/r vs. 150/100 mg GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 1367.24 | 1503.87 | 90.91 | 81.38, 101.57 |
| $AUC_{tau}$ (ng•h/mL) | 18640.07 | 17394.64 | 107.16 | 95.09, 120.76 |
| $C_{tau}$ (ng/mL) | 474.61 | 343.73 | 138.08 | 118.30, 161.16 |

GS-9137/r = 150 or 85 mg of GS-9137 + 100 mg of ritonavir once-daily when administered alone or with atazanavir, respectively; atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir, once-daily, CI = confidence interval

a N = 20 per treatment; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

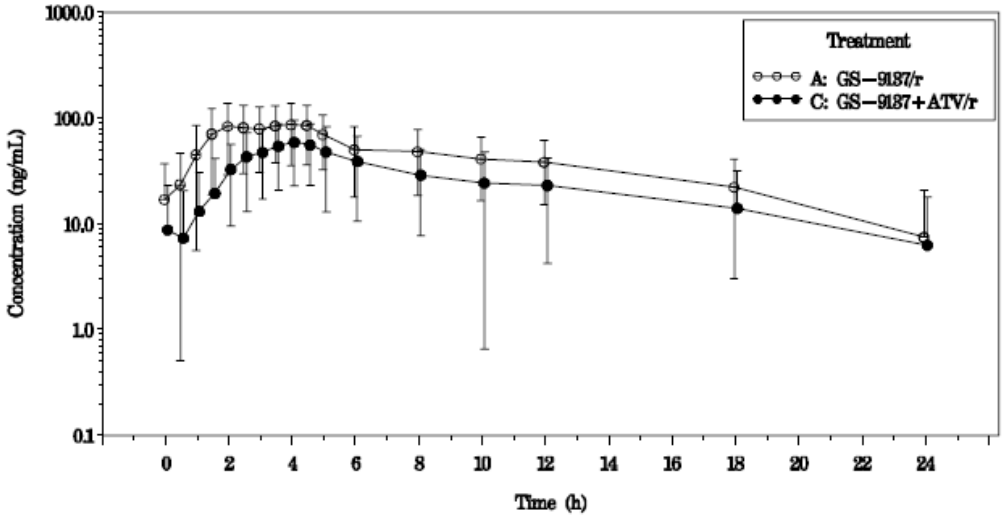
b Test Treatment = 85 mg of GS-9137 + atazanavir/r, Reference Treatment = 150/100 mg of GS-9137/r, each treatment given for 10 days

Source: Section 11.1, Table 6

The mean plasma concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were marginally lower following coadministration of GS-9137 85 mg and atazanavir/r compared to those observed following administration of GS-9137/r 150/100 mg (see Figure 3). Measures of M4 exposure were also significantly lower upon statistical comparison, with 90% CI values below the predefined no-effect bounds (see Table 4). The mean ratio of M4:GS-9137 following administration of GS-9137 85 mg with

atazanavir/r was 3.7%, compared to a ratio of 6.0% following administration of GS-9137/r 150/100 mg alone.

**Figure 3: Steady-state M4 plasma concentrations after administration of GS-9137/ alone or at a lower dose with atazanavir/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




GS-9137/r = 150 or 85 mg of GS-9137 + 100 mg of ritonavir once-daily when administered alone or with atazanavir, respectively, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily

Values presented as mean ± SD. The pharmacokinetic analysis set includes 20 subjects who had evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.4

**Table 4: Statistical comparisons of M4 PK parameters after administration of GS-9137/r alone or at a lower dose with atazanavir/r** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of M4 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **85 mg GS-9137 + Atazanavir/r vs. 150/100 mg GS-9137/r** | | | | |
| $C_{max}$ (ng/mL)[c] | 58.63 | 104.13 | 56.30 | 45.42, 69.79 |
| $AUC_{tau}$ (ng•h/mL)[d] | 713.83 | 1051.86 | 67.86 | 52.80, 87.23 |

GS-9137/r = 150 or 85 mg of GS-9137 + 100 mg of ritonavir once-daily when administered alone or with atazanavir, respectively, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily, CI = confidence interval, Q1 = first quartile, Q3 = third quartile

a The pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair. $C_{tau}$ values for M4 are not presented because relatively few subjects had quantifiable levels of M4 at the end of the dosing interval.

b Test Treatment = 85 mg of GS-9137 + atazanavir/r, Reference Treatment = 150/100 mg of GS-9137/r, each treatment given for 10 days

c N = 19 for Test Treatment, Reference Treatment, and geometric least-squares mean ratio (GMR%)

d N = 16 for Reference Treatment, N = 13 for Test Treatment and the geometric least-squares mean ratio

Source: Section 11.1, Table 6

The pharmacokinetic profile of atazanavir was similar following administration with or without GS-9137. The 90% CI values for $C_{max}$, $AUC_{tau}$, and $C_{tau}$ generated during a statistical comparison of the two treatments fell within the prespecified no-effect bounds.

Plasma concentrations of ritonavir were higher following administration of atazanavir/r 300/100 mg compared to those observed following administration of GS-9137/r 150/100 mg ($AUC_{tau}$: 12,805 vs. 5805 ng·h/mL, $C_{max}$: 1981 vs. 843 ng/mL, $C_{tau}$: 91 vs 64 ng/mL). Therefore, statistical comparisons of ritonavir PK parameters using GS-9137+atazanavir/r as the test treatment resulted in significantly higher GLSM $C_{max}$ and $AUC_{tau}$ values when GS-9137/r was used as the reference treatment, but similar values when atazanavir/r was designated as the reference treatment.

***Results of safety analysis***

Nervous system disorders (e.g. headache) were the most common AEs in the GS-9137/r treatment groups and hepatobiliary disorders were the most common AEs in the atazanavir/r treatment groups (e.g. jaundice). There were seven discontinuations due to study drug-related adverse events: four during treatment with atazanavir/r (two subjects with dermatitis, one with insomnia, and one with toxic myopathy plus increased blood CPK) and three during treatment with GS-9137 and atazanavir/r (two subjects with dermatitis and one with papular rash). Four Grade 4 laboratory abnormalities were recorded (three cases of elevated total bilirubin and one of elevated CPK), all in subjects receiving atazanavir/r with or without GS-9137. There were no serious adverse events or deaths during this trial. Overall, GS-9137 did not appear to impact the frequency of atazanavir-related AEs.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, atazanavir, and ritonavir following administration of GS-9137/r 150/100 mg, atazanavir/r 300/100 mg, or GS-9137 85 mg and atazanavir/r 300/100 mg. A previous drug-drug interaction trial demonstrated altered pharmacokinetics when GS-9137 200 mg was coadministered with atazanavir/r 300/100 mg (Study GS-US-183-0108); the GS-9137 dose was prospectively decreased to 85 mg in this study to account for the pharmacokinetic interaction observed in the presence of atazanavir/r.

Coadministration of GS-9137 85 mg and atazanavir/r resulted in similar GS-9137 Cmax and AUCtau but a significantly higher Ctau (38%) compared to administration of GS-9137/r 150/100 mg; the increase in Ctau is unlikely to be clinically relevant. Plasma concentrations of M4 were significantly lower in the presence of atazanavir, which may be attributed to inhibition of glucuronidation by atazanavir. M4 is a minor metabolite and is markedly less potent (10- to 38-fold) than GS-9137 in antiviral activity assays, so this small decrease in M4 exposures is unlikely to be clinically relevant.

Atazanavir pharmacokinetics were unaffected by the presence of GS-9137. Likewise, ritonavir plasma concentrations were unaffected by the presence of GS-9137, although they were higher when ritonavir was coadministered with atazanavir. Since the antiviral activity of both GS-9137 and atazanavir have been well-established in the presence of

ritonavir exposures comparable to those observed in the current study, these differences in ritonavir plasma concentrations will not impact efficacy.

No further adjustments to the doses of GS-9137, ritonavir, or atazanavir are recommended by the Applicant when GS-9137 and atazanavir/r are coadministered. Administration of the 85 mg dose of GS-9137 in combination with atazanavir/ritonavir 300/100 mg is supported by the results of this study.

**Trial GS-US-183-0108**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and Atazanavir Sulfate/r**

**Trial Period**
14 Feb to 17 Aug 2006
Final report date: 22 May 2007 (submitted to IND 72,177)

**Trial Site**
MDS Pharma Services, Lincoln, Nebraska, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). In clinical practice, GS-9137 may be coadministered with the PI atazanavir (trade name Reyataz®) boosted by the HIV PI ritonavir (RTV). GS-9137 and atazanavir are both substrates of CYP3A; when given in combination with ritonavir, exposures are elevated due to the inhibition of CYP3A activity by ritonavir. This study was conducted to determine whether the pharmacokinetics of GS-9137, ritonavir, or atazanavir were affected by concomitant administration of GS-9137 and ritonavir-boosted atazanavir.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetic parameters of GS-9137, atazanavir, or ritonavir are affected when coadministered compared to GS-9137/r or atazanavir/r administered alone

The secondary objective of the trial was to:

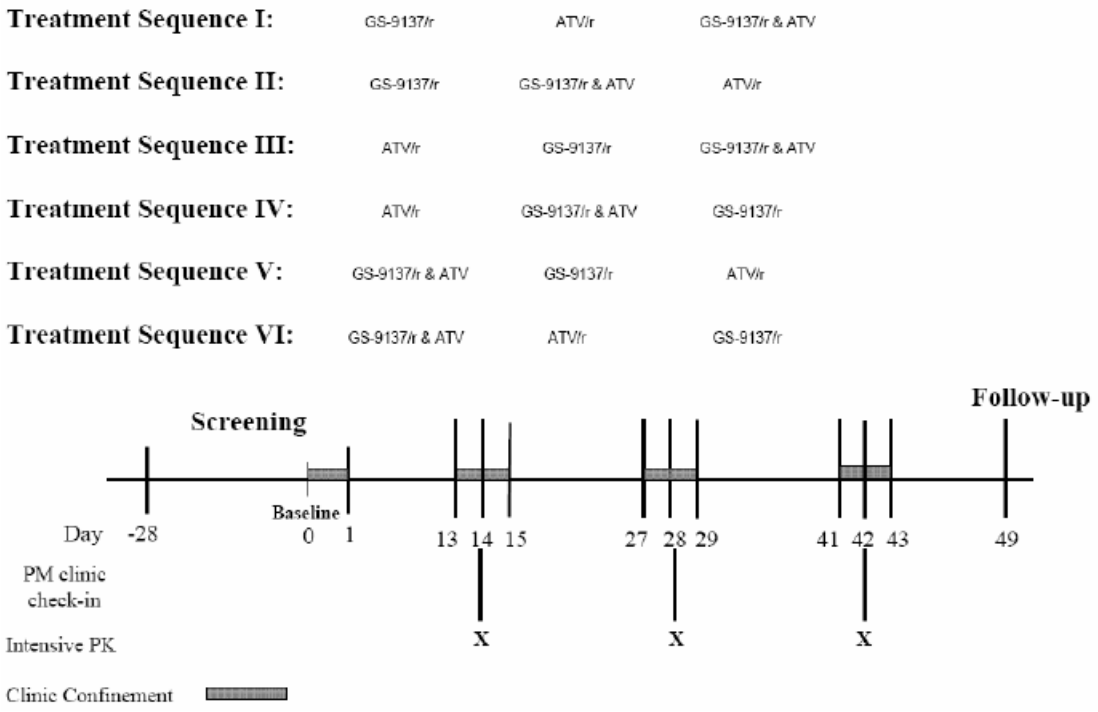
- evaluate the safety of GS-9137/r or atazanavir/r alone, and the combination of atazanavir, ritonavir, and GS-9137

**Trial Design**
This was an open-label, multiple-dose, drug interaction study. There were three treatment periods, each lasting 14 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A GS-9137/r 200/100 mg QD
Treatment B atazanavir/r 300/100 mg QD
Treatment C GS-9137 200 mg plus atazanavir/r 300/100 QD

Subjects were randomized to one of six treatment sequences: ABC, ACB, BAC, BCA, CAB, or CBA. The study schema for all six sequences is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




### Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water and within 5 minutes of consuming a meal at approximately the same time every morning. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 14, 15, 28, 29, and 42. Evening meals that were similar in calorie and fat content were provided on Days 0, 13, 14, 27, 28, 41, and 42. On mornings of intensive PK sampling days (Days 14, 28, and 42), water was restricted beginning 1 h before until 2 h after dosing, and subjects fasted after drug administration until after the 4 h postdose blood draw.

### Rationale for Dose Selection

The GS-9137 dose of 200 mg QD was selected for this study on the basis of results from studies during clinical development that demonstrated that GS-9137/r is well-tolerated at doses up to 200/100 mg QD. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The atazanavir/r dose of 300/100 mg QD was selected for this study because it is the same dose that is currently marketed for treatment-experienced adults infected with HIV-1.

**Investigational Product**

Tablets containing 200 mg of GS-9137 were manufactured by Japan Tabacco, Inc. (Lot 401). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lots 329122E23 and 377702E21). Capsules containing 150 mg of atazanavir (Reyataz®) were manufactured by Bristol-Myers Squibb Co. (New York, New York, USA; Lots 5L313A. 5L4308A, 6B3079A, 6D3122A).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 19 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, and/or atazanavir were collected on the specified study days at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 14, 28, and 42 | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 18:00, 20:00, 22:00, and 24:00 |

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137 and atazanavir. In addition, $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{1/2}$, $C_{tau}$, and $AUC_{tau}$ were calculated for GS-9137, its metabolite M4, ritonavir, and atazanavir. All

pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences between treatments (GS-9137 PK parameters between Treatments C and A; atazanavir PK parameters between Treatments C and B; ritonavir PK parameters between Treatments C and A and Treatments C and B) were calculated. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143%.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200. and GS-9202 in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16480V1-3) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 4 May and 19 Jul 2006 and stored at -80˚C. Analysis was performed between 12 May and 15 Aug 2006. The first day of sample collection was 5 Mar 2006, so the maximum sample storage time was 136 days, which is within the validated long-term frozen stability duration (at -80˚C) of 268 days for GS-9137, GS-9200, GS-9202, and RTV.

Concentrations of atazanavir and ritonavir in plasma samples were determined using LC-MS/MS (TSLM06010 and TLSM06121, the latter calibrated for higher concentrations of atazanavir) by (b) (4). Frozen plasma samples were received between 27 Apr and 28 Jun 2006 and stored at -70˚C. Analysis was performed between 28 Apr and 30 Aug 2006. The first day of sample collection was 5 Mar 2006, so the maximum sample storage time was 115 days, which is within the validated long-term frozen stability duration (at -70˚C) of 173 days.

The GS-9137, GS-9200, and GS-9202 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For ritonavir, the calibration standards ranged from 1-1000 (TSLM06010) and 5-2500 (TSLM06121) ng/mL and the QC concentrations were 3.0, 400, and 800 (TSLM06010) and 15.0, 1000, and 2000 ng/mL (TSLM06121). For atazanavir, the calibration standards ranged from 1-1000 (TSLM06010) and 10-5000 (TSLM06121) ng/mL and the QC concentrations were 3.0, 400, and 800 (TSLM06010) and 30.0, 2000, and 4000 (TSLM06121) ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, atazanavir, and ritonavir in human plasma** (source: Study Report Table 5-4)

| Parameter | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Atazanavir | | Ritonavir | |
|---|---|---|---|---|---|---|---|
| | | | | Low | High | Low | High |
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 10,000 | 20 to 10,000 | 1 to 1,000 | 10 to 5,000 | 1 to 1,000 | 5 to 2,500 |
| LLQ (ng/mL) | 20 | 20 | 20 | 1 | 10 | 1 | 5 |
| Inter-Assay Precision Range[a] | 4.1% to 11.1% | 5.0% to 14.0% | 4.9% to 15.2% | 6.8% to 12.0% | 2.9% to 3.0% | 3.8% to 10.8% | 2.4% to 6.1% |
| Inter-Assay Accuracy Range[b] | −8.3% to −4.8% | −8.5 %to −3.5% | −4.5% to −3.0% | −0.5% to −14.0% | −1.5% to −5.7% | −1.4% to −13.2% | −1.8% to −13.6% |
| Stability in Frozen Matrix (days) | 93[c] | 93[c] | 93[c] | 173[d] | 173[d] | 173[d] | 173[d] |

LLQ = lower limit of quantitation

a Relative standard deviation

b Difference from nominal concentrations

c Data on file at (b) (4)

d Data generated by (b) (4) to be incorporated into Method Validation report.

Source: Appendix 10

***Trial population***

A total of 61 healthy adult subjects were enrolled in the study, received study drug, and were included in the safety analysis set; 32 subjects completed the study. Twenty-nine subjects discontinued prior to the end of the study: 13 withdrew consent, 12 were withdrawn by the investigator due to AEs, three were withdrawn by the investigator because of a positive drug urine screen, and one was withdrawn by the investigator because he took prohibited medications. The study was suspended by the investigator on Day 15 due to a high incidence of treatment-related adverse events; the study was reinitiated three weeks later with additional safety assessments in place. A high number of subjects discontinued prior to study reinitiation, so a make-up group of 30 subjects was randomized and dosed with study drug. Of the 32 subjects who completed the study, six were from the original group and the remaining 26 were from the make-up group.

Of the safety analysis set (n=61), the majority of subjects were white (82%); the remainder were black (6.6%), Hispanic (4.9%), Asian (3.3%), or American Indian (3.3%). Half of the subjects were female (50.8%). Subjects had a mean age of 26 years (range: 19 to 45 years).

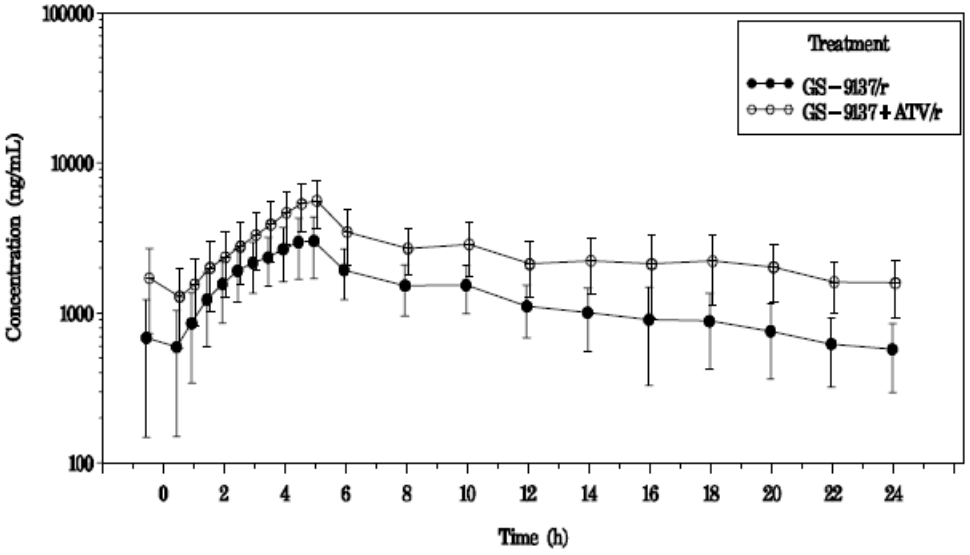
***Results of pharmacokinetic analyses***

In this study, the pharmacokinetics of GS-9137, ritonavir, and atazanavir were compared following coadministration of GS-9137 200 mg and atazanavir/r versus administration of GS-9137 200 mg or atazanavir/r alone.

Following 14 days of GS-9137 200 mg QD coadministration with atazanavir/r 300/100 mg QD, plasma concentrations of GS-9137 were significantly higher compared to administration of GS-9137/r alone (see Figure 2). The PK parameters for GS-9137 alone and with atazanavir/r are listed in Table 2. When GS-9137 was coadministered with

atazanavir/r, its half-life increased from 11.9 to 16.2 h, most likely due to a decrease in GS-9137 clearance due to inhibition of glucuronidation by atazanavir (see Table 2). The 90% CI values for GS-9137 $AUC_{tau}$ and $C_{max}$ fell outside the prespecified bounds of 70-143%, and the GLSM $C_{tau}$ value was 288% of the $C_{tau}$ following administration of GS-9137alone (90% CI 253-327, see Table 3).

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Values presented as mean ± SD. The pharmacokinetic analysis set includes 33 subjects who had evaluable pharmacokinetic profiles for the treatment pair.
Source: Section 11.1, Figure 1.1

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with atazanavir** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 33) | GS-9137 + Atazanavir/r (N = 33) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 3248.6 (43.2) | 5825.6 (35.5) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 30,566.2 (38.4) | 60,878.5 (35.9) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 573.1 (48.2)[b] | 1580.5 (41.2) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.52 (4.50, 5.00) | 5.00 (4.50, 5.00) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 11.89 (8.80, 14.65) | 16.21 (11.48, 19.95) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir once-daily, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

a The pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b N = 32

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with atazanavir** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Atazanavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 5495.35 | 2971.72 | 184.92 | 168.52, 202.92 |
| $AUC_{tau}$ (ng•h/mL) | 57497.82 | 28821.05 | 199.50 | 184.58, 215.62 |
| $C_{tau}$ (ng/mL) | 1461.21 | 507.69 | 287.81 | 253.26, 327.08 |

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir, once-daily, CI = confidence interval

a N = 33 per treatment with the exception of $C_{tau}$ in Reference Treatment when N = 32; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

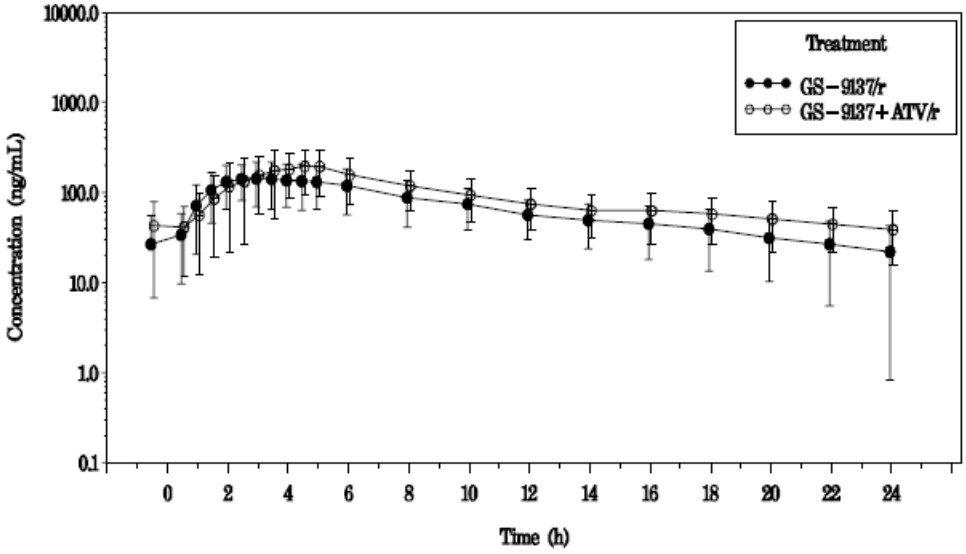
b Test Treatment = GS-9137 + atazanavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 days

Source: Section 11.1, Table 6

The mean plasma concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were marginally higher following coadministration of GS-9137 and atazanavir/r compared to those observed following administration of GS-9137/r alone (see Figure 3). The 90% CIs for M4 $C_{max}$ and $AUC_{tau}$ were within the prespecified no-effect boundaries, but the 90% CIs for M4 $C_{tau}$ fell slightly above (see Table 4). Increases in mean M4 plasma concentrations were less than proportional compared to increases in GS-9137 plasma concentrations (mean M4:GS-9137 ratios were 3.5% and 5.7% with and without atazanavir, respectively), suggesting that formation and elimination of M4 were affected by atazanavir. The Applicant hypothesizes that inhibition of MRP2 by atazanavir,

ritonavir, or both may decrease M4 elimination, since M4 appears to be an MRP2 substrate *in vitro*.

**Figure 3: Steady-state M4 plasma concentrations after administration of GS-9137/ alone or with atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. The pharmacokinetic analysis set includes 33 subjects who had evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.4

**Table 4: Statistical comparisons of M4 PK parameters after administration of GS-9137/r alone or with atazanavir** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of M4 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Atazanavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 193.39 | 163.79 | 118.07 | 104.61, 133.27 |
| $AUC_{tau}$ (ng•h/mL) | 1911.85 | 1522.99 | 125.53 | 113.91, 138.34 |
| $C_{tau}$ (ng/mL) | 42.59 | 30.56 | 139.38 | 119.14, 163.07 |

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir once-daily, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

a N = 33 per treatment with the exception of $C_{tau}$; Test Treatment N = 28; Reference treatment N = 20; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 + atazanavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 days

Source: Section 11.1, Table 6

The pharmacokinetic profile of atazanavir was slightly lower following administration with GS-9137, but the differences did not reach statistical significance. The 90% CI values for $C_{max}$ and $AUC_{tau}$ generated during a statistical comparison of the two treatments fell within the prespecified no-effect bounds, but the 90% CI values for $C_{tau}$

were below the no-effect bounds, although the mean $C_{tau}$ values were within the recommended range to achieve an adequate inhibitory quotient (see Table 5).

**Table 5: Statistical comparisons of atazanavir PK parameters after administration of atazanavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-6)

| Test versus Reference Comparison of Atazanavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Atazanavir/r vs. Atazanavir/r** | | | | |
| $C_{max}$ (ng/mL) | 5232.73 | 6206.36 | 84.31 | 78.19, 90.92 |
| $AUC_{tau}$ (ng•h/mL) | 47,672.02 | 60,188.71 | 79.20 | 73.57, 85.27 |
| $C_{tau}$ (ng/mL) | 863.95 | 1319.17 | 65.49 | 59.08, 72.60 |

GS-9137 = 200 mg of GS-9137 once-daily, atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir once-daily, CI = confidence interval

a N = 33 per treatment with the exception of $C_{tau}$: Test Treatment N = 32; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 + atazanavir/r, Reference Treatment = atazanavir /r, each treatment given for 14 days

Source: Section 11.1, Table 6

Plasma concentrations of ritonavir were higher following administration of atazanavir/r 300/100 mg compared to those observed following administration of GS-9137/r 200/100 mg ($AUC_{tau}$: 14628 vs. 6327 ng·h/mL, $C_{max}$: 2690 vs. 1043 ng/mL, $C_{tau}$: 93 vs 54 ng/mL). Therefore, statistical comparisons of ritonavir PK parameters using GS-9137+atazanavir/r as the test treatment resulted in significantly higher GLSM $C_{max}$ and $AUC_{tau}$ values when GS-9137/r was used as the reference treatment, but similar values when atazanavir/r was designated as the reference treatment.

***Results of safety analysis***

By the time the study was halted on Day 15, four subjects (out of 31) had been withdrawn by the investigator due to AEs and an additional seven subjects had AEs that would subsequently lead to study discontinuation per the investigator. Elevated bilirubin was the most common AE that led to study discontinuation (n=6).

In the total safety analysis set (n=61), nervous system disorders (e.g. headache) were the most common AEs in the GS-9137/r treatment groups and hepatobiliary disorders were the most common AEs in the atazanavir/r treatment groups (e.g. jaundice). All subjects with AEs of hepatobiliary disorders and increased blood bilirubin were being treated with atazanavir/r with or without GS-9137. There were nine discontinuations due to study drug-related adverse events: eight during treatment with atazanavir/r (six subjects with elevated blood bilirubin and three with rash) and one during treatment with GS-9137 and atazanavir/r (elevated blood bilirubin). Fifty subjects receiving atazanavir/r with or without GS-9137 experienced graded elevations in total bilirubin; hyperbilirubinemia is a common consequence of treatment with atazanavir. There were no serious adverse events or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, atazanavir, and ritonavir following administration of GS-9137/r 200/100 mg, atazanavir/r 300/100 mg, or GS-9137 200 mg and atazanavir/r 300/100 mg. Coadministration of GS-9137 and atazanavir/r resulted in significantly higher GS-9137 $C_{max}$, $AUC_{tau}$, and $C_{tau}$ (increases of 85%, 100%, and 188%, respectively) compared to administration of GS-9137/r 200/100 mg. Plasma concentrations of M4 were higher in the presence of atazanavir, although the increase in exposures was less than proportional compared to GS-9137, suggesting that in addition to inhibition of M4 formation, atazanavir also inhibited the elimination of M4, possibly via MRP2.

Atazanavir $C_{max}$ and $AUC_{tau}$ were unaffected by the presence of GS-9137. Atazanavir trough concentrations were reduced by approximately 35%, remaining within the range recommended to sustain adequate antiviral activity. Likewise, ritonavir plasma concentrations were unaffected by the presence of GS-9137, although they were higher when ritonavir was coadministered with atazanavir. Since the antiviral activity of both GS-9137 and atazanavir have been well-established in the presence of ritonavir exposures comparable to those observed in the current study, these differences in ritonavir plasma concentrations will not impact efficacy.

Due to the magnitude of the increase in GS-9137 exposures upon coadministration with ritonavir-boosted atazanavir, the Applicant recommends a decreased GS-9137 dose for use in combination with ritonavir-boosted atazanavir. The results of the current study support a GS-9137 dose reduction for coadministration with atazanavir/ritonavir 300/100 mg QD.

**Trial GS-US-183-0110**
**A Phase 1, Open Label, Drug Interaction Study to Assess the Pharmacokinetics of GS-9137/r and Didanosine or Stavudine**

**Trial Period**
21 Nov to 21 Dec 2005
Final report date: 25 Oct 2006 (submitted to IND 72,177)

**Trial Site**
MDS Pharma Services, Phoenix, Arizona, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 boosted by the HIV PI ritonavir (GS-9137/r) may be coadministered with the NRTIs didanosine or stavudine. This study was conducted to determine whether the pharmacokinetics of GS-9137, didanosine, or stavudine were affected by concomitant administration of GS-9137/r and didanosine or stavudine.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetic parameters of GS-9137, didanosine, or stavudine are affected after coadministration of ritonavir-boosted GS-9137 (GS-9137/r) with either didanosine or stavudine compared to administration of GS-9137/r, didanosine, or stavudine alone
-

The secondary objective of the trial was to:

- evaluate the safety of coadministration of ritonavir-boosted GS-9137 with either didanosine or stavudine

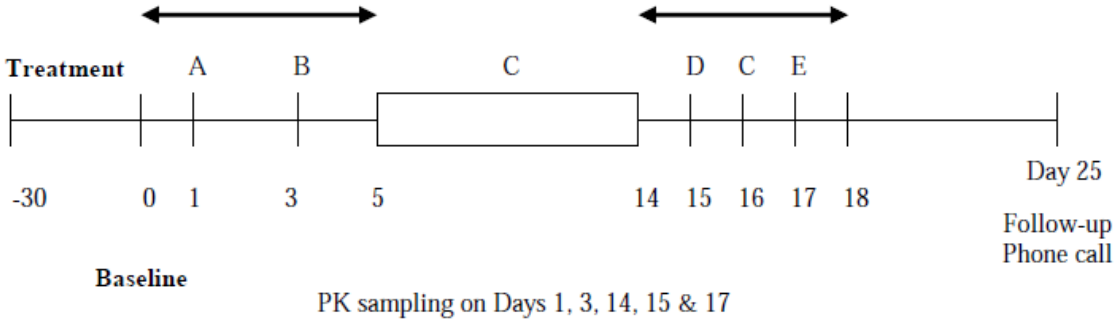
**Trial Design**
This was a single-sequence, open-label, drug interaction study. There were five treatments administered sequentially over a period of 18 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A didanosine 400 mg, single dose (fasting) on Day 1
Treatment B stavudine 40 mg, single dose (fed) on Day 3
Treatment C GS-9137/r 200/100 mg QD (fed) on Days 5-14 and Day 16

Treatment D: didanosine 400 mg (fasted) and GS-9137/r 200/100 (fed), single dose on Day 15
Treatment E: stavudine 40 mg and GS-9137/r 200/100 (fed), single dose on Day 17

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




## Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water and within 5 minutes of consuming a meal at approximately the same time every morning (or evening, for the second daily dose of tipranavir/r). Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 14, 15, 28, 42 and 43. Evening meals that were similar in calorie and fat content were provided on Days 0, 1, 13, 14, 27, 28, 41, and 42. On mornings of intensive PK sampling days (Days 14, 28, and 42), water was restricted beginning 1 h before until 2 h after dosing, and subjects fasted after drug administration until after the 4 h postdose blood draw.

## Rationale for Dose Selection

The GS-9137 dose of 200 mg QD was selected for this study on the basis of results from studies during clinical development that demonstrated that GS-9137/r is well-tolerated at doses up to 200/100 mg QD. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The tipranavir/r dose of 500/100 mg BID was selected for this study because it is the same dose that is currently marketed for treatment-experienced adults infected with HIV-1.

## Investigational Product

Tablets containing 200 mg of GS-9137 were manufactured by Japan Tabacco, Inc. (Lot 401). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lots 329122E23). Capsules containing 250 mg of tipranavir (Aptivus®) were manufactured byBoehringer Ingelheim (Ridgefield, Connecticut, USA; Lot 2390504A).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, and/or tipranavir were collected on Days 14, 28, and 42 at the times (in hours post-dose) listed below:

| | |
|---|---|
| Treatments A and C | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, and 24:00 |
| Treatment B | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, and 12:00 |

Sampling timepoints are less extensive after Treatment B (tipranavir/r) because the half-life of tipranavir is only 6 h, compared to a GS-9137 half-life of approximately 13 h.

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137 and tipranavir. In addition, $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{1/2}$, $C_{tau}$, and $AUC_{tau}$ were calculated for GS-9137, its metabolite M4, ritonavir, and tipranavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate

estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences between treatments (GS-9137 PK parameters between Treatments C and A; tipranavir PK parameters between Treatments C and B; ritonavir PK parameters between Treatments C and A and Treatments C and B) were calculated. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143% for GS-9137 and 80-143% for tipranavir.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200, and GS-9202 in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16480V1) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 23 Mar and 27 Apr 2006 and stored at -80˚C. Analysis was performed between 21 Apr and 30 May 2006. The first day of sample collection was 12 Mar 2006, so the maximum sample storage time was 79 days, which is within the validated long-term frozen stability duration (at -80˚C) of 93 days for GS-9137, GS-9200, and GS-9202.

Concentrations of tipranavir and ritonavir in plasma samples were determined using LC-MS/MS (SAP.736, which has both low and high range calibration curves) by (b) (4). Frozen plasma samples were received on 19 Apr 2006 and stored at -20˚C. Analysis was performed between 5 and 28 May 2006. The first day of sample collection was 12 Mar 2006, so the maximum sample storage time was 77 days, which is within the validated long-term frozen stability duration (at -20˚C) of 218 and 360 days for ritonavir and tipranavir, respectively.

The GS-9137, GS-9200, and GS-9202 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For tipranavir (typically high range) and ritonavir (typically low range), the calibration standards ranged from 25.0-2000 (low range) and 1000 to 20000 (high range) ng/mL and the QC concentrations were 75.0, 640, and 1520 (low range) and 1600, 8000, and 75000 ng/mL (high range). All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, tipranavir, and ritonavir in human plasma** (source: Study Report Table 5-3)

| Parameter | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Tipranavir | | Ritonavir | |
|---|---|---|---|---|---|---|---|
| | | | | Low | High | Low | High |
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 10,000 | 20 to 10,000 | 25 to 2,000 | 1,000 to 20,000 | 25 to 2,000 | 1,000 to 20,000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 25 | 1,000 | 25 | 1,000 |
| Inter-Assay Precision Range[a] | 4.1% to 11.1% | 5.0% to 14.0% | 4.9% to 15.2% | 5.1% to 7.0% | 4.8% to 7.2% | 5.4% to 6.9% | 5.6% to 8.7% |
| Inter-Assay Accuracy Range[b] | −8.3% to −4.8% | −8.5 %to −3.5% | −4.5% to −3.0% | −5.2% to −1.6% | −7.6% to 4.0% | −8.3% to 2.4% | −5.4% to 0.3% |
| Stability in Frozen Matrix (days) | 93[c] | 93[c] | 93[c] | 26 | 21 | 26 | 21 |

a Relative standard deviation

b Difference from nominal concentrations

c Data on file at (b) (4)

LLQ = lower limit of quantitation

Source: Appendix 15

***Trial population***

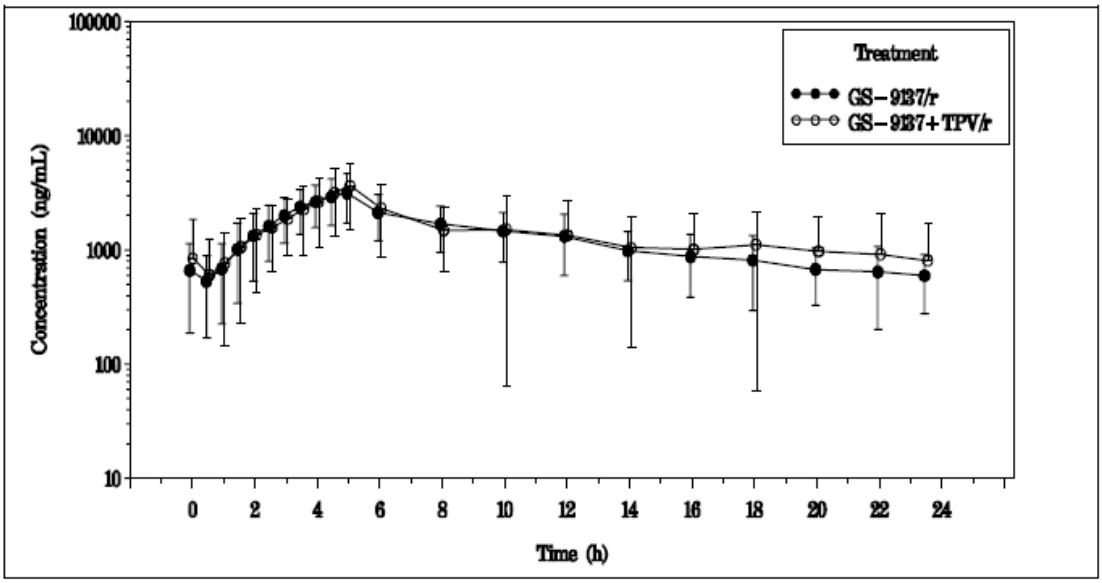
A total of 34 healthy adult subjects were enrolled in the study and received study drug; 26 subjects completed the study. Eight subjects discontinued prior to the end of the study: three withdrew consent, four were withdrawn by the investigator due to AEs, and one was withdrawn by the investigator because of a positive pregnancy test. Of the safety analysis set (n=34), the majority of subjects were Hispanic (76.5%); the remainder were white (20.6%) or black (2.1%). Slighty more than half of the subjects were female (52.9%). Subjects had a mean age of 31 years (range: 20 to 44 years).

***Results of pharmacokinetic analyses***

In this study, the pharmacokinetics of GS-9137, ritonavir, and tipranavir were compared following coadministration of GS-9137 200 mg and tipranavir/r versus administration of GS-9137 200 mg or tipranavir/r alone.

Following 14 days of GS-9137 200 mg QD coadministration with tipranavir/r 500/100 mg BID, plasma concentrations of GS-9137 were similar compared to administration of GS-9137/r alone at timepoints up to 14 h postdose (see Figure 2). At 16 h postdose and for the remainder of sampling timepoints, mean GS-9137 concentrations began to trend slightly higher after administration with tipranavir/r than after administration alone, although differences did not reach statistical significance.

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with tipranavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Values presented as mean ± SD. The pharmacokinetic analysis set includes 26 subjects. Subjects 4, 14, 15, 16, 19, 25, 26, and 33 were excluded because they did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.1

The PK parameters for GS-9137 alone and with tipranavir/r are listed in Table 2. When GS-9137 was coadministered with tipranavir/r, GS-9137 exposures were similar to administration of GS-9137/r alone (see Table 2). The lower bounds of the 90% CI values for GS-9137 $C_{tau}$ (69.8%, see Table 3) fell below the prespecified bounds of 70-143%, but this is not expected to be clinically relevant.

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with tipranavir** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 26) | GS-9137 + Tipranavir/r (N = 26) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 3208.9 (43.7) | 3691.6 (59.0) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 30,649.6 (44.9) | 33,406.0 (76.9) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 596.5 (53.7) | 803.6 (111.5) |
| $T_{max}$ (hours) Median (Q1, Q3) | 5.00 (4.55, 5.00) | 5.00 (5.00, 5.00) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 11.70 (10.09, 15.93) | 8.81 (6.78, 19.85) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

a The pharmacokinetic analysis set excludes Subjects 4, 14, 15, 16, 19, 25, 26, and 33 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir once-daily, tipranavir/r = 500 mg of tipranavir + 200 mg of ritonavir twice-daily, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with tipranavir** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Tipranavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 3084.1 | 2909.3 | 106.0 | 89.4, 125.7 |
| $AUC_{tau}$ (ng•h/mL) | 25,835.3 | 27,962.2 | 92.4 | 78.7, 108.4 |
| $C_{tau}$ (ng•h/mL) | 462.4 | 511.7 | 90.4 | 69.8, 116.9 |

a N = 26/treatment; the pharmacokinetic analysis set excludes Subjects 4, 14, 15, 16, 19, 25, 26, and 33 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

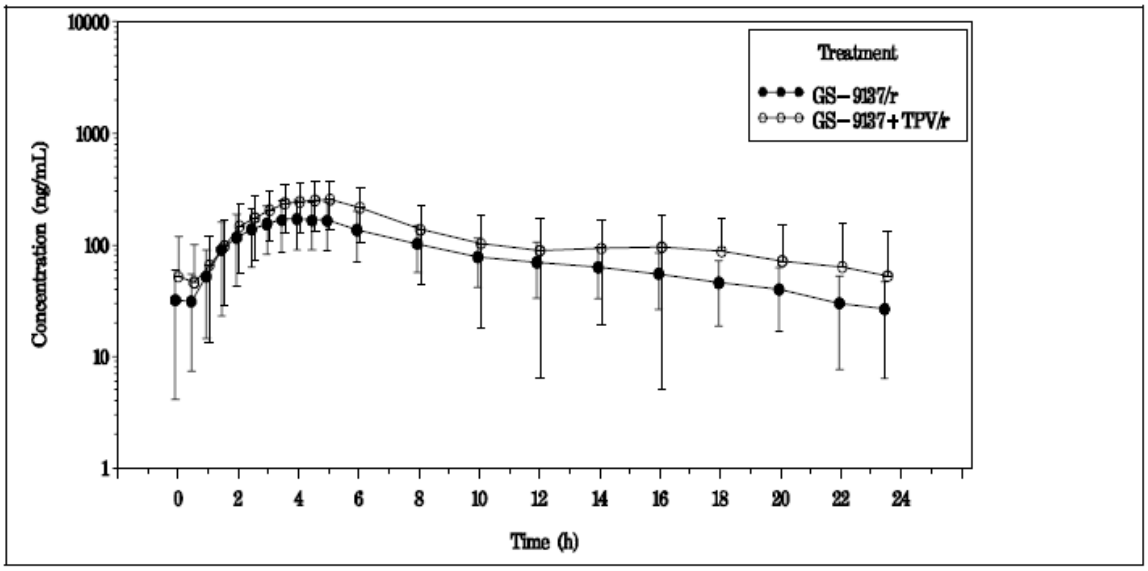
b Test Treatment = GS-9137 + tipranavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; tipranavir/r = 500 mg of tipranavir + 200 mg of ritonavir, twice-daily, CI = confidence interval

Source: Section 11.1, Table 6

The mean plasma concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were higher following coadministration of GS-9137 and tipranavir/r compared to those observed following administration of GS-9137/r alone (see Figure 3). The 90% CIs for M4 $C_{max}$, $AUC_{tau}$, and $C_{tau}$ fell above the prespecified no-effect boundaries (see Table 4). Note that these increases in M4 plasma concentrations occurred in the absence of changes in GS-9137 exposures. The Applicant hypothesizes that inhibition of MRP2 by tipranavir, ritonavir, or both may decrease M4 elimination, since M4 appears to be an MRP2 substrate *in vitro*.

**Figure 3: Steady-state M4 plasma concentrations after administration of GS-9137/ alone or with tipranavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. The pharmacokinetic analysis set includes 26 subjects. Subjects 4, 14, 15, 16, 19, 25, 26, and 33 were excluded because they did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.4

**Table 4: Statistical comparisons of M4 PK parameters after administration of GS-9137/r alone or with tipranavir** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of M4 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Tipranavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 254.2 | 191.3 | 132.8 | (112.2,157.2) |
| $AUC_{tau}$ (ng•h/mL) | 2378.4 | 1795.1 | 132.5 | (112.9,155.5) |
| $C_{tau}$ (ng•h/mL)[c] | 49.8 | 33.4 | 149.2 | (117.2,189.9) |

a N = 26/treatment; the pharmacokinetic analysis set excludes Subjects 4, 14, 15, 16, 19, 25, 26, and 33 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 plus tipranavir/r, Reference Treatment = tipranavir/r, each treatment given for 14 consecutive days

c N = 20 and 19, respectively, for Test and Reference Treatment.

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; tipranavir/r = 500 mg of tipranavir + 200 mg of ritonavir, twice-daily, CI = confidence interval

Source: Section 11.1, Table 6

The pharmacokinetic profile of tipranavir was similar regardless of whether or not it was coadministered with GS-9137. The 90% CI values for $C_{max}$ and $AUC_{tau}$ generated during a statistical comparison of the two treatments fell within the prespecified no-effect bounds, but the 90% CI values for $C_{tau}$ were below the no-effect bounds, although the mean $C_{tau}$ values were within the recommended range to achieve an adequate inhibitory quotient (see Table 5). Of note, coadministration of tipranavir/r with ethinyl estradiol reduces tipranavir trough concentrations by approximately 30%, but no dose adjustments are recommended.

**Table 5: Statistical comparisons of tipranavir PK parameters after administration of tipranavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-6)

| Test versus Reference Comparison of Tipranavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Tipranavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 79,439.0 | 86,759.5 | 91.6 | 83.8, 100.1 |
| $AUC_{tau}$ (ng•h/mL) | 584,651.5 | 657,751.4 | 88.9 | 80.0, 98.8 |
| $C_{tau}$ (ng•h/mL) | 27,141.3 | 30,544.6 | 88.9 | 77.4, 102.0 |

a N = 26/treatment; the pharmacokinetic analysis set excludes Subjects 4, 14, 15, 16, 19, 25, 26, and 33 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 + tipranavir/r, Reference Treatment = tipranavir/r, each treatment given for 14 consecutive days

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; tipranavir/r = 500 mg of tipranavir + 200 mg of ritonavir, twice-daily, CI = confidence interval

Source: Section 11.1, Table 6

Plasma concentrations of ritonavir after coadministration with tipranavir (i.e. ritonavir 100 mg BID) in the presence or absence of GS-9137 were similar. Plasma concentrations of ritonavir after coadministration with GS-9137 (i.e. ritonavir 100 mg QD) were similar to historical data from previous trials with GS-9137. The half-life of ritonavir was 2.1 h after coadministration with tipranavir compared to 6.2 h after coadministration with GS-9137, which the Applicant theorizes may be due to the inductive effects of tipranavir on P-gp or CYP3A leading to more efficient clearance of ritonavir. Due to the differences in dosing intervals, the pharmacokinetics of ritonavir were not compared between Treatments A (ritonavir 100 mg QD) and B or C (ritonavir 100 mg BID), but the 90% CI values for ritonavir $C_{max}$, $AUC_{tau}$, and $C_{tau}$ generated during a statistical comparison of Treatments B and C fell within the prespecified no-effect bounds.

***Results of safety analysis***

Gastrointestinal system disorders and nervous system disorders (e.g. headache) were the most common AEs across the three treatment groups. The most common treatment-related adverse events were diarrhea and headache in the GS-9137/r treatment group, headache in the tipranavir/r treatment group, and nausea in the GS-9137 plus tipranavir/r treatment group. There were four discontinuations due to study drug-related adverse events: three during treatment with tipranavir/r plus GS-9137 (Grade 1 and 2 elevated AST and ALT, respectively; Grade 1 suicidal ideation; and Grade 2 rash) and one during treatment with tipranavir/r (Grade 1 elevated ALT). The incident of suicidal ideation was not considered by the investigator to be related to study drug. There were no serious adverse events or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, tipranavir, and ritonavir following administration of GS-9137/r 200/100 mg QD, tipranavir/r 500/100 mg BID, or GS-9137 200 mg QD plus tipranavir/r 500/100 mg BID.

Coadministration of GS-9137 and tipranavir/r did not result in clinically relevant changes to the pharmacokinetics of each individual component compared to administration of that component alone. Exposures of the glucuronide metabolite of GS-9137 (M4) were slightly higher upon administration of GS-9137 and tipranavir/r, which may be due to inhibition of M4 elimination via MRP2. The results of the current study indicate that no dose adjustments are needed when GS-9137 200 mg QD and tipranavir/r 500/100 mg BID are coadministered.

**Trial GS-US-183-0111**
**A Phase 1, Open Label, Drug Interaction Study to Assess the Pharmacokinetics of GS-9137/r and Didanosine or Stavudine**

**Trial Period**
21 Nov to 21 Dec 2005
Final report date: 25 Oct 2006 (submitted to IND 72,177)

**Trial Site**
MDS Pharma Services, Phoenix, Arizona, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 boosted by the HIV PI ritonavir (GS-9137/r) may be coadministered with the NRTIs didanosine or stavudine. This study was conducted to determine whether the pharmacokinetics of GS-9137, didanosine, or stavudine were affected by concomitant administration of GS-9137/r and didanosine or stavudine.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetic parameters of GS-9137, didanosine, or stavudine are affected after coadministration of ritonavir-boosted GS-9137 (GS-9137/r) with either didanosine or stavudine compared to administration of GS-9137/r, didanosine, or stavudine alone
-

The secondary objective of the trial was to:

- evaluate the safety of coadministration of ritonavir-boosted GS-9137 with either didanosine or stavudine

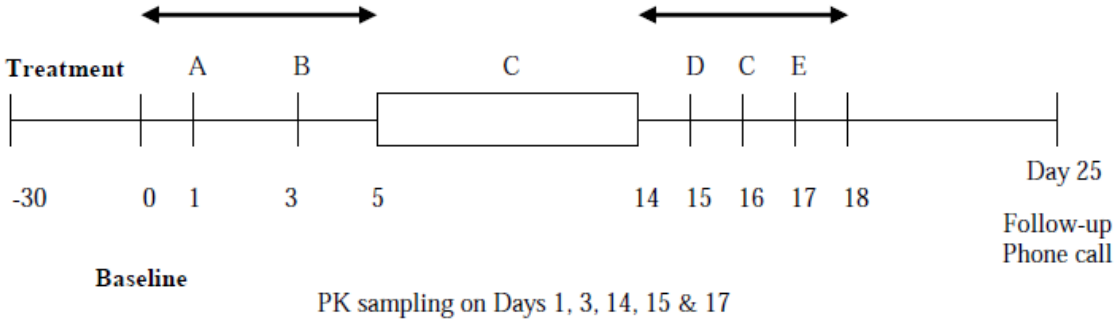
**Trial Design**
This was a single-sequence, open-label, drug interaction study. There were five treatments administered sequentially over a period of 18 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A didanosine 400 mg, single dose (fasting) on Day 1
Treatment B stavudine 40 mg, single dose (fed) on Day 3
Treatment C GS-9137/r 200/100 mg QD (fed) on Days 5-14 and Day 16

Treatment D: didanosine 400 mg (fasted) and GS-9137/r 200/100 (fed), single dose on Day 15
Treatment E: stavudine 40 mg and GS-9137/r 200/100 (fed), single dose on Day 17

Absorption of both didanosine and stavudine is rapid, and the elimination half-lives of both drugs are less than two hours, rendering multiple dosing unnecessary in this study. (Didanosine is typically dosed QD and stavudine BID.) The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




## Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water either 2 h before (didanosine) or immediately after (GS-9137/r, stavudine) a meal at approximately the same time every morning. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1 to 5 and 14 to 18. Evening meals that were similar in calorie and fat content were provided on Days 0 to 4 and 13 to 17.

## Rationale for Dose Selection

The GS-9137 dose of 200 mg QD was selected for this study on the basis of results from studies during clinical development that demonstrated that GS-9137/r is well-tolerated at doses up to 200/100 mg QD. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose given once-daily has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The didanosine dose of 400 mg QD and the stavudine dose of 40 mg QD were selected for this study because they are the same doses that are currently marketed as second-line treatments for HIV-infected adults.

## Investigational Product

Tablets containing 200 mg of GS-9137 were manufactured by Japan Tabacco, Inc. (Lot U401A1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lots 247022E21). Delayed release enteric-coated capsules containing 400 mg of didanosine (Videx® EC) were manufactured by Bristol Myers Squibb (New York, New York, USA; Lot 5H3113A).

Capsules containing 40 mg of stavudine (Zerit®) were manufactured by Bristol Myers Squibb (New York, New York, USA; Lot 5G03137A).

### Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

### Concomitant Medications

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

### Sample Collection

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), stavudine, and/or didanosine were collected at the times (in hours post-dose) listed below:

| | |
|---|---|
| Treatment A (Day 1) | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |
| Treatment B (Day 3) | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |
| Treatment C (Day 14) | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |
| Treatment D (Day 15) | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 (post-GS-9137/r dose) |

| | |
|---|---|
| Treatment E (Day 17) | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |

Urine was collected for Treatments A, C, D, and E on the days specified above at the following intervals: 0 (predose) and 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose. If no differences in plasma pharmacokinetics were identified, urine concentrations were not analyzed.

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137 and GS-9200 and $AUC_{0\text{-}last}$, $AUC_{inf}$, and $C_{max}$ for didanosine and stavudine. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were reported when the percentage of the extrapolated area ($\%AUC_{exp}$) was <30%.

Differences between the primary pharmacokinetic parameters (GS-9137 and GS-9200 multiple-dose PK parameters with or without didanosine or stavudine; didanosine and stavudine single-dose PK parameters with or without GS-9137/r) were calculated using a parametric analysis of variance (SAS® PROC MIXED; SAS Institute, Cary, North Carolina, USA) following natural log transformation. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143% for didanosine $C_{max}$ and GS-9137 and 80-125% for didanosine AUC and stavudine.

## Trial Results

***Bioanalytical methods***

Concentrations of GS-9137, GS-9200, and GS-9202 in plasma samples were determined using LC-MS/MS (Method (b) (4)06-009) by (b) (4). Frozen plasma samples were received between 4 Jan and 14 Mar 2006 and stored at -70˚C. Analysis was performed between 5 Jan and 15 Apr 2006. The first day of sample collection was 3 Dec 2005, so the maximum sample storage time was 134 days, which is within the validated long-term frozen stability duration (at -70˚C) of 585 days for GS-9137, GS-9200, and GS-9200.

Concentrations of didanosine in plasma samples were determined using LC-MS/MS (Method (b) (4)42-0201) by (b) (4). Frozen plasma samples were received between 4 Jan and 8 Mar 2006 and stored at -70˚C. Analysis was performed between 13 Jan and 3 Feb 2006. The first day of sample collection was 3 Dec 2005, so the maximum sample storage time was 62 days, which is within the validated long-term frozen stability duration (at -70˚C) of 87 days.

Concentrations of stavudine in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0201) by (b) (4). Frozen plasma samples were received between 4 Jan and 8 Mar 2006 and stored at -70˚C. Analysis was performed between 13 Jan and 2 Feb 2006. The first day of sample collection was 3 Dec 2005, so the maximum sample storage time was 61 days, which is within the validated long-term frozen stability duration (at -70˚C) of 87 days.

The GS-9137, GS-9200, and GS-9202 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 60.0, 3500, and 7500 ng/mL. For didanosine and stavudine, the calibration standards ranged from 5-3000 ng/mL and the QC concentrations were 15, 500, and 2500 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, didanosine, and stavudine in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | Didanosine | Stavudine | M4 (GS-9200) | M1 (GS-9202) |
|---|---|---|---|---|---|
| Calibration Range (ng/mL) | 20 to 10,000 | 5 to 3,000 | 5 to 3000 | 20 to 10,000 | 20 to 10,000 |
| LLQ[a] (ng/mL) | 20 | 5 ng/mL | 5 ng/mL | 20 | 20 |
| Interday Precision Range[b] | 0% to 4.9% | 2.6% to 4.0% | 1.6% to 5.1% | 1.2% to 7.3% | 1.4% to 7.3% |
| Interday Accuracy Range[c] | −2.0% to 2.0% | −4.8% to 2.6% | 0.2% to 5.5% | −1.5% to 2.9% | −2.7% to 1.7% |
| Stability in Frozen Matrix (days) | 93[d] | 87 | 87 | 93[d] | 93[d] |

a LLQ, lower limit of quantitation
b Relative standard deviation
c Difference from nominal concentrations
d Data on file at (b) (4)
Source: Appendix 14

***Trial population***

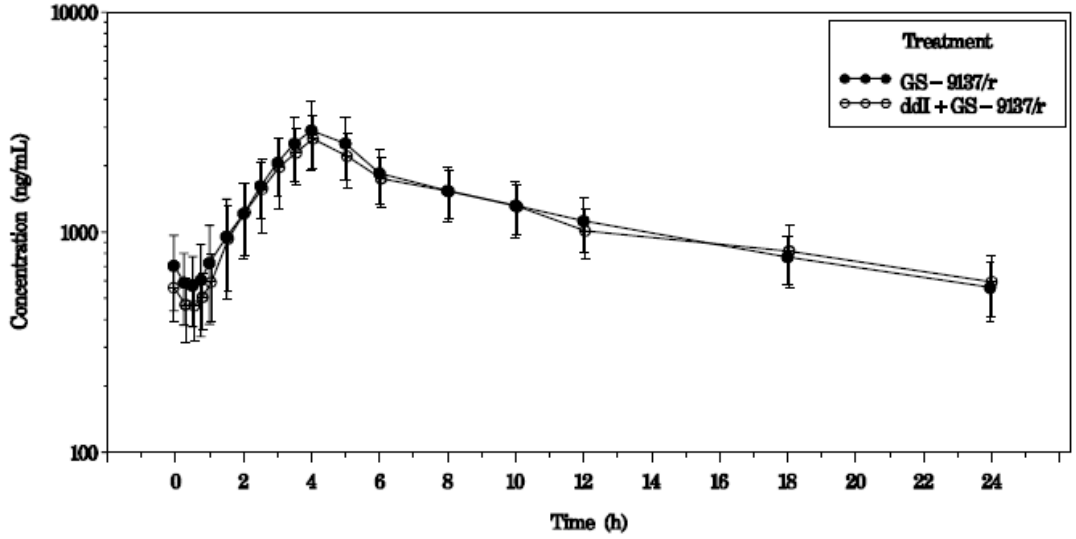
A total of 32 healthy adult subjects were enrolled in the study and received study drug; all subjects completed the study, although one was excluded from the stavudine pharmacokinetic analysis set due to a sample analysis error. Of the safety analysis set (n=32), the majority of subjects were Hispanic (78.1%); the remainder were white (15.6%), black (3.1%), or Asian (3.1%). Half of the subjects were female (50.0%). Subjects had a mean age of 30 years (range: 19 to 44 years).

***Results of pharmacokinetic analyses***

In this study, the pharmacokinetics of multiple-dose GS-9137 and single-dose stavudine and didanosine were compared following coadministration of GS-9137/r and didanosine or stavudine versus administration of GS-9137/r, didanosine, or stavudine alone.

The concentration-time profiles of GS-9137 were similar following coadministration of GS-9137/r and didanosine or stavudine compared to administration of GS-9137/r alone (see Figures 2 and 3, respectively).

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with didanosine** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)

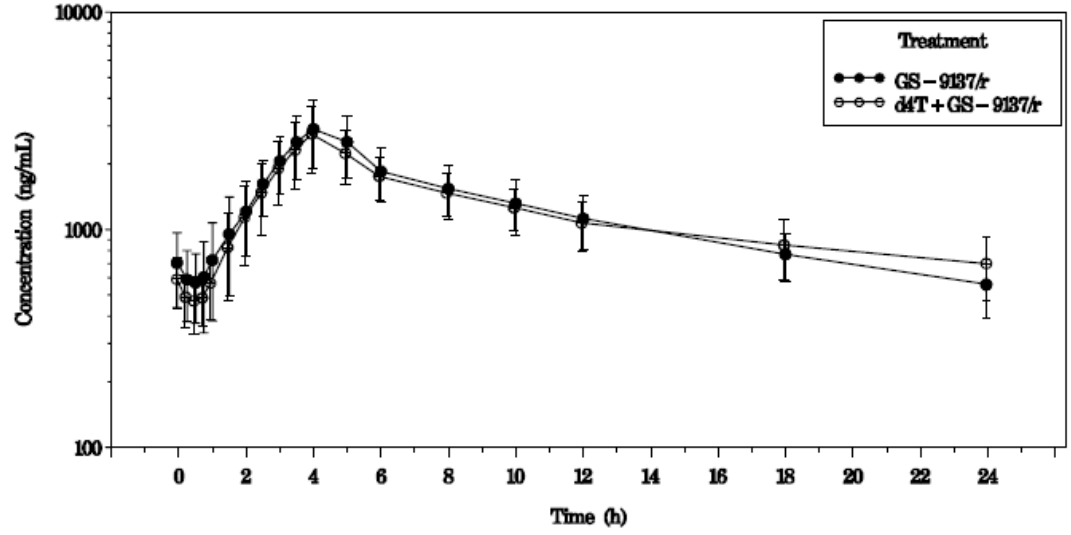



Values presented as mean ± SD

Source: Section 11.1, Figure 1

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir (administered on Days 5–14 and 16), ddI = didanosine 400 mg (administered on Day 15 with GS-9137/r).

**Figure 3: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with stavudine** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD

Source: Section 11.1, Figure 1

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir (administered on Days 5-14 and 16; d4T = stavudine 40 mg administered on Day 17 with GS-9137/r.

The PK parameters for GS-9137 after administration of GS-9137/r alone and with didanosine are listed in Table 2. When GS-9137/r was coadministered with didanosine, GS-9137 exposures were similar to administration of GS-9137/r alone (see Table 2). The lower bounds of the 90% CI values for the ratios of the geometric least-squares means of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ after coadministration of GS-9137/r alone or with didanosine were within the prespecified no-effect bounds of 70-143% (see Table 3).

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with didanosine** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 PK Parameter | GS-9137/r Alone (N = 32) | GS-9137/r + Didanosine (N = 32) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 2962.5 (33.4) | 2758.1 (26.8) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 28836.8 (23.7) | 27760.3 (21.5) |
| $C_{tau}$ (ng/mL) Mean (% CV) | 560.3 (30.7) | 595.5 (30.9) |
| $T_{max}$ (h) Median (Q1, Q3)[a] | 4.00 (4.00, 4.02) | 4.00 (4.00, 4.00) |
| $T_{1/2}$ (h) Median (Q1, Q3)[a] | 11.14 (9.44, 12.84) | 12.12 (10.86, 13.58) |

a Q1 (first quartile), Q3 (third quartile)
GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir (administered on Days 5–14 and 16), didanosine = 400 mg (administered on Day 1 alone and on Day 15 with GS-9137/r).
Source: Section 11.1, Table 5; Appendix 14, Listings 21 and 22

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with didanosine** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| **Analyte: GS-9137** | | | | |
| GS-9137/r + Didanosine vs.GS-9137/r Alone | | | | |
| $C_{max}$ (ng/mL) | 2660.85 | 2800.33 | 95.02 | 89.68,100.68 |
| $C_{tau}$ (ng/mL) | 567.58 | 533.29 | 106.43 | 100.72,112.46 |
| $AUC_{tau}$ (ng•h/mL) | 27093.32 | 28007.30 | 96.74 | 92.46,101.21 |

a N = 32/treatment; GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir; didanosine = 400 mg
Test Treatment = GS-9137/r + didanosine (single dose administered on Day 15).
Reference Treatment = GS-9137/r (administered on 10 consecutive days, Days 5–14).
Source: Section 11.1, Table 6

The PK parameters for GS-9137 after administration of GS-9137/r alone and with stavudine are listed in Table 4. When GS-9137/r was coadministered with stavudine,

GS-9137 exposures were similar to administration of GS-9137/r alone (see Table 4). The lower bounds of the 90% CI values for the ratios of the geometric least-squares means of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ after coadministration of GS-9137/r alone or with stavudine were within the prespecified no-effect bounds of 70-143%, although $C_{tau}$ was approximately 24% higher after coadministration (see Table 5).

**Table 4: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with stavudine** (PK analysis set; source: Study Report Table 7-3)

| GS-9137 PK Parameter | GS-9137/r Alone (N = 32) | GS-9137/r + Stavudine (N = 32) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 2962.5 (33.4) | 2810.0 (30.1) |
| $AUC_{tau}$ (ng·h/mL) Mean (%CV) | 28836.8 (23.7) | 28259.2 (21.0) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 560.3 (30.7) | 699.6 (32.6) |
| $T_{max}$ (h) Median (Q1, Q3)[a] | 4.00 (4.00, 4.02) | 4.00 (4.00, 4.02) |
| $T_{1/2}$ (h) Median (Q1, Q3)[a] | 11.14 (9.44, 12.84) | 14.40 (12.32, 15.93) |

a Q1 (first quartile), Q3 (third quartile)

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir (administered on Days 5–14 and 16), stavudine = 40 mg administered on Day 3 alone and on Day 17 with GS-9137/r).

Source: Section 11.1, Table 5; Appendix 14, Listings 21, 22

**Table 5: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with stavudine** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| **Analyte: GS-9137** | | | | |
| GS-9137/r + Stavudine vs.GS-9137/r Alone | | | | |
| $C_{max}$ (ng/mL) | 2688.25 | 2800.33 | 96.00 | 89.92, 102.48 |
| $C_{tau}$ (ng/mL) | 663.10 | 533.29 | 124.34 | 116.61, 132.58 |
| $AUC_{tau}$ (ng•h/mL) | 27650.55 | 28007.30 | 98.73 | 93.89, 103.82 |

a N = 32/treatment; GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, stavudine = 40 mg

Test Treatment = GS-9137/r + stavudine (single dose administered on Day 17).

Reference Treatment = GS-9137/r (administered on 10 consecutive days, Days 5–14).

Source: Section 11.1, Table 6; Appendix 14, Listing 21, 22

The concentration-time profile of the GS-9137 glucuronide metabolite M4 (GS-9200) was unaltered following coadministration of GS-9137/r and didanosine or stavudine

compared to those observed following administration of GS-9137/r alone (data not shown). The 90% CIs for M4 $C_{max}$, $AUC_{tau}$, and $C_{tau}$ were within the prespecified no-effect boundaries (data not shown).

Concentrations of the hydroxylation metabolite M1 (GS-9202) were below quantifiable limits at all sampling timepoints in all subjects, indicating negligible formation in the presence of the CYP3A inhibitor ritonavir.

The absorption phase of the didanosine concentration-time profile appeared to be slightly slower after coadministration with GS-9137/r compared to administration of didanosine alone, but the terminal phase was superimposable. Didanosine exposures were also lower following coadministration with GS-9137/r, with the 90% CIs for $C_{max}$, $AUC_{inf}$, and $AUC_{0\text{-last}}$ falling below the prespecified no-effect bounds (see Table 6). Similar decreases in didanosine exposure have been observed in previous studies following coadministration with ritonavir, indinavir, loperamide, and ketoconazole (possibly due to interactions with P-gp) and are not considered to be clinically relevant.

**Table 6: Statistical comparisons of didanosine PK parameters after administration of didanosine alone or with GS-9137/r** (PK analysis set; source: Study Report Table 7-8)

| Test versus Reference Comparison of Plasma PK Parametersa | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| **Analyte: Didanosine** | | | | |
| Didanosine + GS-9137/r vs. Didanosine | | | | |
| $C_{max}$ (ng/mL) | 785.96 | 934.48 | 84.11 | 67.35, 105.03 |
| $AUC_{inf}$ (ng•h/mL) | 2139.67 | 2489.76 | 85.94 | 74.91, 98.59 |
| $AUC_{0\text{-last}}$ (ng•h/mL) | 2101.83 | 2459.56 | 85.46 | 74.32, 98.26 |

a N = 31/treatment; the pharmacokinetic analysis set excludes Subject 12 who did not have evaluable data from a treatment pair.

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, didanosine = 400 mg

Test Treatment = GS-9137/r + didanosine (single dose administered on Day 15).

Reference Treatment = didanosine (single dose administered on Day 1).

Source: Section 11.1, Table 6

Conversely, the absorption phase of the stavudine concentration-time profile was similar after coadministration with GS-9137/r compared to administration of didanosine alone, but elimination appeared to be slightly slower ($t_{1/2}$ of 1.57 and 1.63 h after administration of stavudine alone or with GS-9137/r, respective). However, statistical analysis did not identify a significant alteration in stavudine pharmacokinetics after coadministration with GS-9137/r compared to administration alone, with the 90% CIs for $C_{max}$, $AUC_{inf}$, and $AUC_{0\text{-last}}$ falling within the prespecified no-effect bounds (see Table 7).

**Table 7: Statistical comparisons of stavudine PK parameters after administration of didanosine alone or with GS-9137/r** (PK analysis set; source: Study Report Table 7-10)

| Test versus Reference Comparison of Plasma PK Parametersa | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test (Mean) | Reference (Mean) | | |
| **Analyte: Stavudine** | | | | |
| Stavudine + GS-9137/r vs. Stavudine | | | | |
| $C_{max}$ (ng/mL) | 516.30 | 518.20 | 99.63 | 93.40, 106.28 |
| $AUC_{inf}$ (ng•h/mL) | 1815.86 | 1701.41 | 106.73 | 105.39, 108.08 |
| $AUC_{0\text{-}last}$ (ng•h/mL) | 1790.22 | 1680.25 | 106.54 | 105.17, 107.93 |

a N = 32/treatment; GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, stavudine = 40 mg.
Test Treatment = GS-9137/r + stavudine (single dose administered on Day 17).
Reference Treatment = stavudine (single dose administered on Day 3).
Source: Section 11.1, Table 6

***Results of safety analysis***

Gastrointestinal system disorders (e.g. diarrhea, nausea) and nervous system disorders (e.g. dizziness) were the most common AEs across the treatment groups. AEs in the GS-9137/r treatment group were generally consistent with those reported for ritonavir. Treatment-related adverse events were distributed across all treatment groups and were all mild (Grade 1). There were no discontinuations due to adverse events, serious adverse events, or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, didanosine, and stavudine following administration of GS-9137/r 200/100 mg QD or single doses of didanosine 400 mg or stavudine 40 mg, or coadministration of GS-9137/r and didanosine or stavudine.

Coadministration of GS-9137/r and didanosine or stavudine did not result in clinically relevant changes to the pharmacokinetics of each individual component compared to administration of that component alone. Concentrations of didanosine ($C_{tau}$, $C_{max}$, and AUC) were approximately 15% lower upon coadministration with GS-9137/r. Similar decreases have been observed when didanosine is coadministered with ritonavir, indinavir, loperamide, and ketoconazole, suggesting a possible role of P-gp. The magnitude of the decrease in didanosine exposures is not considered clinically relevant. The results of the current study indicate that no dose adjustments are needed when GS-9137/r 200/100 mg QD and didanosine 400 mg or stavudine 40 mg are coadministered.

**Trial GS-US-183-0112**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and Etravirine**

**Trial Period**
30 Jan to 15 Mar 2007
Final report date: 22 Jan 2009 (submitted to IND 72,177)

**Trial Site**
Seaview Research, Miami, Florida, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 boosted by the HIV PI ritonavir (GS-9137/r) may be coadministered with the NNRTI etravirine. This study was conducted to determine whether the pharmacokinetics of GS-9137or etravirine were affected by concomitant administration of GS-9137/r and etravirine.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetics of GS-9137or etravirine are affected after coadministration of ritonavir-boosted GS-9137 (GS-9137/r) with etravirine compared to administration of GS-9137/r or etravirine alone
-

The secondary objective of the trial was to:

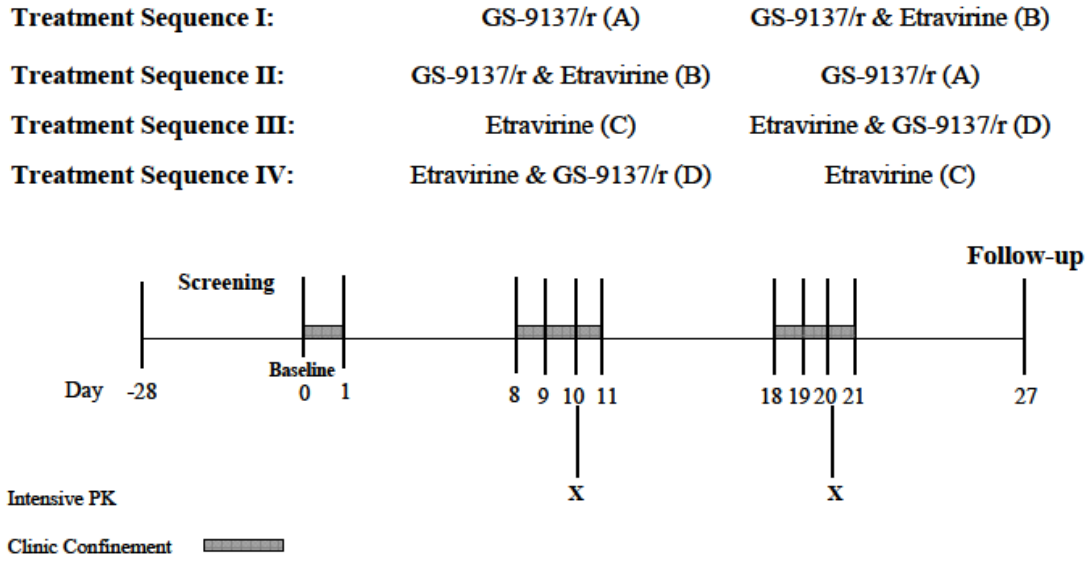
- evaluate the safety and tolerability of short-term administration of GS-9137/r or etravirine alone and in combination

**Trial Design**
This was a two-period, open-label, drug interaction study. Subjects were randomized to one of two groups, each of which received two treatments (A and B or C and D) administered over a period of 10 days per treatment in one of two sequences, followed by a follow-up visit seven days after the last dose of study drug. All treatments were administered in the fed state.

| | |
|---|---|
| Treatment A (reference) | GS-9137/r 150/100 mg QD |
| Treatment B (test) | GS-9137/r 150/100 mg QD plus etravirine 200 mg BID |

| | |
|---|---|
| Treatment C (reference) | etravirine 200 mg BID |
| Treatment D (test) | etravirine 200 mg BID plus GS-9137/r 150/100 mg QD |

**Figure 1: Study schema** (source: Study Report Figure 5-1)




Source: Appendix 1

## Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water within 5 minutes of completion a meal at approximately the same time every day (e.g. 8:00 AM for GS-9137/r and morning doses of etravirine and 8:00 PM for evening doses of etravirine). Standardized meals (400 kcal and 13 g of fat) were provided at the clinic on the mornings of Days 1, 9, 10, 11, 19, and 20 and the evenings of Days 8, 9, 10, 18, 19, and 20. On days of intensive PK sampling (Days 10 and 20), water was restricted from 1 h before until 2 h after study drug administration and food was restricted until after the 4 h blood draw, at which time a standardized meal was provided.

## Rationale for Dose Selection

The GS-9137 dose of 150 mg QD boosted with ritonavir 100 mg QD was selected for this study because it is the dosing regimen planned for evaluation in Phase 3 trials. The etravirine dose of 200 mg BID is that approved for the treatment of HIV. Study drugs were administered for 10 days in order to evaluate steady-state pharmacokinetics.

## Investigational Product

Tablets containing 150 mg of GS-9137 were manufactured by Gilead Sciences, Inc. (Foster City, California, USA; Lot AJ0609D1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 441402E21). Tablets containing 100 mg of etravirine were manufactured by (b) (4) .

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood samples for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), and/or etravirine in plasma were collected on Days 10 and 20 at the times (in hours post-dose) listed below:

| | |
|---|---|
| Treatments A and B | 0:00 (predose), 1:00, 2:00, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 |
| Treatments C and D | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, and 12:00 |

For Treatments B, C, and D, the evening dose of etravirine was administered following collection of the 12 h postdose blood sample.

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137, GS-9200, ritonavir, and etravirine. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of

the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable.

Differences between the primary pharmacokinetic parameters for Treatments A and B or Treatments D and C were calculated using SAS® (SAS Institute, Cary, North Carolina, USA) following natural log transformation. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143% for GS-9137 and 80-125% for etravirine.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200, GS-9202, and ritonavir in plasma samples were determined using LC-MS/MS (Methods (b) (4) 06-009 and (b) (4) 06-204) by (b) (4) . Frozen plasma samples were received between 1 and 8 Mar 2007 and stored at -70˚C. Analyses were completed by 3 Apr 2007. The first day of sample collection was 23 Feb 2007, so the maximum sample storage time was 39 days, which is within the validated long-term frozen stability duration (at -70˚C) of 93 days for ritonavir and 268 days for GS-9137, GS-9200, and GS-9200.

Concentrations of etravirine in plasma samples were determined using LC-MS/MS (Method R293496/LCMS/005-b) by (b) (4) . Frozen plasma samples were received between 1 and 8 Mar 2007 and stored at -20˚C. Analyses were performed between 22 and 27 Mar 2007. The first day of sample collection was 23 Feb 2007, so the maximum sample storage time was 32 days, which is within the validated long-term frozen stability duration (at -20˚C) of 57 days.

The GS-9137, GS-9200, and GS-9202 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 60.0, 3500, and 7500 ng/mL. For ritonavir, the calibration standards ranged from 5-2500 ng/mL and the QC concentrations were 15, 1000, and 2000 ng/mL. For etravirine, the calibration standards ranged from 2-5000 ng/mL and the QC concentrations were 5.5, 110, and 3800 ng/mL. All inter-assay accuracy and precision estimates for GS-9137, GS-9200, GS-9202, and ritonavir (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations). The inter-assay accuracy and precision estimates for etravirine were included in the bioanalytical study report and were also within the acceptable range.

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, and ritonavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 | M1 | Ritonavir |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 10,000 | 20 to 10,000 | 5 to 2500 |
| LLQ (ng/mL) | 20 | 20 | 20 | 5 |
| Inter-Assay Precision Range[a] | 0.0% to 4.9% | 1.2% to 7.3% | 1.4% to 7.3% | 2.4% to 6.1% |
| Inter-Assay Accuracy Range[b] | −2.0% to 2.0% | −1.5% to 2.9% | −2.7% to 1.7% | −3.6% to −1.8% |
| Stability in Frozen Matrix (days) | 268 | 268 | 268 | 96 |

LLQ, lower limit of quantitation
a Relative standard deviation
b Difference from nominal concentrations
Source: Appendix 10

***Trial population***

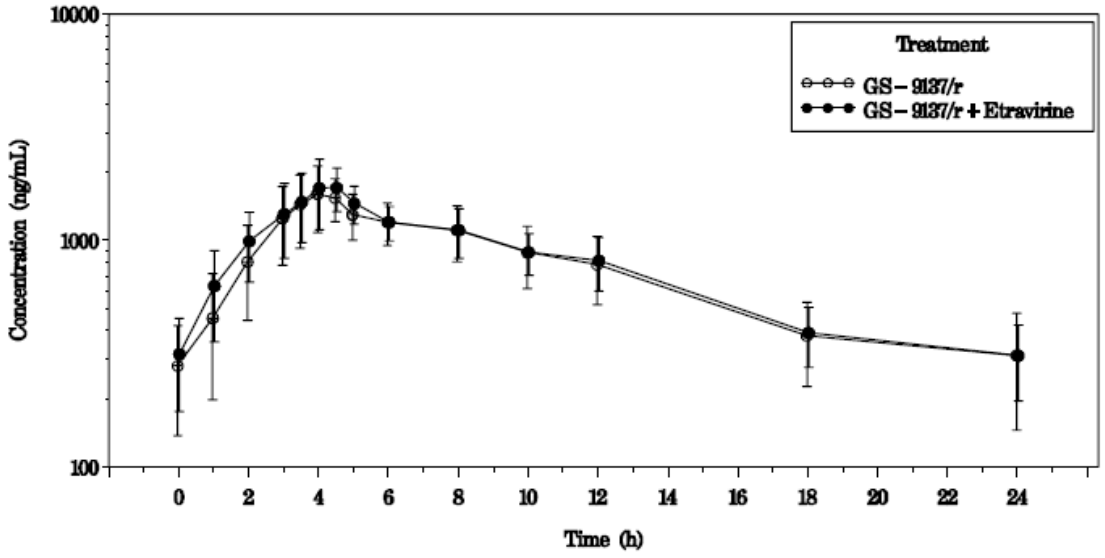
A total of 34 healthy adult subjects were enrolled in the study and received study drug; 31 subjects completed the study. Three subjects, all in Group 1, withdrew consent and discontinued the study early. Of the safety analysis set (n=34), the majority of subjects were white (93.5%); the remainder were black (6.5%). Half of the subjects were female (50.0%). Subjects had a mean age of 33 years (range: 18 to 45 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of GS-9137, M4, ritonavir, and etravirine were compared following coadministration of GS-9137/r and etravirine or GS-9137/r or etravirine alone.

The concentration-time profiles of GS-9137 were similar following coadministration of GS-9137/r and etravirine compared to administration of GS-9137/r alone (see Figure 2). The slope of the absorption phase (0 to 3 h postdose) differed slightly in the presence of etravirine, but GS-9137 pharmacokinetic parameters were similar (see Table 2) and the 90% CI values for the ratios of the geometric least-squares means of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ were within the prespecified no-effect bounds of 70-143% (see Table 3), indicating no significant changes in GS-9137 pharmacokinetics after coadministration with etravirine.

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with etravirine** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Values presented as mean ± SD. The PK analysis set includes 17 subjects. Subjects 1003, 1006, and 1007 did not have evaluable profiles for each treatment pair and were excluded from the analysis set.

Source: Section 11.1, Figure 1.1

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with etravirine** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 17) | GS-9137/r + Etravirine (N = 17) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 1701.6 (28.2) | 1827.1 (28.4) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 17566.2 (27.3) | 18453.3 (19.5) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 311.3 (53.4) | 310.5 (36.8) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.00 (4.00, 4.50) | 4.50 (4.00, 4.50) |
| $T_{½}$ (hours) Median (Q1, Q3) | 8.04 (6.63, 8.76) | 8.21 (6.84, 9.17) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r, 150 mg of GS-9137 plus 100 mg of ritonavir administered once daily; etravirine, 200 mg of etravirine administered twice daily; CV, coefficient of variation; Q1, first quartile; Q3, third quartile

a Subjects 1003, 1006, and 1007 did not have evaluable PK profiles for each treatment pair and were thus excluded from the analysis set.

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or with etravirine** (PK analysis set; source: Study Report Table 7-2)

| Test vs. Reference Comparison PK Parameter[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137/r + Etravirine vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 1758.6 | 1648.3 | 106.7 | 100.8, 112.9 |
| $AUC_{tau}$ (ng•h/mL) | 18112.1 | 17032.8 | 106.3 | 99.9, 113.2 |
| $C_{tau}$ (ng/mL) | 288.9 | 272.7 | 106.0 | 97.0, 115.8 |

GS-9137/r, 150 mg of GS-9137 plus 100 mg of ritonavir administered once daily; etravirine, 200 mg of etravirine administered twice daily

a N = 17/treatment; Subjects 1003, 1006, and 1007 did not have evaluable PK profiles for each treatment pair and were thus excluded from the analysis set

b Test Treatment, GS-9137/r + etravirine; Reference Treatment, GS-9137/r; each treatment was given for 10 consecutive days

Source: Section 11.1, Table 6

The concentration-time profile of the GS-9137 glucuronide metabolite M4 (GS-9200) was unaltered following coadministration of GS-9137/r and etravirine compared to those observed following administration of GS-9137/r alone (data not shown). The 90% CIs for M4 $C_{max}$ and $AUC_{tau}$ were within the prespecified no-effect boundaries. Although M4 $C_{tau}$ decreased by 43%, this change is not thought to be clinically relevant since M4 is not pharmacologically active (see Table 4). The mean $AUC_{tau}$ ratios for M4 to GS-9137 were 7.1 and 6.7% after administration of GS-9137/r alone and with etravirine, respectively (data not shown).

**Table 4: Summary of steady-state M4 (GS-9200) PK parameters after administration of GS-9137/r alone or with etravirine** (PK analysis set; source: Study Report Table 7-3)

| M4 Plasma PK Parameters[a] | GS-9137/r (N = 17) | GS-9137/r + Etravirine (N = 17) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 138.7 (27.1) | 115.7 (25.9) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 1209.7 (34.4) | 1186.8 (28.2) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 10.2 (146.6) | 5.9 (188.0) |
| $T_{max}$ (hours) Median (Q1, Q3) | 3.50 (3.00, 4.50) | 3.53 (3.00, 4.50) |
| $T_{½}$ (hours) Median (Q1, Q3) | 8.81 (7.57, 10.81) | 9.29 (6.64, 11.78) |
| $T_{last}$ (hours) Median (Q1, Q3) | 18.00 (18.00, 24.00) | 18.00 (11.95, 18.03) |

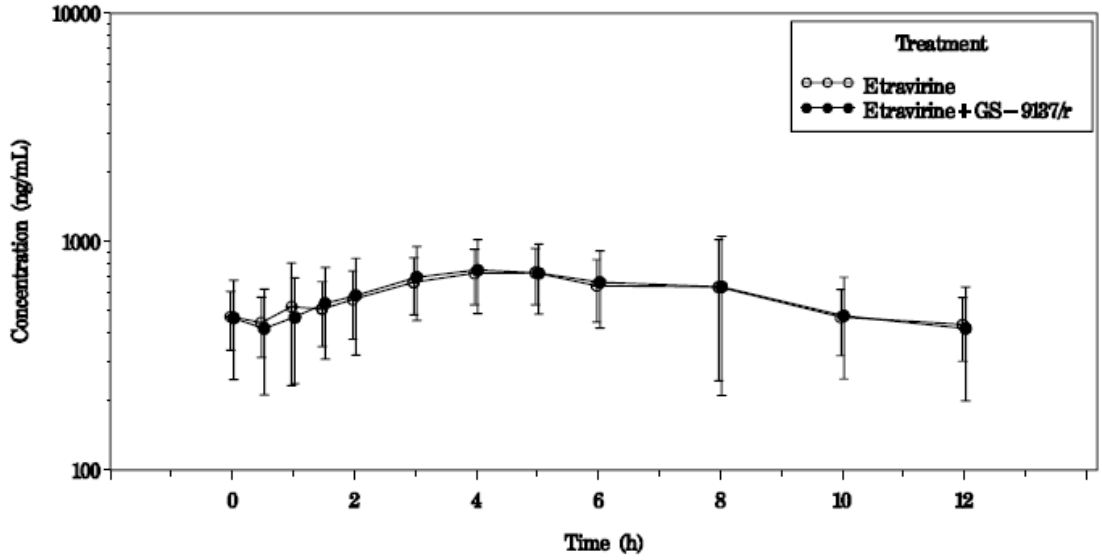
GS-9137/r, 150 mg of GS-9137 plus 100 mg of ritonavir administered once daily; etravirine, 200 mg of etravirine administered twice daily; CV, coefficient of variation; Q1, first quartile; Q3, third quartile

a Subjects 1003, 1006, and 1007 did not have evaluable PK profiles for each treatment pair and were thus excluded from the analysis set.

Source: Section 11.1, Table 5.4

The concentration-time profiles of etravirine were similar following coadministration of GS-9137/r and etravirine compared to administration of etravirine alone (see Figure 3). Etravirine pharmacokinetic parameters were similar and the 90% CI values for the ratios of the geometric least-squares means of etraivrine $C_{max}$, $C_{tau}$, and $AUC_{tau}$ were within the prespecified no-effect bounds of 80-125% (data not shown), indicating no significant changes in etravirine pharmacokinetics after coadministration with GS-9137/r.

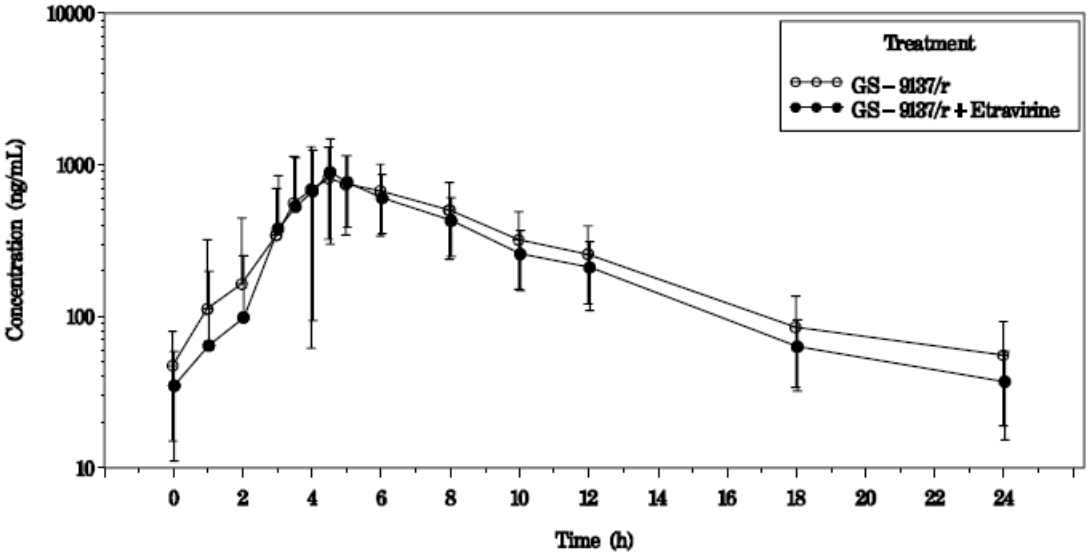
**Figure 3: Steady-state etravirine plasma concentrations after administration of etravirine alone or with GS-9137/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-3)




Values presented as mean ± SD
Source: Section 11.1, Figure 1.2

Overall, ritonavir exposures were similar following coadministration of GS-9137/r and etravirine compared to administration of GS-9137/r alone (see Figure 4). Ritonavir concentrations were slightly lower during the absorption and elimination phases in the presence of etravirine, resulting in a 30% decrease in $C_{tau}$ (see Table 5); this is not expected to be clinically relevant since ritonavir is used at subtherapeutic levels as a pharmacokinetic booster for GS-9137, and GS-9137 pharmacokinetics were unchanged. The 90% CI values for the ratios of the geometric least-squares means of ritonavir $C_{max}$ and $AUC_{tau}$ were within the prespecified no-effect bounds of 70-143% (data not shown).

**Figure 4: Steady-state ritonavir plasma concentrations after administration of GS-9137/r alone or with etravirine** (mean ± SD; PK analysis set; source: Study Report Figure 7-4)




Values presented as mean ± SD
Source: Section 11.1, Figure 1.3

**Table 5: Summary of steady-state ritonavir PK parameters after administration of GS-9137/r alone or with etravirine** (PK analysis set; source: Study Report Table 7-7)

| Ritonavir Plasma PK Parameters[a] | GS-9137/r (N = 17) | GS-9137/r + Etravirine (N = 17) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 970.1 (57.1) | 956.4 (61.9) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 6345.1 (46.9) | 5546.4 (44.9) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 55.3 (65.7) | 36.9 (58.8) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.50 (4.00, 5.00) | 4.50 (4.00, 5.00) |
| $T_{½}$ (hours) Median (Q1, Q3) | 4.61 (4.34, 5.13) | 4.27 (4.14, 4.47) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r, 150 mg of GS-9137 plus 100 mg of ritonavir administered once daily; etravirine, 200 mg of etravirine administered twice daily; CV, coefficient of variation; Q1, first quartile; Q3, third quartile

a Subjects 1003, 1006, and 1007 did not have evaluable PK profiles for each treatment pair and were thus excluded from the analysis set.

Source: Section 11.1, Table 5.3

***Results of safety analysis***

Gastrointestinal system disorders (e.g. diarrhea) and nervous system disorders (e.g. headache) were the most common AEs across the treatment groups. The only AE considered to be related to administration of GS-9137/r was diarrhea, which was reported in one subject. There were no discontinuations due to adverse events, serious adverse events, or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, ritonavir, and etravirine following administration of GS-9137/r 150/100 mg QD, etravirine 200 mg BID, or coadministration of GS-9137/r and etravirine.

Coadministration of GS-9137/r and etravirine did not result in clinically relevant changes to the pharmacokinetics of each individual component compared to administration of that component alone. The results of the current study indicate that no dose adjustments are needed when GS-9137/r 150/100 mg QD and etravirine 200 mg BID are coadministered.

## Trial GS-US-183-0115
## A Phase 1, Open Label, Pharmacokinetic Drug Interaction Study of GS-9137/r and Abacavir Sulfate

### Trial Period
19 Jan to 26 Feb 2006
Final report date: 27 Oct 2006 (submitted to IND 72,177)

### Trial Site
MDS Pharma Services, Phoenix, Arizona, USA

### Trial Rationale
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 boosted by the HIV PI ritonavir (GS-9137/r) may be coadministered with the NRTI abacavir (Ziagen®). This study was conducted to determine whether the pharmacokinetics of GS-9137 or abacavir were affected by concomitant administration of GS-9137/r and abacavir sulfate.

### Trial Objectives
The primary objective of the trial was to:

- evaluate whether the pharmacokinetic parameters of GS-9137 or abacavir are affected after coadministration of ritonavir-boosted GS-9137 (GS-9137/r) and abacavir sulfate compared to their administration alone

The secondary objective of the trial was to:

- evaluate the safety of coadministration of ritonavir-boosted GS-9137 and abacavir sulfate

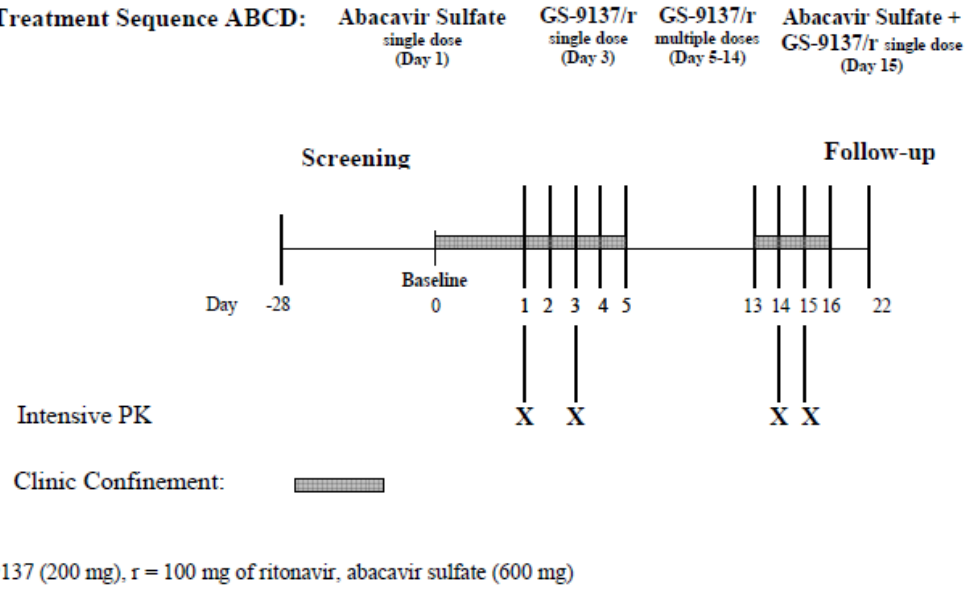
### Trial Design
This was a fixed-sequence, open-label, drug interaction study. There were four treatments administered sequentially over a period of 15 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A abacavir 600 mg, single dose on Day 1
Treatment B GS-9137/r 200/100, single dose on Day 3
Treatment C GS-9137/r 200/100 mg QD on Days 5-14

Treatment D: abacavir 600 mg and GS-9137/r 200/100, single dose on Day 15

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




GS-9137 (200 mg), r = 100 mg of ritonavir, abacavir sulfate (600 mg)

The half-life of abacavir after a single dose is approximately 1.5 h, so a washout period of 48 h is sufficient for elimination before administration of the first dose of GS-9137/r on Day 3.

### Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water immediately after a meal at approximately the same time every morning (GS-9137/r and the morning dose of abacavir sulfate) or evening (the evening dose of abacavir sulfate). Dosing was observed at the clinic on Days 1, 2, 5, 14, and 15 and unobserved at home on Days 6 to 13. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1 to 5, 14, and 15. Evening meals that were similar in calorie and fat content were provided on Days 0 to 4 and 13 to 15.

### Rationale for Dose Selection

The GS-9137 dose of 200 mg QD was selected for this study on the basis of results from studies during clinical development that demonstrated that GS-9137/r is well-tolerated at doses up to 200/100 mg QD; this dose is expected to provide an upper limit of drug exposures expected in planned clinical studies. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose given once-daily has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The abacavir dose of 600 mg BID was selected for this study because it is the same dose that is currently marketed for the treatment of HIV in adults.

### Investigational Product

Tablets containing 200 mg of GS-9137 were manufactured by Japan Tobacco, Inc. (Lot 401). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 329052E21). Film-coated tablets containing 300 mg of abacavir (Ziagen®) were manufactured by GlaxoSmithKline (Research Triangle Park, North Carolina, USA; Lot 5ZP0759).

### Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

### Concomitant Medications

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

### Sample Collection

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), and/or abacavir were collected at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 1, 14, and 15 | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, and 24:00 |
| Day 3 | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, 24:00, 28:00, 32:00, 36:00, 40:00, 44:00, and 48:00 |

Urine was collected for quantification of GS-9137, M1, M4, and/or abacavir on Days 1 and 15 at the following intervals: 0 (predose) and 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose.

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137, GS-9200, and abacavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were evaluated for validity on a profile-by-profile basis by the pharmacokineticist. Absence of a pharmacokinetic interaction was defined by the 90% confidence intervals falling between 70% and 143%.

## Trial Results

***Bioanalytical methods***

Concentrations of GS-9137 and GS-9200 in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16480 v1) by Gilead Sciences, Inc. (Foster City, California, USA). Frozen plasma samples were received between 7 and 23 Feb 2006 and stored at -80˚C. Analysis was performed between 2 and 23 Mar 2006. The first day of sample collection was 26 Jan 2006, so the maximum sample storage time was 56 days, which is within the validated long-term frozen stability duration (at -80˚C) of 93 days for GS-9137and GS-9200.

Concentrations of abacavir in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0604) by (b) (4)
Frozen plasma samples were received between 7 and 16 Feb 2006 and stored at -70˚C. Analysis was performed between 27 Feb and 14 Mar 2006. The first day of sample collection was 26 Jan 2006, so the maximum sample storage time was 47 days, which is within the validated long-term frozen stability duration (at -70˚C) of 80 days.

The GS-9137 and GS-9200 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750.0, and 7500 ng/mL. For abacavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 250, 1000, and 4000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, and abacavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Abacavir |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 10,000 | 20 to 10,000 | 5 to 5, 000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 5 |
| Inter-Assay Precision Range[a] | 4.1% to 11.1% | 5.0% to 14.0% | 4.9% to 15.2% | 4.1% to 7.7% |
| Inter-Assay Accuracy Range[b] | –8.3% to –4.8% | –8.5 %to –3.5% | –4.5% to –3.0% | –7.7% to 1.5% |
| Stability in Frozen Matrix (days) | 93[c] | 93[c] | 93[c] | 80[d] |

a Relative standard deviation
b Difference from nominal concentrations
c Data on file at (b) (4)
d Data on file at (b) (4)
LLQ = lower limit of quantitation
Source: Appendix 15

***Trial population***

A total of 26 healthy adult subjects were enrolled in the study and received study drug; 24 subjects completed the study. Two subjects were withdrawn by the investigator on Day 13: one did not return for the check-in visit, and one tested positive for amphetamines. Of the safety analysis set (n=26), the majority of subjects were Hispanic (92.3%); the remainder were white (3.8%) or of mixed ancestry (3.8%). Half of the subjects were female (50.0%). Subjects had a mean age of 32 years (range: 21 to 44 years).

***Results of pharmacokinetic analyses***

In this study, the pharmacokinetics of single- and multiple-dose GS-9137 and single-dose abacavir were compared following coadministration of GS-9137/r and abacavir versus administration of GS-9137/r or abacavir alone.

Although the effects of abacavir on the pharmacokinetics of a single dose of ritonavir-boosted GS-9137 were not assessed, the GS-9137 concentration-time curve indicated that ritonavir acted as a pharmacokinetic enhancer throughout the 48 h sample collection period, as there was no evidence of a rapid decline in GS-9137 concentrations (data not shown).

The PK parameters for single-dose and multiple-dose GS-9137 after administration of GS-9137/r alone and with abacavir are listed in Table 2. GS-9137 exposures were higher after multiple doses of GS-9137/r compared to a single dose. The steady-state pharmacokinetic parameters of GS-9137 were similar after coadministration of GS-9137/r and abacavir and after administration of GS-9137/r alone.

**Table 2: Summary of single-dose and steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with abacavir** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | Single-Dose GS-9137/r (N = 26) | Steady-State GS-9137/r (N = 24) | Steady-State GS-9137/r + Abacavir Sulfate (N = 24) |
|---|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 2003.2 (37.8) | 3501.9 (32.5) | 3109.2 (26.2) |
| $AUC_{tau/inf}$ (ng•h/mL)[b] Mean (%CV) | 29461.3 (33.3) | 35,129.3 (28.0) | 33,476.8 (22.2) |
| $C_{tau/last}$ (ng/mL)[c] Mean (%CV) | 87.4 (56.5) | 669.7 (33.7) | 697.7 (30.2) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.00 (4.00, 5.00) | 4.00 (4.00, 4.51) | 4.01 (4.00, 5.00) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 8.75 (7.07, 10.27) | 9.87 (9.39, 10.32) | 10.25 (9.48, 11.17) |
| $T_{last}$ (hours) Median (Q1, Q3) | 47.97 (47.97, 47.97) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |
| $\%AUC_{exp}$ (%) Mean | 4.0 | NA | NA |

a The pharmacokinetic analysis set for multiple-dose GS-9137/r and multiple-dose GS-9137/r + abacavir sulfate excludes Subjects 11 and 18 because they did not have evaluable pharmacokinetic profiles for each treatment.

b $AUC_{tau}$ for steady-state GS-913/r and steady-state GS-9137/r + abacavir sulfate, $AUC_{inf}$ for single-dose GS-9137/r

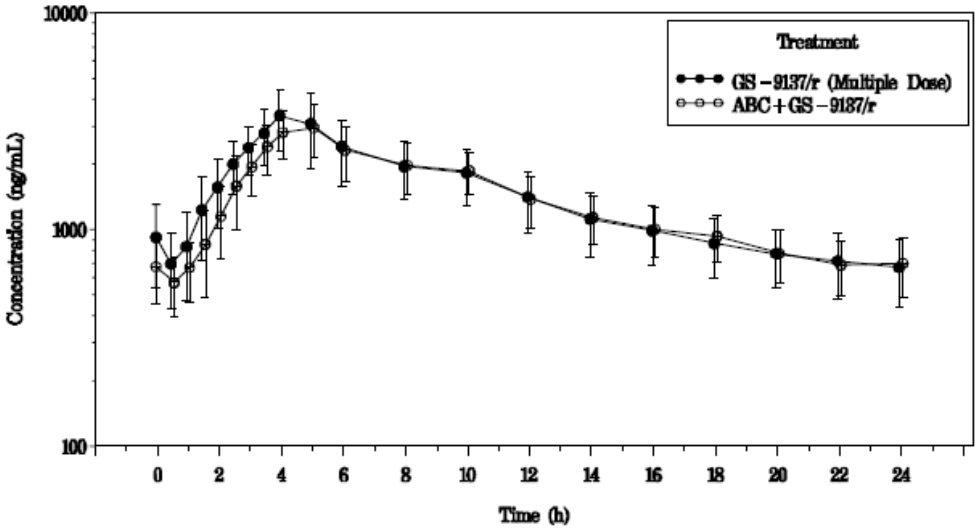
c $C_{tau}$ for steady-state GS-913/r and steady-state GS-9137/r + abacavir sulfate, $C_{last}$ for single-dose GS-9137/r

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, abacavir sulfate = 600 mg, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile, NA = not applicable

Source: Section 11.1, Table 5

Coadministration of abacavir and GS-9137/r appeared to slightly decrease the extent of GS-9137 absorption, although the steady-state concentration-time profiles of GS-9137 were superimposible after $t_{max}$ (see Figure 1) and statistical comparisons of $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated a lack of interaction as defined by the associated 90% confidence intervals contained within the predefined no-effect bounds (see Table 3).

**Figure 1: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with abacavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. The pharmacokinetic analysis set excludes Subjects 11 and 18 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1

**Table 3: Statistical comparisons of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with abacavir** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **Abacavir + GS-9137/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 2997.22 | 3252.58 | 92.15 | 83.97, 101.13 |
| $C_{tau}$ (ng/mL) | 667.27 | 622.31 | 107.23 | 97.67, 117.72 |
| $AUC_{tau}$ (ng•h/mL) | 32,627.57 | 33,194.00 | 98.29 | 91.04, 106.12 |

a N = 24/treatment; the pharmacokinetic analysis set excludes Subjects 11 and 18 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

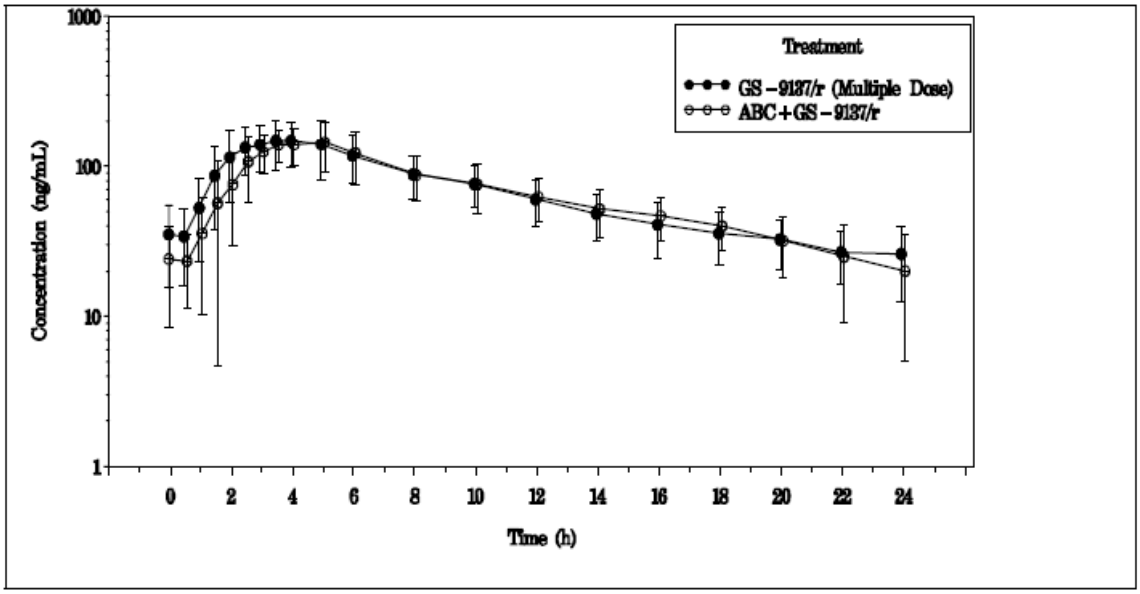
b Test Treatment = GS-9137/r + abacavir sulfate, Reference Treatment = 10 daily doses of GS-9137/r

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, abacavir sulfate = 600 mg, GMR = geometric least-squares mean ratio, CI = confidence interval

Source: Section 11.1, Table 6

Similarly to GS-9137, concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) also appeared to be slightly lower before $T_{max}$ following coadministration of GS-9137/r and abacavir compared to those observed following administration of GS-9137/r alone (see Figure 2), although steady-state M4 $C_{max}$, $AUC_{tau}$, and $C_{tau}$ were similar between the two treatments (see Table 4). For both treatments, M4 exposures were less than 6% of the corresponding GS-9137 exposures.

**Figure 2: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or with abacavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. The pharmacokinetic analysis set excludes Subjects 11 and 18 because they did not have an evaluable pharmacokinetic profile for the treatment pair.

Source: Section 11.1, Figure 1

**Table 4: Summary of steady-state GS-9200 PK parameters after administration of GS-9137/r alone or with abacavir** (PK analysis set; source: Study Report Table 7-3)

| M4 Plasma PK Parameters[a] | Single-Dose GS-9137/r (N = 26) | Steady-State GS-9137/r (N = 24) | Steady-State GS-9137/r + Abacavir Sulfate (N = 24) |
|---|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 110.3 (46.1) | 171.1 (37.5) | 167.8 (30.4) |
| $AUC_{tau/inf}$ (ng•h/mL)[b] Mean (%CV) | 1504.6 (36.0) | 1683.4 (27.9) | 1604.4 (27.8) |
| $C_{tau/last}$ (ng/mL)[c] Mean (%CV) | 23.2 (11.6) | 26.0 (51.9) | 20.1 (74.8) |
| $T_{max}$ (hours) Median (Q1, Q3) | 3.50 (3.00, 5.00) | 3.00 (2.50, 4.00) | 3.74 (3.00, 5.00) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 10.31 (7.92, 11.65) | 9.22 (8.16, 9.95) | 9.58 (7.69, 10.69) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (20.00, 24.02) | 24.00 (24.00, 24.00) | 24.00 (21.01, 24.00) |
| $\%AUC_{exp}$ (%) Mean | 24.4 | NA | NA |

a The pharmacokinetic analysis set for multiple-dose GS-9137/r and multiple-dose GS-9137/r + abacavir sulfate excludes Subjects 11 and 18 because they did not have evaluable pharmacokinetic profiles for each treatment.

b $AUC_{tau}$ for steady-state GS-9137/r and steady-state GS-9137/r + abacavir sulfate, $AUC_{inf}$ for single-dose GS-9137/r

c $C_{tau}$ for steady-state GS-9137/r and steady-state GS-9137/r + abacavir sulfate, $C_{last}$ for single-dose GS-9137/r

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, abacavir sulfate = 600 mg, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

Source: Section 11.1, Table 5

Concentrations of the hydroxylation metabolite M1 (GS-9202) were too low to provide substantive pharmacokinetic data for any of the treatments examined.

The abacavir concentration-time profiles were similar after coadministration with GS-9137/r compared to administration of abacavir alone, with the 90% CIs for the ratios of the geometric least-squares means for abacavir $C_{max}$, $AUC_{inf}$, and $AUC_{0\text{-last}}$ falling within the prespecified no-effect bounds of 80 to 143% (see Table 5).

**Table 5: Statistical comparisons of abacavir PK parameters after administration of abacavir alone or with GS-9137/r** (PK analysis set; source: Study Report Table 7-5)

| Test versus Reference Comparison of Abacavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **Abacavir Sulfate + GS-9137/r vs. Abacavir Sulfate** | | | | |
| $C_{max}$ (ng/mL) | 3686.09 | 4206.37 | 87.63 | 82.04, 93.60 |
| $AUC_{0\text{-last}}$ (ng/mL) | 12,773.63 | 15,301.80 | 83.48 | 80.65, 86.41 |
| $AUC_{inf}$ (ng•h/mL) | 12,797.40 | 15,323.50 | 83.51 | 80.69, 86.44 |

a N = 24/treatment; the pharmacokinetic analysis set excludes Subjects 11 and 18 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = steady-state GS-9137/r + a single dose of abacavir sulfate, Reference Treatment = a single dose of abacavir sulfate

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, abacavir sulfate = 600 mg, GMR = geometric least-squares mean ratio, CI = confidence interval

Source: Section 11.1, Table 6.

***Results of safety analysis***

Gastrointestinal system disorders (e.g. diarrhea, nausea) and nervous system disorders (e.g. dizziness) were the most common AEs across the treatment groups. Treatment-related adverse events were distributed across all treatment groups and were all mild (Grade 1). There were no discontinuations due to adverse events, serious adverse events, or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, and abacavir following administration of GS-9137/r 200/100 mg QD or single dose abacavir 600 mg, or coadministration of GS-9137/r and abacavir.

Coadministration of GS-9137/r and abacavir did not result in clinically relevant changes to the pharmacokinetics of each individual component compared to administration of that component alone. The results of the current study indicate that no dose adjustments are needed when GS-9137/r 200/100 mg QD and abacavir 600 mg are coadministered.

**Trial GS-US-183-0116**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and Lopinavir/r (Kaletra®)**

**Trial Period**
13 Jun to 30 Jul 2006
Final report date: 21 May 2007 (submitted to IND 72,177)

**Trial Site**
Covance Inc., Dallas, Texas, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. The protease inhibitor lopinavir also uses ritonavir as a pharmacoenhancer; lopinavir with ritonavir is available as a fixed-dose combination tablet (Kaletra®), which may be coadministered with GS-9137 in clinical practice. This study was conducted to determine whether the pharmacokinetics of GS-9137, ritonavir, or lopinavir were affected by concomitant administration of GS-9137 and lopinavir/r.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetic parameters of GS-9137, lopinavir, or ritoanvir are affected upon coadministration of GS-9137 (GS-9137/r) and lopinavir/r compared to GS-9137/r or lopinavir/r administered alone

The secondary objective of the trial was to:

- evaluate the safety of coadministration of GS-9137 plus lopinavir/r, and GS-9137/r or lopinavir/r administered alone

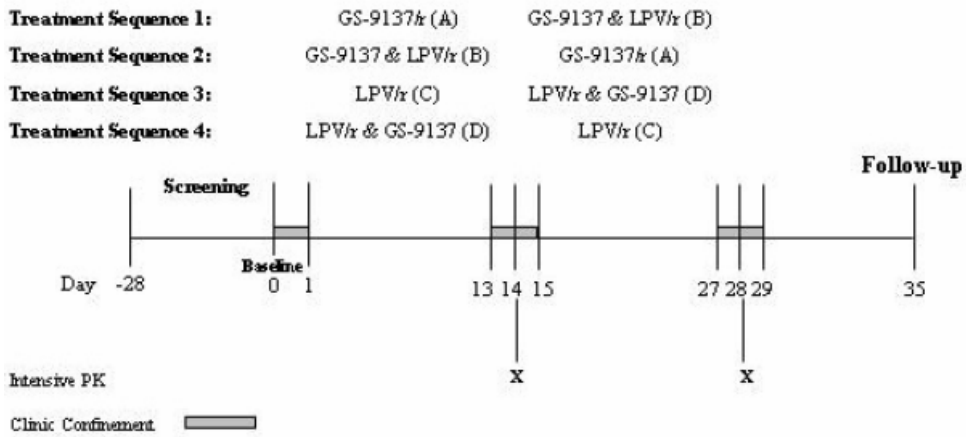
**Trial Design**
This was an open-label steady-state drug interaction study. Subjects were randomized to one of three treatments in four treatment sequences, with each sequence consisting of two 14 day treatment periods followed by a follow-up visit seven days after the last dose of study drug.

Treatment A GS-9137/r 125/100 mg QD
Treatment B GS-9137 125 mg QD and lopinavir/r 400/100 mg BID

Treatment C lopinavir/r 400/100 mg BID
Treatment D: GS-9137 125 mg QD and lopinavir/r 400/100 mg BID

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




## Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water immediately after a meal at approximately the same time every morning (GS-9137 and the morning dose of lopinavir/r) or evening (the evening dose of lopinavir/r). Dosing was observed at the clinic on Days 1, 14, and 28 and unobserved at home on Days 2 to 13 and 15 to 27. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 14, and 28. Evening meals that were similar in calorie and fat content were provided on Days 13, 14, 27, and 28.

## Rationale for Dose Selection

The GS-9137 dose of 125 mg QD was selected for this study because it is the highest GS-9137 dose being examined in an ongoing Phase 2 study. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose given once-daily has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The lopinavir/r dose of 400/100 mg BID was selected for this study because it is the same dose that is currently marketed for the treatment of HIV in adults.

## Investigational Product

Tablets containing 125 mg of GS-9137 were manufactured by Gilead Sciences, Inc. (Lot AJ603A1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 377752E21). Film-coated tablets containing 200 mg of lopinavir and 50 mg of ritonavir (Kaletra®) were manufactured by Abbott Laboratories (Lot 360749Y40).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), and ritonavir (Group 1) or lopinavir and ritonavir (Group 2) were collected on Days 14 and 28 at the times (in hours post-dose) listed below:

| | |
|---|---|
| Group 1 | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, and 24:00 |
| Group 2 | 0:00 (predose), 1:00, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, and 12:00 |

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137, GS-9200, ritonavir, and lopinavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were evaluated for validity on a profile-by-profile basis by the pharmacokineticist. Absence of a pharmacokinetic interaction was defined by the 90% confidence intervals falling between 70% and 143%.

**Trial Results**

***Bioanalytical methods***

Concentrations of GS-9137, GS-9200, and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511 v2-4) by Gilead Sciences, Inc. (Durham, North Carolina, USA). Frozen plasma samples were received between 11 and 26 Jul 2006 and stored at -80˚C. Analysis was performed between 18 Aug and 1 Sept 2006. The first day of sample collection was 10 Jul 2006, so the maximum sample storage time was 52 days, which is within the validated long-term frozen stability duration (at -80˚C) of 93 days for GS-9137and GS-9200 and 102 days for ritonavir.

Concentrations of lopinavir in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0212) by (b) (4). Frozen plasma samples were received between 11 and 26 Jul 2006 and stored at -70˚C. Analysis was performed between 11 Jul and 7 Aug 2006. The first day of sample collection was 10 Jul 2006, so the maximum sample storage time was 28 days, which is within the validated long-term frozen stability duration (at -70˚C) of 217 days.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750.0, and 7500 ng/mL. For GS-9200, the calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50.0, 150.0, and 750.0 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For lopinavir, the calibration standards ranged from 100-10000 ng/mL and the QC concentrations were 100, 200, 1500, and 8000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, lopinavir, and ritonavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 Metabolite | M1 Metabolite | Ritonavir | Lopinavir |
|---|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 1000 | 20 to 1000 | 5 to 5000 | 100 to 10,000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 5 | 100 |
| Inter-Assay Precision Range[a] | 4.9% to 7.7% | 5.4% to 10.8% | 5.4% to 10.1% | 8.0% to 10.6% | 5.9% to 8.6% |
| Inter-Assay Accuracy Range[b] | −2.7% to 0.6% | −7.7% to 1.4% | −5.2% to 2.8% | −7.3% to −2.6% | −3.7% to -2.7% |
| Stability in Frozen Matrix (days) | 93 | 93 | 93 | 102 | 217 |

LLQ = lower limit of quantitation

a Relative standard deviation

b Difference from nominal concentrations

Source: Appendix 10

***Trial population***

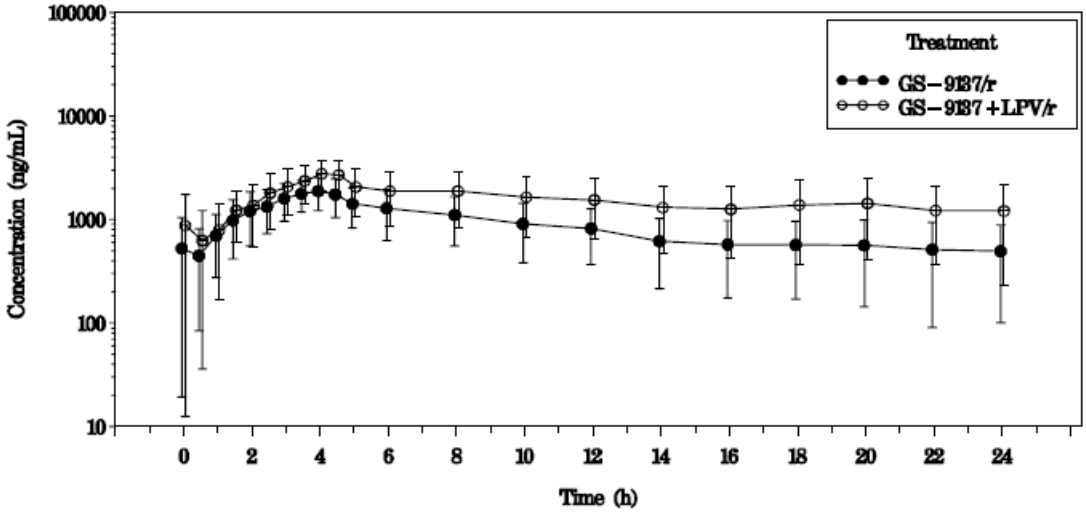
A total of 32 healthy adult subjects were enrolled in the study and received study drug; 27 subjects completed the study. Three subjects withdrew consent, one subject was withdrawn by the investigator, and one subject was withdrawn due to tolerability. Of the safety analysis set (n=32), the majority of subjects were white (56.3%); the remainder were black (31.3%), of other ancestry (9.4%), or native Hawaiian or Pacific Islander (3.1%). Subjects were predominantly male (65.6%). Subjects had a mean age of 31 years (range: 20 to 45 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of GS-9137 and lopinavir/r were compared following coadministration of GS-9137 and lopinavir/r versus administration of GS-9137/r or lopinavir/r alone.

Coadministration of GS-9137 and lopinavir/r increased mean GS-9137 plasma concentrations (see Figure 1 and Table 2). The increases in GS-9137 exposures could be due to increased bioavailability, decreased clearance, or both, mediated by lopinavir, ritonavir, or both. Data on the pharmacokinetics of the M4 metabolite (GS-9200, shown in Table 4 below) suggest that the interaction is likely to result from changes in GS-9137 metabolism.

**Figure 1: Steady-state GS-9137 plasma concentrations after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




Values presented as mean ± SD. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

Source: Section 11.1, Figure 1.1

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 14) | GS-9137 + Lopinavir/r (N = 14) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 1926.9 (34.0) | 2883.7 (34.8) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 20685.4 (53.4) | 36909.5 (56.4) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 492.4 (79.4) | 1210.2 (81.1) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.00 (3.50, 4.00) | 4.00 (4.00, 4.50) |
| $T_{½}$ (hours) Median (Q1, Q3) | 13.85 (6.31, 19.01) | 15.59 (6.48, 25.07) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir +100 mg of ritonavir twice daily, CV, coefficient of variation; Q1, first quartile; Q3, third quartile

a Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

Source: Section 11.1, Table 5.1

Statistical comparisons of $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated a significant increase in GS-9137 exposures as defined by the associated 90% confidence intervals that rose above the predefined no-effect bounds (see Table 3).

**Table 3: Statistical comparisons of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Lopinavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 2741.7 | 1806.9 | 151.74 | 128.76, 178.82 |
| $AUC_{tau}$ (ng•h/mL) | 31,693.9 | 18,112.6 | 174.98 | 149.67, 204.57 |
| $C_{tau}$ (ng•h/mL) | 879.8 | 369.6 | 238.06 | 180.95, 313.18 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir +100 mg of ritonavir twice daily; CI, confidence interval

a N = 14/treatment. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

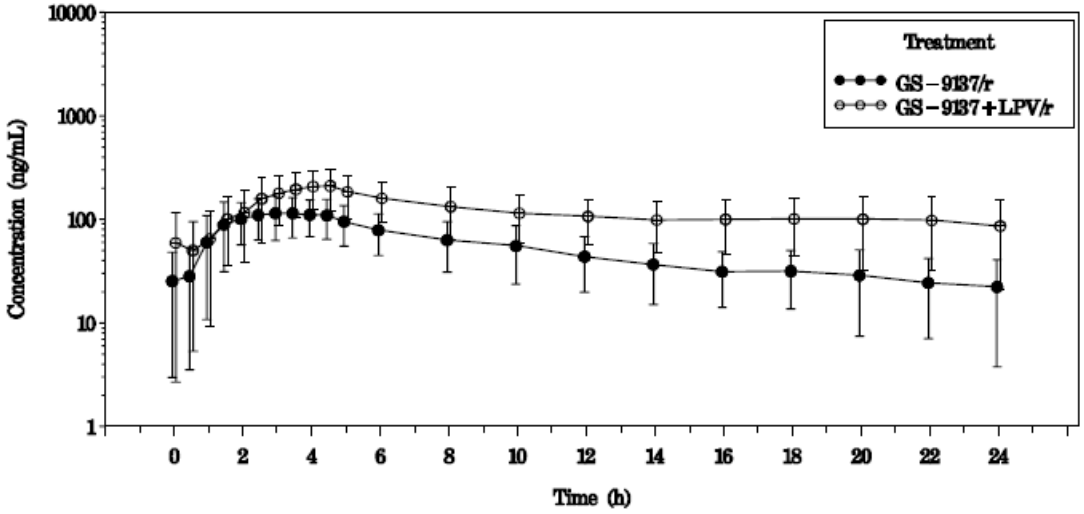
b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = GS-9137/r; each treatment given for 14 consecutive days

Source: Section 11.1, Table 6.1

Similarly to GS-9137, concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were also higher following coadministration of GS-9137 and lopinavir/r compared to those observed following administration of GS-9137/r alone (see Figure 2), with

corresponding increases in $C_{max}$, $AUC_{tau}$, and $C_{tau}$, as well as a slight delay in $T_{max}$ (see Table 4).

**Figure 2: Steady-state M4 plasma concentrations after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

Source: Section 11.1, Figure 1.4

**Table 4: Summary of steady-state M4 PK parameters after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (PK analysis set; source: Study Report Table 7-3)

| M4 Plasma PK Parameters[a] | GS-9137/r (N = 14) | GS-9137 + Lopinavir/r (N = 14) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 131.1 (38.8) | 225.5 (41.1) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 1297.9 (42.0) | 2821.2 (48.0) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 22.3 (83.2) | 86.2 (76.1) |
| $T_{max}$ (hours) Median (Q1, Q3) | 3.50 (3.00, 3.50) | 4.25 (3.50, 4.50) |
| $T_{½}$ (hours) Median (Q1, Q3) | 11.47 (7.94, 15.91) | 14.11 (11.87, 17.35) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (22.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir + 100 mg of ritonavir twice daily; CV, coefficient of variation; Q1, first quartile; Q3, third quartile

a Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

Source: Section 11.1, Table 5.4

Statistical comparisons of $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated a significant increase in GS-9137 exposures as defined by the associated 90% confidence intervals that rose above the predefined no-effect bounds (see Table 5).

**Table 5: Statistical comparisons of M4 PK parameters after administration of GS-9137/r alone or GS-9137 with lopinavir/r** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of M4 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Lopinavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 210.7 | 121.9 | 172.91 | 141.93, 210.65 |
| $AUC_{tau}$ (ng•h/mL) | 2492.3 | 1186.0 | 210.14 | 176.61, 250.03 |
| $C_{tau}$ (ng•h/mL) | 90.1 | 27.6 | 326.93 | 249.39, 428.59 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir +100 mg of ritonavir twice daily; CI, confidence interval

a N = 14/treatment with the exception of $C_{tau}$; Test Treatment n = 12; Reference treatment n = 10; Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 6.1

Changes to both GS-9137 and M4 exposures indicate that lopinavir and/or ritonavir affected both the formation and elimination of M4. The increase in GS-9137 exposures may be explained by published data indicating that lopinavir is a potent inhibitor of UGT1A1/3, which in turn would lead to a reduction in M4 formation and a corresponding increase in GS-9137 concentrations. The increase in M4 exposures may be explained by published data indicating that ritonavir is an inhibitor of MRP2, which has recently been shown to play a role in M4 elimination (AD-183-2014).

Concentrations of the hydroxylation metabolite M1 (GS-9202) were too low to provide substantive pharmacokinetic data for any of the treatments examined.

The lopinavir concentration-time profiles were similar after coadministration with GS-9137 compared to administration of lopinavir/r alone, with the 90% CIs for the ratios of the geometric least-squares means for lopinavir $C_{max}$ and $AUC_{tau}$ falling within the prespecified no-effect bounds of 80 to 125% (see Table 7). The upper bound of the 90% CI for $C_{tau}$ fell slightly below 80% (78.7%), but this was not considered to be clinically relevant because similar decreases in lopinavir trough levels are observed upon coadministration with atorvastatin and pravastatin; no dose adjustments of lopinavir/r are recommended with lopinavir/r and atorvastatin or pravastatin are taken concomitantly.

**Table 6: Statistical comparisons of lopinavir PK parameters after administration of lopinavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-6)

| Test versus Reference Comparison of Lopinavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Lopinavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 16,275.5 | 16,405.6 | 99.21 | 87.99, 111.85 |
| $AUC_{tau}$ (ng•h/mL) | 145,661.1 | 150,844.0 | 96.56 | 85.32, 109.29 |
| $C_{tau}$ (ng•h/mL) | 9625.8 | 10,423.8 | 92.34 | 78.73, 108.32 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir + 100 mg of ritonavir once daily; CI, confidence interval

a N = 13/treatment. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = lopinavir/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 6.1

Due to differences in the dose and dosing interval, ritonavir pharmacokinetics were only compared in Group 2 (lopinavir/r vs. lopinavir/r with GS-9137). In this comparison, the ritonavir concentration-time profiles were similar, with the 90% CIs for the ratio of the geometric least-squares means for ritonavir $AUC_{tau}$ falling within the prespecified no-effect bounds of 80 to 143% (see Table 7). The upper bound of the 90% CI for $C_{max}$ fell slightly above 143% (148.5%), which, given the width of the confidence interval, is likely due to the small sample size.

**Table 7: Statistical comparisons of ritonavir PK parameters after administration of lopinavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-8)

| Test versus Reference Comparison of Ritonavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| Lopinavir/r + GS-9137 vs. lopinavir/r | | | | |
| $C_{max}$ (ng/mL) | 1483.3 | 1305.7 | 113.60 | 86.89, 148.52 |
| $AUC_{tau}$ (ng•h/mL) | 7645.0 | 7449.8 | 102.62 | 86.99, 121.06 |
| $C_{tau}$ (ng/mL) | 262.4 | 297.0 | 88.34 | 74.39, 104.90 |

GS-9137 = 125 mg once daily; lopinavir/r = 400 mg of lopinavir + 100 mg of ritonavir twice daily; CI, confidence interval

a N = 13/lopinavir/r + GS-9137 vs. lopinavir/r treatment

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = lopinavir/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 6.1

***Results of safety analysis***

Coadministration of GS-9137 and lopinavir/r resulted in a higher incidence of adverse events (e.g. gastrointestinal system disorders, including diarrhea and nausea), and a lower

incidence of nervous system disorders (e.g. headache), compared to administration of GS-9137/r alone. Coadministration of GS-9137 and lopinavir/r resulted in a lower incidence of headache and a similar rate of gastrointestinal disorders. One subject had an adverse event of rash that began at the end of the GS-9137 and lopinavir/r administration period and resolved with treatment. One subject withdrew due to an adverse event unrelated to study drug (a possible methicillin-resistant *Staphylococcus aureus* abscess that required the administration of prohibited concomitant medications). There were no discontinuations due to serious adverse events or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, and lopinavir following administration of GS-9137/r 125/100 mg QD, lopinavir/r 400/100 mg BID, or coadministration of GS-9137 and lopinavir/r.

Coadministration of GS-9137/r and lopinavir resulted in a significant increase in GS-9137 exposure (52 and 75% increases in $C_{max}$ and $AUC_{tau}$, respectively). These increases are expected to be clinically relevant and necessitate a reduction in GS-9137 dose when coadministered with lopinavir/r. The pharmacokinetics of lopinavir were not substantially altered following coadministration of lopinavir/r and GS-9137 and no lopinavir dose adjustments are needed when GS-9137 and lopinavir/r are coadministered.

**Trial GS-US-183-0118**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and Maraviroc**

**Trial Period**
7 Feb to 27 Apr 2007
Final report date: 8 Feb 2008 (submitted to IND 72,177)

**Trial Site**
Northwest Kinetics, Tacoma, Washington, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 boosted by the HIV PI ritonavir (GS-9137/r) may be coadministered with the chemokine coreceptor 5 (CCR5) antagonist maraviroc (Selzentry®). This study was conducted to determine whether the pharmacokinetics of GS-9137 or maraviroc were affected by concomitant administration of GS-9137/r and maraviroc.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetics of GS-9137 or maraviroc are affected after GS-9137/r and maraviroc are coadministered compared to GS-9137/r or maraviroc administration alone

The secondary objective of the trial was to:

- evaluate the safety of administration of GS-9137/r or maraviroc alone or in combination

**Trial Design**
This was an open-label, drug interaction study. There were two groups which received two treatments each in one of two sequences. Treatments were administered for 10 days each, followed by a follow-up visit seven days after the last dose of study drug.

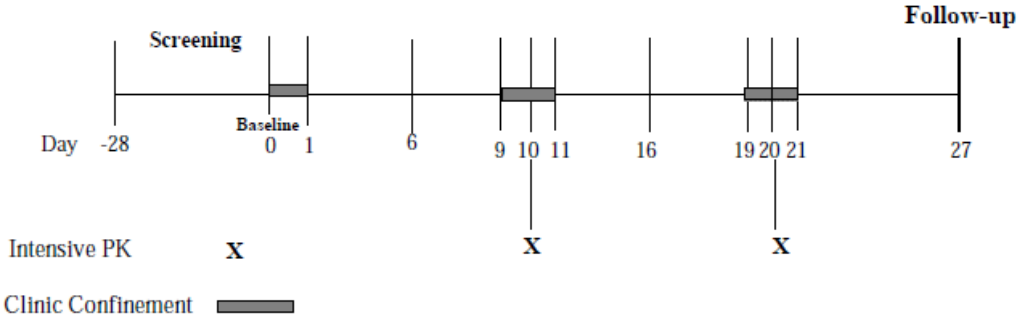
Treatment A GS-9137/r 150/100 mg QD
Treatment B GS-9137/r 150/100 mg QD and maraviroc 150 mg BID
Treatment C maraviroc 150 mg BID

Treatment D: maraviroc 150 mg BID and GS-9137/r 150/100 mg QD

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)

| | | |
|---|---|---|
| **Treatment Sequence I:** | GS-9137/r (A) | GS-9137/r & Maraviroc (B) |
| **Treatment Sequence II:** | GS-9137/r & Maraviroc (B) | GS-9137/r (A) |
| **Treatment Sequence III:** | Maraviroc (C) | Maraviroc & GS-9137/r (D) |
| **Treatment Sequence IV:** | Maraviroc & GS-9137/r (D) | Maraviroc (C) |




## Drug Administration

All doses of study drug were taken in an open-label fashion with 240 mL of water. Doses of GS-9137/r were taken immediately after a meal at approximately the same time every morning. Doses of maraviroc were taken at least 1 h before (morning or evening) or 2 h after a meal (evening). Dosing was observed at the clinic on Days 1, 6, 9, 10, 11, 16, 19, and 20 and unobserved at home on the remaining days. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 6, 9, 10, 11, 16, 19, 20, and 21.

## Rationale for Dose Selection

The GS-9137/r dose of 150/100 mg QD was selected for this study because it is one of the doses that is being used in Phase 3 clinical trials. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose given once-daily has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The maraviroc dose of 150 mg BID was selected for this study because it is the dose that is approved for use in treatment-experienced patients receiving a potent CYP3A inhibitor (e.g. a PI- or delavirdine-containing background regimen). Maraviroc is also approved in doses of 600 mg BID (for patients receiving a concomitant potent CYP3A inducer) and 300 mg BID (for patients who are not receiving a concomitant CYP3A inhibitor nor an inducer).

## Investigational Product

Tablets containing 150 mg of GS-9137 were manufactured by Gilead Sciences, Inc. (Lot AJ0609D1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 415132E21). Film-coated tablets containing 150 mg of maraviroc (Selzentry®) were manufactured by Pfizer, Ltd. (Sandwich, Kent, UK; Lot 06-045021).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

For subjects in Group 1, blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), and ritonavir. For subjects in Group 2, blood was collected for the analysis of maraviroc. Blood samples were collected on Days 10 and 20 at the times listed below:

Group 1 0:00 (predose), 1:00, 2:00, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00 hours after the GS-9137/r dose

Group 2 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, and 12:00 hours after the morning dose of maraviroc

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137 and GS-9200 and $C_{max}$ and $AUC_{tau}$ for maraviroc. All pharmacokinetic parameters were estimated using a nonlinear model derived using

standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were evaluated for validity on a profile-by-profile basis by the pharmacokineticist. Absence of a pharmacokinetic interaction was defined by the 90% confidence intervals falling between 70% and 143% for GS-9137 and ritonavir, 162% and 247% for maraviroc $AUC_{12}$, and 136% and 295% for maraviroc $C_{max}$ (due to the effects of ritonavir).

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200, GS-9202, and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511 v7) by Gilead Sciences, Inc. (Foster City, California, USA). Frozen plasma samples were received between 20 and 27 Mar 2007 and stored at -80˚C. Analysis was performed between 29 Mar and 6 Apr 2007. The first day of sample collection was 12 Mar 2007, so the maximum sample storage time was 25 days, which is within the validated long-term frozen stability duration (at -80˚C) of 268 days for GS-9137, GS-9200, GS-9202, and ritonavir.

Concentrations of maraviroc in plasma samples were determined using LC-MS/MS (Method (b) (4) 04-011) by (b) (4). Frozen plasma samples were received between 20 and 27 Mar 2007 and stored at -20˚C. Analysis was performed between 30 Mar and 6 Apr 2007. The first day of sample collection was 12 Mar 2007, so the maximum sample storage time was 25 days, which is within the validated long-term frozen stability duration (at -20˚C) of 2 years.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750.0, and 7500 ng/mL. For GS-9200 and GS-9202, the calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50, 150, and 750 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For maraviroc, the calibration standards ranged from 0.5-500 ng/mL and the QC concentrations were 1.5, 50, 150, and 4000 ng/mL. All inter-assay accuracy and precision estimates for GS-9137, GS-9200, GS-9202, and ritonavir (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations). The validation data for maraviroc were not made available to the Applicant.

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, and ritonavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Ritonavir |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 1000 | 20 to 1000 | 5 to 5000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 5 |
| Inter-Assay Precision Range[a] | 2.1% to 6.3% | 4.7% to 14.7% | 3.5% to 10.9% | 8.0% to 11.6% |
| Inter-Assay Accuracy Range[b] | -13.0% to -2.4% | -4.5% to 1.5% | -5.1% to -3.3% | -2.0% to 9.4% |
| Stability in Frozen Matrix (days) | 268 | 268 | 268 | 268 |

LLQ, lower limit of quantitation

a Percentage coefficient of variation

b Difference from nominal concentrations

Source: Appendix 10

***Trial population***

A total of 36 healthy adult subjects were enrolled in the study and received study drug; 28 subjects completed the study. Four subjects withdrew consent, three committed protocol violations (two due to incorrect dosing and one due to a positive result for cocaine on the urine drug screen), and one discontinued for safety or tolerability reasons. Of the safety analysis set (n=36), the majority of subjects were white (66.7%); the remainder were black (27.8%), American Indian or Alaska Native (2.8%), or Asian (2.8%). Subjects were predominantly male (61.1%) and had a mean age of 25 years (range: 18 to 44 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of GS-9137 and maraviroc were compared following coadministration of GS-9137/r and maraviroc versus administration of GS-9137/r or maraviroc alone.

The steady-state PK parameters for GS-9137 after administration of GS-9137/r alone and with maraviroc are listed in Table 2. The steady-state pharmacokinetic parameters of GS-9137 were similar after coadministration of GS-9137/r and maraviroc compared to after administration of GS-9137/r alone.

**Table 2: Summary of single-dose and steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with maraviroc** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 17) | GS-9137/r + Maraviroc (N = 17) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 1594.5 (39.3) | 1584.3 (25.9) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 19,129.9 (34.8) | 20,335.8 (28.7) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 404.4 (51.6) | 426.7 (36.9) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.50 (4.00, 5.00) | 4.50 (4.00, 4.50) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 11.38 (9.61, 12.47) | 11.07 (9.48, 12.05) |

GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily when administered alone or with maraviroc; maraviroc, 150 mg twice daily; %CV, percentage coefficient of variation; Q1, first quartile; Q3, third quartile

a The pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Table 5.1

Statistical comparisons of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated a lack of interaction as defined by the associated 90% confidence intervals contained within the predefined no-effect bounds (see Table 3).

**Table 3: Statistical comparisons of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or with maraviroc** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137/r + Maraviroc vs. GS-9137/r Alone** | | | | |
| $C_{max}$ (ng/mL) | 1544.45 | 1527.43 | 101.11 | 88.67, 115.31 |
| $AUC_{tau}$ (ng•h/mL) | 19,622.54 | 18,421.77 | 106.52 | 96.44, 117.65 |
| $C_{tau}$ (ng/mL) | 400.01 | 366.14 | 109.25 | 94.74, 125.99 |

GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily when administered alone or with maraviroc; maraviroc, 150 mg twice daily

a N = 17 per treatment; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment, GS-9137/r + maraviroc; Reference Treatment, GS-9137/r alone; each treatment given for 10 days

Source: Section 11.1, Table 6

Similarly to GS-9137, concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were not significantly changed following coadministration of GS-9137/r and maraviroc compared to those observed following administration of GS-9137/r alone. Steady-state M4 $C_{max}$, $AUC_{tau}$, and $C_{tau}$ were similar between the two treatments (see Table 4).

**Table 4: Summary of steady-state GS-9200 PK parameters after administration of GS-9137/r alone or with maraviroc** (PK analysis set; source: Study Report Table 7-3)

| M4 Plasma PK Parameters[a] | GS-9137/r (N = 17) | GS-9137/r + Maraviroc (N = 17) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 112.9 (54.1) | 122.2 (45.3) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 1148.4[b] (60.0) | 1189.0 (53.3) |
| $T_{max}$ (hours) Median (Q1, Q3) | 3.00 (2.00, 4.00) | 3.03 (2.00, 4.50) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 10.28[b] (8.60, 12.93) | 10.28 (7.92, 11.49) |

GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily when administered alone or with maraviroc; maraviroc, 150 mg twice daily; %CV, percentage coefficient of variation; Q1, first quartile; Q3, third quartile

a The pharmacokinetic analysis set excludes subjects who did not have evaluable profiles for the treatment pair.

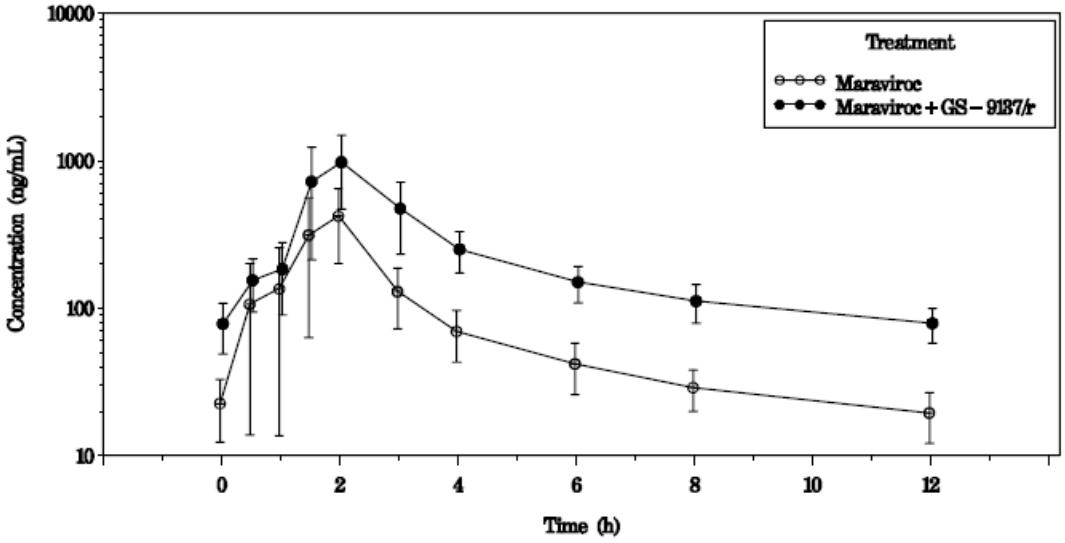
b n = 16

Source: Section 11.1, Table 5.4

Concentrations of the hydroxylation metabolite M1 (GS-9202) were too low to provide substantive pharmacokinetic data for any of the treatments examined.

The maraviroc concentration-time profiles were higher throughout the dosing interval after coadministration with GS-9137/r compared to administration of didanosine alone (see Figure 1). The upper bounds of the 90% CIs for the ratios of the geometric least-squares means for maraviroc $C_{max}$ and $AUC_{tau}$ fell above the prespecified no-effect bounds, which had prospectively been adjusted upwards to compensated for the expected increase in maraviroc plasma concentrations due to inhibition of CYP3A metabolism by ritonavir (see Table 5).

**Figure 1: Steady-state maraviroc plasma concentrations after administration of maraviroc alone or with GS-9137/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-3)




GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir; maraviroc, 150 mg twice daily administered alone or with GS-9137/r

Values presented as mean ± SD. The pharmacokinetic analysis set includes 11 subjects who had evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Figure 1.2

**Table 5: Statistical comparisons of maraviroc PK parameters after administration of maraviroc alone or with GS-9137/r** (PK analysis set; source: Study Report Table 7-5)

| Test versus Reference Comparison of Maraviroc Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **Maraviroc + GS-9137/r vs. Maraviroc Alone** | | | | |
| $C_{max}$ (ng/mL) | 885.50 | 412.16 | 214.84 | 171.43, 269.26 |
| $AUC_{tau}$ (ng•h/mL) | 2653.40 | 927.68 | 286.03 | 232.93, 351.23 |
| $C_{tau}$ (ng/mL) | 76.01 | 17.96 | 423.33 | 347.21, 516.13 |

Maraviroc, 150 mg twice daily when administered alone or with GS-9137/r; GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily

a N = 11 per treatment; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment, maraviroc + GS-9137/r; Reference Treatment, maraviroc alone; each treatment given for 10 days

Source: Section 11.1, Table 6

The ritonavir concentration-time profiles were similar after administration of GS-9137/r alone compared to administration of GS-9137/r and maraviroc, with the 90% CIs for the ratios of the geometric least-squares means for $C_{max}$, $C_{tau}$, and $AUC_{tau}$ falling within the prespecified no-effect bounds of 70% to 143% (see Table 6).

**Table 6: Statistical comparisons of ritonavir PK parameters after administration of GS-9137/r alone or with maraviroc** (PK analysis set; source: Study Report Table 7-7)

| Test versus Reference Comparison of Ritonavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137/r + Maraviroc vs. GS-9137/r Alone** | | | | |
| $C_{max}$ (ng/mL) | 834.91 | 909.94 | 91.75 | 78.36, 107.43 |
| $AUC_{tau}$ (ng•h/mL) | 6746.20 | 6873.74 | 98.14 | 91.04, 105.81 |
| $C_{tau}$ (ng/mL) | 73.03 | 70.73 | 103.25 | 88.70, 120.19 |

GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily when administered alone or with maraviroc; maraviroc, 150 mg twice daily

a N = 17 per treatment; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment, GS-9137/r + maraviroc; Reference Treatment, GS-9137/r alone; each treatment given for 10 days

Source: Section 11.1, Table 6

***Results of safety analysis***

In Group 1, the GS-9137/r plus maraviroc group experienced a greater frequency of adverse events (42.1%) compared to the GS-9137/r group (22.2%). In Group 2, the maraviroc group experienced a greater frequency of adverse events (35.7%) compared to the GS-9137/r plus maraviroc group (26.7%). Upper respiratory tract infection, headache, and hot flushes were the only adverse events reported in more than one subject (two subjects each); the latter two were considered to be related to study drug. There was one discontinuation due to an adverse event of moderate orthostatic hypotension in a subject receiving GS-9137/r plus maraviroc. There were no deaths or discontinuations due to serious adverse events during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, and maraviroc following administration of GS-9137/r 150/100 mg QD or maraviroc 150 mg BID, or coadministration of GS-9137/r and maraviroc.

Coadministration of GS-9137/r and maraviroc did not result in clinically relevant changes to the pharmacokinetics of GS-9137 compared to administration of that GS-9137/r alone. As expected, there was a significant increase (two- to four-fold) in maraviroc exposures due to the CYP3A inhibitory effects of ritonavir. The maraviroc dose selected for this trial is that approved for concomitant administration with CYP3A inhibitors; the maraviroc exposures observed in this trial are consistent with those observed when maraviroc is administered with other CYP3A inhibitors. The results of the current study indicate that no dose adjustments are needed when GS-9137/r 150/100 mg QD and maraviroc 150 mg BID are coadministered.

**Trial GS-US-183-120**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and TMC114/r**

**Trial Period**
10 May to 10 Aug 2006
Final report date: 29 Oct 2007 (submitted to IND 72,177)

**Trial Site**
Patricia Chandler, MD, Dallas, Texas, USA

**Trial Rationale**
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 may be coadministered with the PI darunavir (Prezista®), which, like GS-9137, is coadministered with the CYP3A inhibitor ritonavir (darunavir/r) in order to increase exposures. This study was conducted to determine whether the pharmacokinetics of GS-9137 or darunavir were affected by concomitant administration of GS-9137 plus darunavir/r.

**Trial Objectives**
The primary objective of the trial was to:

- determine if the pharmacokinetics of GS-9137, darunavir, or ritonavir were affected when GS-9137 (125 mg once-daily) plus darunavir/r (600/100 mg twice-daily) were coadministered compared to GS-9137/r (125/100 mg once-daily) or darunavir/r (600/100 mg twice-daily) administered alone

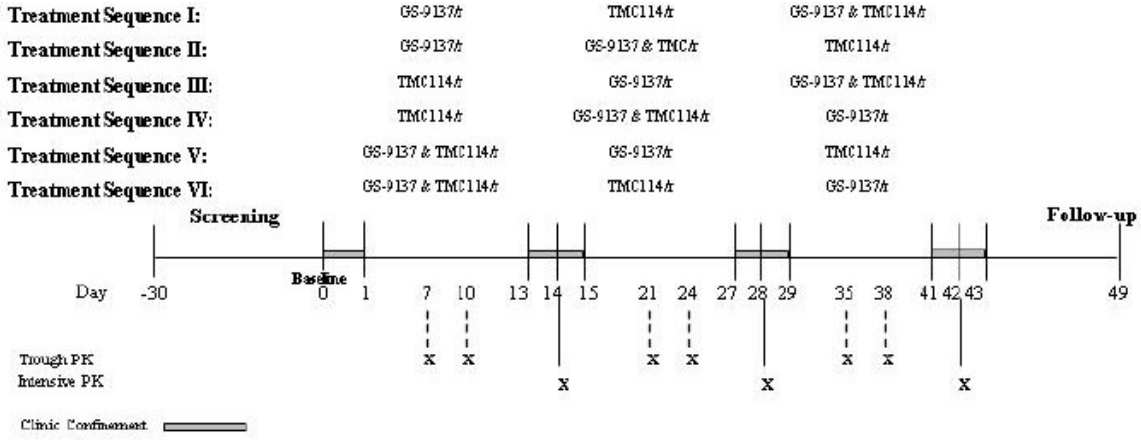
The secondary objective of the trial was to:

- evaluate the safety of coadministration of GS-9137 plus darunavir/r and GS-9137/r or darunavir/r administered alone

**Trial Design**
This was a multiple-sequence, open-label, multiple-dose drug interaction study. Subjects were randomized to one of six sequences (1 to 6) of three treatments (A, B, or C). Each treatment was administered over a period of 14 days for a total treatment period of 42 consecutive days, followed by a follow-up visit seven days after the last dose of study drug. All treatments were administered in the fed state.

Treatment A GS-9137/r 125/100 mg QD
Treatment B darunavir/r 300/100 mg BID
Treatment C GS-9137 125 mg QD plus darunavir/r 300/100 mg BID

**Figure 1: Study schema** (source: Study Report Figure 5-1)




GS-9137/r (125/100 mg once-daily), darunavir (TMC114)/r (600/100 mg twice-daily)

## Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water within 5 minutes of completion a meal at approximately the same time every day (e.g. 8:00 AM for GS-9137 and morning doses of darunavir/r and 8:00 PM for evening doses of darunavir/r). Standardized meals (400 kcal and 13 g of fat) were provided at the clinic on the mornings of Days 1, 14, 15, 28, 29, and 42 and the evenings of Days 1, 13, 14, 27, 28, 41, and 42. On days of intensive PK sampling (Days 14, 28, and 42), water was restricted from 1 h before until 2 h after study drug administration and food was restricted until after the 4 h blood draw, at which time a standardized meal was provided.

## Rationale for Dose Selection

The GS-9137 dose of 125 mg QD boosted with ritonavir 100 mg QD was selected for this study because it is the highest dose examined in the ongoing Phase 2 study and is expected to provide an upper limit of GS-9137 exposures in upcoming Phase 3 studies. The darunavir/r dose of 600/100 mg BID is that approved for the treatment of HIV. Study drugs were administered for 14 days in order to evaluate steady-state pharmacokinetics.

## Investigational Product

Tablets containing 150 mg of GS-9137 were manufactured by Japan Tobacco, Inc. and [redacted] (b) (4) Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 366592E21). Tablets containing 300 mg of darunavir were manufactured by Tibotec, Inc. (Titusville, New Jersey; Lot PD1842).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood samples for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, and/or darunavir in plasma were collected on Days 14, 28, and 42 at the times (in hours post-dose) listed below:

| | |
|---|---|
| Treatments A and C | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, 20:00, 22:00, and 24:00 |
| Treatment B | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, and 12:00 |

In addition, blood samples were collected for the analysis of GS-9137 plasma trough concentrations on Days 7, 10, 21, 24, 35, and 38. GS-9137 plasma protein binding was also determined in samples collected 4 h post-dose (approximate GS-9137 $C_{max}$) on Day 14 from subjects receiving Treatment A.

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137, GS-9200, ritonavir, and darunavir. All pharmacokinetic parameters

were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable.

Differences between the primary pharmacokinetic parameters for Treatments A or B and Treatment C were calculated using SAS® (SAS Institute, Cary, North Carolina, USA) following natural log transformation. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143% for GS-9137 and 80-143% for darunavir.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200, GS-9202, and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511 v1) by Gilead Sciences, Inc. (Durham, North Carolina, USA). Frozen plasma samples were received between 7 Jun and 22 Aug 2006 and stored at -80˚C. Analyses were completed by 31 Aug 2006. The first day of sample collection was 27 May 2006, so the maximum sample storage time was 96 days, which is within the validated long-term frozen stability duration (at -70˚C) of 102 days for ritonavir and 585 days for GS-9137, GS-9200, and GS-9200.

Concentrations of darunavir in plasma samples were determined using LC-MS/MS (Method R319064/LCMS/004-b) by (b) (4) . Frozen plasma samples were received between 13 and 28 Jul 2006 and stored at -20˚C. Analyses were performed between 28 Jul and 22 Aug 2006. The first day of sample collection was 27 May 2006, so the maximum sample storage time was 87 days, which is within the validated long-term frozen stability duration (at -20˚C) of 563 days.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For GS-9200 and GS-9202, the calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50, 150, and 750 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For darunavir, the calibration standards ranged from 5-10000 ng/mL and the QC concentrations were 13.2, 257, and 7560 ng/mL. All inter-assay accuracy and precision estimates for GS-9137, GS-9200, GS-9202, ritonavir, and darunavir (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, ritonavir, and darunavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 (GS-9200) | M1 (GS-9202) | Darunavir | | Ritonavir |
|---|---|---|---|---|---|---|
| | | | | Low | High | |
| Linear Range (ng/mL) | 20 to 10,000 | 20 to 10,000 | 20 to 10,000 | 25 to 2000 | 1000 to 20,000 | 5 to 5000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 25 | 1,000 | 5 |
| Inter-Assay Precision Range[a] | 2.1% to 6.3% | 4.7% to 14.7% | 3.5% to 10.9% | 5.1% to 7.0% | 4.8% to 7.2% | 8.0% to 11.6% |
| Inter-Assay Accuracy Range[b] | −13.0% to −2.4% | −4.5% to 1.5% | −5.1% to −3.3% | −5.2% to −1.6% | −7.6% to 4.0% | −2.0% to 9.4% |
| Stability in Frozen Matrix (days) | 93[c] | 93[c] | 93[c] | 26 | 21 | 107 |

LLQ, lower limit of quantitation

a Relative standard deviation

b Difference from nominal concentrations

c Data on file at (b) (4)

Source: Appendix 10

***Trial population***

A total of 33 healthy adult subjects were enrolled in the study and received study drug; 20 subjects completed the study. Thirteen subjects discontinued the study early: seven subjects withdrew consent; three were withdrawn by the investigator for safety or tolerability reasons (two due to darunavir-related rash and one due to anemia that was not considered to be related to study drug); one was withdrawn at the investigator's discretion (positive pregnancy test); one was lost to follow-up; and one was withdrawn because of a protocol violation (positive test for amphetamines). Of the safety analysis set (n=33), the majority of subjects were white (63.6%); the remainder were black. Subjects were predominantly male (57.6%) with a mean age of 30 years (range: 18 to 45 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of GS-9137, M4, ritonavir, and darunavir were compared following coadministration of GS-9137 and darunavir/r or GS-9137/r or darunavir/r alone.

The pharmacokinetic parameters of GS-9137 were similar following coadministration of GS-9137 and darunavir/r compared to administration of GS-9137/r alone (see Table 2). The 90% CI values for the ratios of the geometric least-squares means of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ were within the prespecified no-effect bounds of 70-143% (see Table 3), indicating no significant changes in GS-9137 pharmacokinetics after coadministration with darunavir/r.

**Table 2: Summary of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with darunavir/r** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 Plasma PK Parameters[a] | GS-9137/r (N = 21) | GS-9137 + Darunavir/r (N = 21) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 1978.9 (39.3) | 2201.2 (31.6) |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 20288.4 (36.5) | 22319.3 (34.8) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 421.0 (46.7) | 512.5 (52.1) |
| $T_{max}$ (hours) Median (Q1, Q3) | 4.00 (3.50, 4.00) | 4.00 (4.00, 4.47) |
| $T_{1/2}$ (hours) Median (Q1, Q3) | 12.49 (10.64, 16.97) | 14.74 (10.01, 23.48) |
| $T_{last}$ (hours) Median (Q1, Q3) | 24.00 (24.00, 24.00) | 24.00 (24.00, 24.00) |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once-daily, darunavir/r = 600 mg of darunavir + 100 mg of ritonavir twice-daily, CV = coefficient of variation, Q1 = first quartile, Q3 = third quartile

a The pharmacokinetic analysis set includes 21 subjects for each treatment.

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with darunavir/r** (PK analysis set; source: Study Report Table 7-2)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Darunavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 2150.80 | 1905.23 | 112.89 | 102.65, 124.15 |
| $AUC_{tau}$ (ng•h/mL) | 21426.63 | 19511.96 | 109.81 | 99.09, 121.69 |
| $C_{tau}$ (ng/mL) | 452.82 | 383.72 | 118.01 | 106.01, 131.37 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir, once-daily; darunavir/r = 600 mg of darunavir + 100 mg of ritonavir, twice-daily, CI = confidence interval

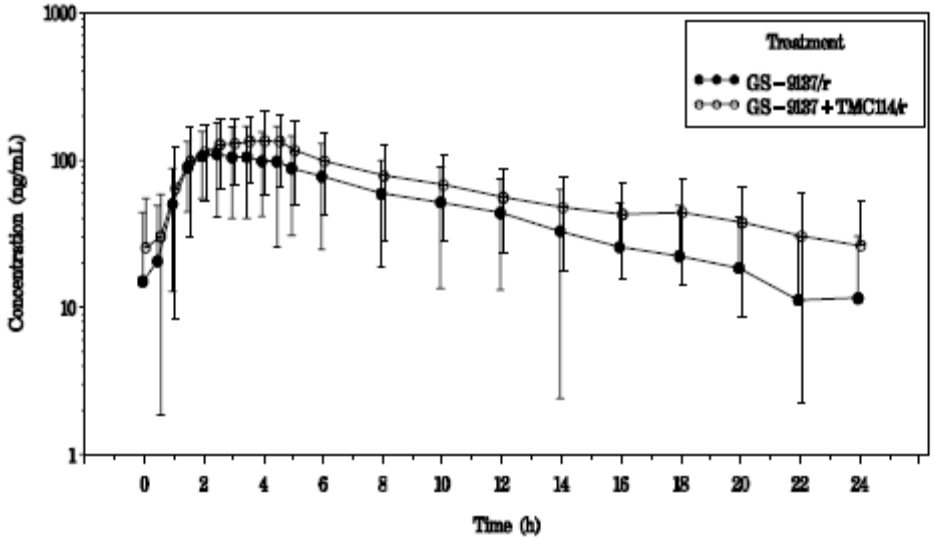
a The pharmacokinetic analysis set includes 21 subjects for each treatment.

b Test Treatment = GS-9137 + darunavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 7

Mean plasma concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) trended higher following coadministration of GS-9137 and darunavir compared to those observed following administration of GS-9137/r alone (Figure 1). The upper bounds of the 90% CIs for M4 $C_{tau}$ and $AUC_{tau}$ fell above 143%, indicating a significant increase in M4 exposures in the presence of darunavir (see Table 4). The M4:parent ratio remained less than 10%; given the relative potencies of GS-9137 and M4, this implies that M4 did not contribute to antiviral activity. The increase in M4 exposures may be explained by published data indicating that PIs inhibit MRP2, which has recently been shown to play a role in M4 elimination (AD-183-2014).

**Figure 1: Steady-state M4 plasma concentrations after administration of GS-9137/r alone or GS-9137 with darunavir/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Values presented as mean ± SD. The pharmacokinetic analysis set includes 21 subjects for each treatment. Subjects 1001, 1007, 1014, 1020, 1024, 1026, 1027, 1030, 1107, and 1114 did not have evaluable pharmacokinetic profiles for either treatment pair and were excluded from the pharmacokinetic analysis set and summary statistics. Subjects 1005 and 1023 were excluded for GS-9137/r only, and Subject 1124 was excluded for darunavir/r only.

Source: Section 11.1, Figure 1.4

**Table 4: Statistical comparisons of M4 (GS-9200) PK parameters after administration of GS-9137/r alone or GS-9137 with darunavir/r** (PK analysis set; source: Study Report Table 7-4)

| Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| GS-9137 + Darunavir/r vs. GS-9137/r | | | | |
| $C_{max}$ (ng/mL) | 140.47 | 119.89 | 117.17 | 110.03, 124.77 |
| $AUC_{tau}$ (ng•h/mL) | 1412.25 | 1061.75 | 133.01 | 121.21, 145.96 |
| $C_{tau}$ (ng/mL) | 37.11 | 22.78 | 162.90 | 137.43, 193.09 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir, once-daily; darunavir/r = 600 mg of darunavir + 100 mg of ritonavir, twice-daily, CI = confidence interval

a The pharmacokinetic analysis set includes 21 subjects for GS-9137/r and GS-9137 + darunavir/r with regard to $C_{max}$ and $AUC_{tau}$, but 7 and 13 subjects, respectively, with regard to $C_{tau}$.

b Test Treatment = GS-9137 + darunavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 7

The concentration-time profiles of darunavir were similar following coadministration of GS-9137 and darunavir/r compared to administration of darunavir/r alone. Darunavir pharmacokinetic parameters were similar and the 90% CI values for the ratios of the geometric least-squares means of darunavir $C_{max}$ and $AUC_{tau}$ were within the

prespecified no-effect bounds of 80-143% (see Table 5). The lower bound of the 90% CI for darunavir $C_{tau}$ was 73.74% (Table 5), but this decrease is not considered to be clinically relevant. Similar decreases in darunavir trough concentrations are observed following coadministration of darunavir/r and nevirapine and sertraline; no darunavir dose adjustments are recommended following coadministration of these medications and darunavir/r.

**Table 5: Statistical comparisons of M4 (GS-9200) PK parameters after administration of GS-9137/r alone or GS-9137 with darunavir/r** (PK analysis set; source: Study Report Table 7-6)

| Test versus Reference Comparison of Darunavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **GS-9137 + Darunavir/r vs. GS-9137/r** | | | | |
| $C_{max}$ (ng/mL) | 6212.68 | 6946.69 | 89.43 | 84.96, 94.14 |
| $AUC_{tau}$ (ng•h/mL) | 47593.27 | 53636.68 | 88.73 | 82.34, 95.63 |
| $C_{tau}$ (ng/mL) | 2583.65 | 3121.65 | 82.77 | 73.74, 92.90 |

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir, once-daily; darunavir/r = 600 mg of darunavir + 100 mg of ritonavir, twice-daily, CI = confidence interval

a The pharmacokinetic analysis set includes 22 subjects for darunavir/r and GS-9137 + darunavir/r with regard to $C_{max}$ and $AUC_{tau}$, but 21 subjects for $C_{tau}$ in the Test Treatment.

b Test Treatment = GS-9137 + darunavir/r, Reference Treatment = darunavir/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 7

Due to differences in the dose and dosing interval, ritonavir pharmacokinetics were only compared between Treatments B and C (darunavir/r vs. darunavir/r with GS-9137). In this comparison, the ritonavir concentration-time profiles were similar, with the 90% CIs for the ratios of the geometric least-squares means for ritonavir $AUC_{tau}$, $C_{tau}$, and $C_{max}$ falling within the prespecified no-effect bounds of 70 to 143% (see Table 6), indicating that ritonavir pharmacokinetics were not significantly altered when darunavir/r was coadministered with GS-9137.

**Table 6: Statistical comparisons of ritonavir PK parameters after administration of lopinavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-8)

| Test versus Reference Comparison of Ritonavir Plasma PK Parameters[a] | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio (%) | 90% CI |
|---|---|---|---|---|
| | Test[b] (Mean) | Reference[b] (Mean) | | |
| **Darunavir/r + GS-9137 vs. Darunavir/r** | | | | |
| $C_{max}$ (ng/mL) | 1332.77 | 1492.12 | 89.32 | 74.23, 107.47 |
| $AUC_{tau}$ (ng/mL) | 6264.61 | 7276.57 | 86.09 | 76.71, 96.62 |
| $C_{tau}$ (ng/mL) | 253.93 | 308.86 | 82.22 | 73.48, 91.99 |

GS-9137 = 125 mg, once-daily; darunavir /r = 600 mg of darunavir + 100 mg of ritonavir, twice-daily, CI = confidence interval

a The pharmacokinetic analysis set includes 22 subjects for darunavir/r and GS-9137 plus darunavir/r. Subjects 1001, 1007, 1014, 1020, 1024, 1026, 1027, 1030, 1107, and 1114 did not have evaluable pharmacokinetic profiles for each treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + darunavir/r, Reference Treatment = darunavir/r, each treatment given for 14 consecutive days

Source: Section 11.1, Table 7

***Results of pharmacokinetic analyses***

The binding of GS-9137 to plasma proteins was determined in plasma samples collected from healthy subjects (n=24) after 14 days of GS-9137/r administration. The unbound fraction of GS-9137 in plasma was 0.96 ± 0.10% (mean ± SD) over the range of concentrations observed (713.3-3886.5 ng/mL). This is similar to the value observed in HIV-1 infected patients (1.19 ± 0.21%, mean ± SD).

***Results of safety analysis***

The incidence of adverse events was highest in subjects treated with GS-9137 with darunavir/r and lowest in subjects treated with GS-9137/r alone. Headache and diarrhea were the most common AEs across the treatment groups. Rash was observed in three subjects receiving darunavir/r-containing treatments; two subjects discontinued the study due to this AE. One subject also discontinued due to Grade 1 anemia while receiving GS-9137/r. There were no deaths or discontinuations due to serious adverse events during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, ritonavir, and darunavir following administration of GS-9137/r 125/100 mg QD, darunavir/r 600/100 mg BID, or coadministration of GS-9137 and darunavir/r.

Coadministration of GS-9137 and darunavir/r did not result in clinically relevant changes to the exposures of each individual component compared to administration of that component alone. Darunavir $C_{tau}$ was significantly lower in the presence of GS-9137, but the decrease was not considered clinically relevant. M4 exposures were higher in the presence of darunavir, although antiviral activity was not expected to be affected, since the M4:parent ratio remained less than 10%. The results of the current study indicate that no dose adjustments are needed when GS-9137 125 mg QD and darunavir/r 600/100 mg BID are coadministered.

## Trial GS-US-183-0123
## A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of GS-9137/r and Fosamprenavir/r

### Trial Period
21 Sept to 21 Nov 2006
Final report date: 31 May 2007 (submitted to IND 72,177)

### Trial Site
SeaView Resarch, Miami, Florida, USA

### Trial Rationale
GS-9137 (elvitegravir, EVG) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). GS-9137 is a substrate of CYP3A; when given in combination with ritonavir, GS-9137 exposures are elevated due to the inhibition of CYP3A activity by ritonavir. In clinical practice, GS-9137 may be coadministered with fosamprenavir (Lexiva®), a prodrug of the PI amprenavir. Like GS-9137, fosamprenavir is coadministered with the CYP3A inhibitor ritonavir (fosamprenavir/r) in order to increase exposures. This study was conducted to determine whether the pharmacokinetics of GS-9137 or fosamprenavir were affected by concomitant administration of GS-9137 plus fosamprenavir/r.

### Trial Objectives
The primary objective of the trial was to:

- Determine if the pharmacokinetic parameters of GS-9137, amprenavir, or ritonavir are affected upon coadministration of GS-9137 (125 mg once daily) plus fosamprenavir/r (700/100 mg twice daily) compared to GS-9137/r or fosamprenavir/r administered alone

The secondary objective of the trial was to:

- evaluate the safety of coadministration of GS-9137 plus fosamprenavir/r, and GS-9137/r or fosamprenavir/r administered alone

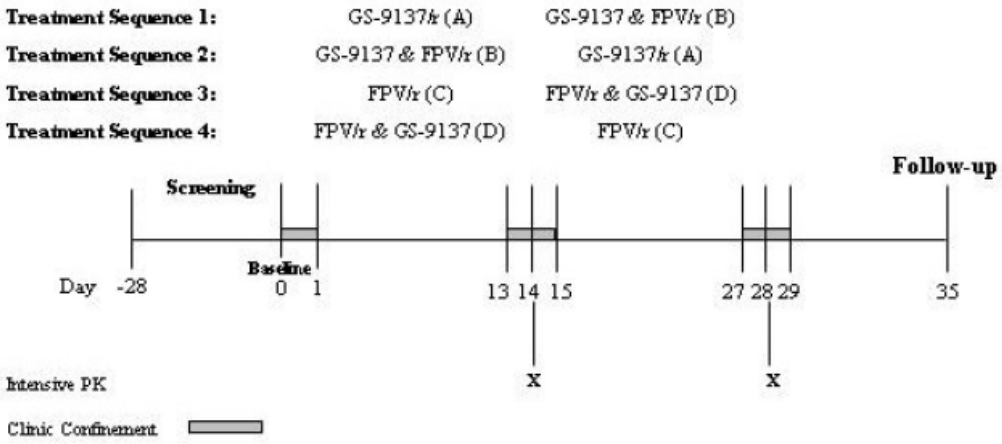
### Trial Design
This was an open-label, multiple-dose drug interaction study. There were four treatment sequences (Treatment Sequences 1 through 4), each containing two of four treatments (Treatments A through D). Each treatment was administered over a period of 14 days, followed by a follow-up visit seven days after the last dose of study drug.

Treatment A GS-9137/r 125/100 mg QD

Treatment B GS-9137 125 mg QD plus fosamprenavir/r 700/100 mg BID
Treatment C fosamprenavir/r 700/100 mg BID
Treatment D fosamprenavir/r 700/100 mg BID plus GS-9137 125 mg QD

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




### Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water immediately after a meal at approximately the same time every morning (GS-9137/r and the morning dose of fosamprenavir/r) or evening (the evening dose of fosamprenavir/r). All morning doses were observed at the clinic; evening doses were observed when subjects were confined to the clinic. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 1, 14, and 28. A light breakfast was also provided on Days 2 through 13 and 15 through 27, just before observed study drug dosing. Evening meals that were similar in calorie and fat content were provided on Days 13, 14, 27, and 28. On days of intensive PK sampling (Days 14 and 28), water was restricted from 1 h before until 2 h after study drug administration and food was restricted until after the 4 h blood draw, at which time a standardized meal was provided.

### Rationale for Dose Selection

The GS-9137/r dose of 125/100 mg QD was selected for this study because it is the highest dose being tested in an ongoing Phase 2 study; this dose is expected to provide an upper limit of drug exposures expected in planned clinical studies. The ritonavir dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose given once-daily has been shown to increase GS-9137 exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The fosamprenavir/r dose of 700/100 mg BID was selected for this study because it is the same dose that is currently marketed for the treatment of HIV in treatment-experienced adults.

**Investigational Product**

Tablets containing 125 mg of GS-9137 were manufactured by Gilead Sciences, Inc. (Foster City, California, USA; Lot AJ603A1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lost 426672E21 and 426632E21). Tablets containing 700 mg of fosamprenavir calcium (Lexiva®) were manufactured by GlaxoSmithKline (Research Triangle Park, North Carolina, USA; Lot R248867).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of GS-9137, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, and/or amprenavir were collected on Days 14 and 28 at the times (in hours post-dose) listed below:

| | |
|---|---|
| Treatments A and B | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00, and 24:00 |
| Treatments C and D | 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, and 12:00 |

**Analytical Plan**

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for GS-9137, GS-9200, ritonavir, and amprenavir. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were evaluated for validity on a profile-by-profile basis by the pharmacokineticist. Absence of a pharmacokinetic interaction was defined by the 90% confidence intervals falling between 70% and 143%.

## Trial Results

### *Bioanalytical methods*

Concentrations of GS-9137, GS-9200, GS-9202, and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511 v4) by Gilead Sciences, Inc. (Durham, North Carolina, USA). Frozen plasma samples were received between 25 Oct and 14 Nov 2006 and stored at -80˚C. Analysis was performed between 9 Nov and 8 Dec 2006. The first day of sample collection was 3 Oct 2006, so the maximum sample storage time was 66 days, which is within the validated long-term frozen stability duration (at -80˚C) of 93 days for GS-9137, GS-9200, and 9202 and 102 days for ritonavir.

Concentrations of abacavir in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0660) by (b) (4). Frozen plasma samples were received between 25 Oct and 8 Nov 2006 and stored at -70˚C. Analysis was performed between 14 and 28 Nov 2006. The first day of sample collection was 17 Oct 2006, so the maximum sample storage time was 42 days, which is within the validated long-term frozen stability duration (at -70˚C) of 42 days.

The GS-9137 calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750.0, and 7500 ng/mL. For GS-9200 and GS-9202, the calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50, 150, and 750 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For amprenavir, the calibration standards ranged from 100-10000 ng/mL and the QC concentrations were 100, 300, 2000, 6000, and 8000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for GS-9137, GS-9200, GS-9202, ritonavir, and amprenavir in human plasma** (source: Study Report Table 5-3)

| | GS-9137 | M4 | M1 | Ritonavir | Amprenavir |
|---|---|---|---|---|---|
| Linear Range (ng/mL) | 20–10,000 | 20–1000 | 20–1000 | 5–5000 | 100–10,000 |
| LLQ (ng/mL) | 20 | 20 | 20 | 5 | 100 |
| Inter-Assay Precision Range[a] | 2.1% to 6.3% | 4.7% to 14.7% | 3.5% to 10.9% | 8.0% to 11.6% | 6.2% to 8.5% |
| Inter-Assay Accuracy Range[b] | −13.0% to −2.4% | −4.5% to 1.5% | −5.1% to −3.3% | −2.0% to 9.4% | −2.1% to 6.4% |
| Stability in Frozen Matrix (days) | 93 | 93 | 93 | 102 | 42 |

LLQ, lower limit of quantitation

a Percentage coefficient of variation

b Difference from nominal concentrations

Source: Appendix 10

***Trial population***

A total of 32 healthy adult subjects were enrolled in the study and received study drug; 30 subjects completed the study. Two subjects discontinued the study early: one was lost to follow-up and the other was withdrawn due to a protocol violation (positive result for cocaine on the Day 13 urine screen). Of the safety analysis set (n=32), the majority of subjects were white (75.0%); the remainder were black (21.9%) or of other ancestry (3.1%). Half of the subjects were female (50.0%). Subjects had a mean age of 31 years (range: 18 to 45 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of GS-9137 and amprenavir were compared following coadministration of GS-9137 and fosamprenavir/r versus administration of GS-9137/r or fosamprenavir/r alone.

The PK parameters for GS-9137 after administration of GS-9137/r alone and GS-9137 with fosamprenavir/r are listed in Table 2. The steady-state pharmacokinetic parameters of GS-9137 were similar after coadministration of GS-9137 and fosamprenavir/r and after administration of GS-9137/r alone. Statistical comparisons of GS-9137 $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated a lack of interaction as defined by the associated 90% confidence intervals contained within the predefined no-effect bounds of 70% to 143% (see Table 3).

**Table 2: Summary of single-dose and steady-state GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with fosamprenavir/r** (PK analysis set; source: Study Report Table 7-1)

| GS-9137 PK Parameter | GS-9137/r Alone (N = 16) | GS-9137 + FPV/r (N = 16) |
|---|---|---|
| $C_{max}$ (ng/mL), Mean (%CV) | 1926.7 (18.8) | 1952.7 (25.8) |
| $AUC_{tau}$ (ng•h/mL), Mean (%CV) | 18,148.6 (19.9) | 17,150.3 (25.0) |
| $C_{tau}$ (ng/mL), Mean (%CV) | 310.9 (44.4) | 302.9 (44.4) |
| $T_{½}$ (h), Median (Q1, Q3) | 9.10 (7.89, 9.49) | 8.85 (7.40, 10.13) |
| $T_{max}$ (h), Median (Q1, Q3) | 4.00 (4.00, 4.50) | 4.00 (4.00, 4.50) |

GS-9137/r, 125 mg of GS-9137 plus 100 mg of ritonavir administered once daily; GS-9137, 125 mg of GS-9137 administered once daily; FPV/r, 700 mg of fosamprenavir and 100 mg of ritonavir administered twice daily; %CV, percentage coefficient of variation; Q1, first quartile; Q3, third quartile

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of steady-state GS-9137 PK parameters after administration of GS-9137/r alone or GS-9137 with fosamprenavir/r** (PK analysis set; source: Study Report Table 7-2)

| Test vs. Reference Treatment PK Parameter | Geometric Least Squares Means | | Geometric Least Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[a] (Mean) | Reference[a] (Mean) | | |
| **GS-9137 + FPV/r versus GS-9137/r (N = 16)** | | | | |
| $C_{max}$ (ng/mL) | 1891.3 | 1893.8 | 99.87 | 90.62, 110.06 |
| $AUC_{tau}$ (ng•h/mL) | 16,631.5 | 17,811.5 | 93.38 | 87.89, 99.21 |
| $C_{tau}$ (ng/mL) | 276.5 | 287.2 | 96.28 | 89.83, 103.20 |

GS-9137, 125 mg of GS-9137 administered once daily; FPV/r, 700 mg of fosamprenavir and 100 mg of ritonavir administered twice daily; GS-9137/r, 125 mg of GS-9137 and 100 mg of ritonavir administered once daily

a Test, GS-9137 plus FPV/r; Reference, GS-9137/r; each treatment administered for 14 days

Source: Section 11.1, Table 6

Plasma concentrations of the GS-9137 glucuronide metabolite M4 (GS-9200) were also similar following coadministration of GS-9137 and fosamprenavir/r compared to those observed following administration of GS-9137/r alone (see Table 4). For both treatments, M4 exposures were less than 10% of the corresponding GS-9137 exposures.

**Table 4: Summary of steady-state GS-9200 PK parameters after administration of GS-9137/r alone or GS-9137 with fosamprenavir/r** (PK analysis set; source: Study Report Table 7-3)

| M4 PK Parameter | GS-9137/r Alone (N = 16) | GS-9137 + FPV/r (N = 16) |
|---|---|---|
| $C_{max}$ (ng/mL), Mean (%CV) | 152.0 (40.2) | 154.8 (39.6) |
| $AUC_{tau}$ (ng•h/mL), Mean (%CV) | 1279.5 (37.2) | 1335.9 (33.4) |
| $T_{½}$ (h), Median (Q1, Q3) | 9.20 (7.62, 11.25) | 9.31 (7.33, 10.95) |
| $T_{max}$ (h), Median (Q1, Q3) | 2.00 (1.75, 3.25) | 4.00 (3.00, 4.50) |

GS-9137/r, 125 mg of GS-9137 and 100 mg of ritonavir administered once daily; GS-9137, 125 mg of GS-9137 administered once daily; FPV/r, 700 mg of fosamprenavir and 100 mg of ritonavir administered twice daily; %CV, percentage coefficient of variation; Q1, first quartile; Q3, third quartile

Source: Section 11.1, Table 5.4

Concentrations of the hydroxylation metabolite M1 (GS-9202) were too low to provide substantive pharmacokinetic data for any of the treatments examined.

The amprenavir concentration-time profiles were similar after coadministration with GS-9137 compared to administration of fosamprenavir/r alone, with the 90% CIs for the ratios of the geometric least-squares means for amprenavir $C_{max}$, $AUC_{inf}$, and $AUC_{0\text{-last}}$ falling within the prespecified no-effect bounds of 70 to 143% (see Table 5).

**Table 5: Statistical comparisons of amprenavir PK parameters after administration of fosamprenavir/r alone or with GS-9137** (PK analysis set; source: Study Report Table 7-5)

| Test vs. Reference Treatment PK Parameter | Geometric Least Squares Means | | Geometric Least Squares Mean Ratio (%) | 90% Confidence Interval |
|---|---|---|---|---|
| | Test[a] (Mean) | Reference[a] (Mean) | | |
| **GS-9137 + FPV/r versus FPV/r (N = 15)** | | | | |
| $C_{max}$ (ng/mL) | 6879.6 | 7027.4 | 97.90 | 90.51, 105.88 |
| $AUC_{tau}$ (ng•h/mL) | 51,445.4 | 51,936.8 | 99.05 | 90.60, 108.29 |
| $C_{tau}$ (ng/mL) | 2838.4 | 2805.5 | 101.17 | 85.33, 119.96 |

GS-9137, 125 mg of GS-9137 administered once daily; FPV/r, 700 mg of fosamprenavir and 100 mg of ritonavir administered twice daily

a Test, GS-9137 plus FPV/r; Reference, FPV/r; each treatment administered for 14 days

Source: Section 11.1, Table 6

The pharmacokinetic parameters of ritonavir were similar after administration of GS-9137/r alone (Treatment A) compared to administration of GS-9137 with fosamprenavir/r (Treatment B), as well as after administration of fosamprenavir/r alone (Treatment C) compared to administration of fosamprenavir/r with GS-9137 (Treatment D), as is seen in Table 6.

**Table 6: Summary of steady-state ritonavir PK parameters after administration of GS-9137/r, GS-9137 with fosamprenavir/r, fosamprenavir/r, or fosamprenavir/r with GS-9137** (PK analysis set; source: Study Report Table 7-6)

| Ritonavir PK Parameter[a] | GS-9137/r (Trt A) (N = 16) | GS-9137 + FPV/r (Trt B) (N = 16) | FPV/r (Trt C) (N = 15) | FPV/r + GS-9137 (Trt D) (N = 15) |
|---|---|---|---|---|
| $C_{max}$ (ng/mL), Mean (%CV) | 1018.5 (42.9) | 992.4 (50.1) | 1191.9 (48.6) | 1076.8 (51.1) |
| $AUC_{tau}$ (ng•h/mL), Mean (%CV) | 6242.0 (30.1) | 4395.4 (37.2) | 4899.5 (31.6) | 4684.1 (34.3) |
| $C_{tau}$ (ng/mL), Mean (%CV) | 60.7 (47.5) | 210.0 (45.8) | 159.8 (43.0) | 158.5 (40.9) |
| $T_{½}$ (h), Median (Q1, Q3) | 7.86 (5.22,12.44) | 3.81 (2.58, 4.10) | 3.01 (2.34, 3.51) | 3.20 (2.94, 3.47) |
| $T_{max}$ (h), Median (Q1, Q3) | 4.50 (4.50, 5.00) | 4.50 (4.00, 4.50) | 4.00 (3.50, 4.00) | 4.00 (4.00, 5.00) |

GS-9137/r, 125 mg of GS-9137 and 100 mg of ritonavir administered once daily; GS-9137, 125 mg of GS-9137 administered once daily; FPV/r, 700 mg of fosamprenavir and 100 mg of ritonavir administered twice daily; %CV, percentage coefficient of variation; Q1, first quartile; Q3, third quartile

a The pharmacokinetic analysis set for Group 1 (Treatments A and B) includes 16 subjects. The pharmacokinetic analysis set for Group 2 (Treatments C and D) includes 15 subjects, excluding one subject who did not have evaluable pharmacokinetic profiles for the treatment pair.

Source: Section 11.1, Table 5.3

***Results of safety analysis***

In Group 1, coadministration of GS-9137 and fosamprenavir/r (Treatment 1) was associated with a higher incidence of adverse events; the only adverse event reported in more than one subject was rash (three subjects receiving GS-9137/r alone and one receiving GS-9137 with fosamprenavir/r). In Group 2, the frequency of adverse events was similar between Treatments C and D (fosamprenavir/r with or without GS-9137), although there was a higher incidence of gastrointestinal events and upper respiratory tract infection with fosamprenavir/r alone. There were no discontinuations due to adverse events, serious adverse events, or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of GS-9137, its glucuronide metabolite M4, and amprenavir following administration of GS-9137/r 125/100 mg QD or fosamprenavir/r 700/100 mg BID, or coadministration of GS-9137 and fosamprenavir/r.

Coadministration of GS-9137 and fosamprenavir/r did not result in clinically relevant changes to the pharmacokinetics of each individual component compared to administration of that component alone. The results of the current study indicate that no dose adjustments are needed when GS-9137 125 mg QD and fosamprenavir/r 700/100 mg BID are coadministered.

## Trial GS-US-183-0125
## A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of Elvitegravir (EVG) and Rifabutin

### Trial Period
1 Oct to 14 Dec 2007
Final report date: 9 Sept 2008 (submitted to IND 72,177)

### Trial Site
Covance Inc., Honolulu, Hawaii, USA

### Trial Rationale
Elvitegravir (EVG, GS-9137) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). Elvitegravir is a substrate of CYP3A; when given in combination with ritonavir, elvitegravir exposures are elevated due to the inhibition of CYP3A activity by ritonavir. Rifabutin is an antibiotic used to help prevent *Mycobacterium avium* disease in patients with HIV infection; it will likely be coadministered with EVG in clinical practice. Rifabutin is a CYP3A substrate and requires a dose reduction when administered with ritonavir-boosted PIs. This study was conducted to determine whether the pharmacokinetics of elvitegravir, rifabutin, or 25-O-desacetyl rifabutin were affected by concomitant administration of EVG/r and rifabutin.

### Trial Objectives
The primary objective of the trial was to:

- evaluate the pharmacokinetics of elvitegravir/r alone and with rifabutin
- evaluate the pharmacokinetics of rifabutin and 25-O-desacetyl rifabutin alone and with elvitegravir/r

The secondary objective of the trial was to:

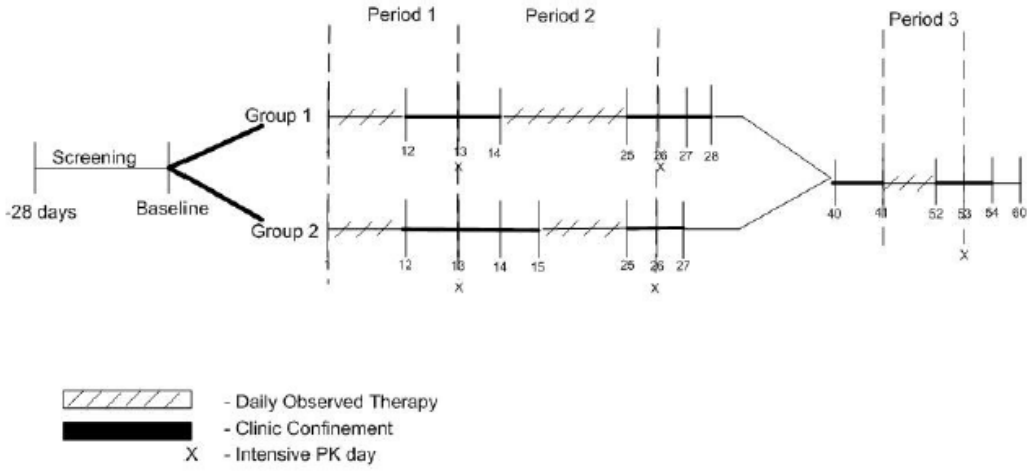
- evaluate the safety of administration of elvitegravir/r alone and in combination with rifabutin

### Trial Design
This was an open-label steady-state drug interaction study. Subjects were randomized to receive one of two sequences (Groups 1 and 2), with each sequence consisting of two 13 day treatment periods (Treatments A and B), followed by a 13 day washout period and a 13 day treatment period (Treatment C). A follow-up visit was scheduled for seven days after the last dose of study drug.

Treatment A elvitegravir/r 300/100 mg QD
Treatment B elvitegravir/r 300/100 mg QD plus rifabutin 150 mg QOD
Treatment C rifabutin 300 mg QD

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




| Treatment | A | B | Washout | C |
|---|---|---|---|---|
| Group 1 | Day 1 – 13 | Day 14 – 27 | Days 28 – 40 | Days 41 – 53 |
| Group 2 | Day 14 – 26 | Day 1 – 13 | Days 27 – 40 | Days 41 – 53 |

Note: Treatment A: elvitegravir, 1 × 300 mg tablet QD plus ritonavir, 1 × 100 mg capsule QD; Treatment B: elvitegravir, 1 × 300 mg tablet QD plus ritonavir, 1 × 100 mg capsule QD, and rifabutin , 1 × 150 mg capsule QOD; Treatment C: rifabutin 2 × 150 mg capsule QD

Source: Appendix 1

### Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water immediately after a meal at approximately the same time every day. All doses were observed at the clinic. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic; subjects were required to consume the entire meal on the first and second days of intensive PK sampling (Days 13, 14, 26, 27, 53, and 54). Evening meals that were similar in calorie and fat content were provided on Days 0, 12, 25, 40, and 52. On days of intensive PK sampling, water was restricted from 1 h before until 2 h after study drug administration and food was restricted until after the 4 h blood draw, at which time a standardized meal was provided.

### Rationale for Dose Selection

The EVG/r dose of 300/100 mg QD (expected to be bioequivalent to the 250/100 mg QD dose) was selected for this study because it was the higher of the two doses under consideration for Phase 3 studies. The ritonavir dose of 100 mg is used as a boosting

agent (once- or twice-daily); this dose given once-daily has been shown to increase EVG exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The rifabutin dose of 300 mg QD used as the reference rifabutin dose in this study is the standard treatment dose. The rifabutin 150 mg QOD dose is that recommended by the USPHS/IDSA guidelines for coadministration with ritonavir-containing regimens (i.e. regimens containing a potent CYP3A inhibitor).

**Investigational Product**

Tablets containing 300 mg of EVG were manufactured by (b) (4) ; Lot AJ0702F1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 525302E24). Hard gelatin capsules containing 150 mg of rifabutin (Mycobutin®) were manufactured by Pfizer, Inc. (New York, New York, USA; Lot E353G).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 18 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before intensive PK sampling periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of EVG and ritonavir in Treatments A and B and for the analysis of rifabutin and 25-O-desacetyl rifabutin in Treatments B and C. Sampling timepoints were at 0:00 (predose), 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, and 24:00, as well as 36:00 and 48:00 on Days 13 (Group 1) and 26 (Group 2).

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for EVG and $AUC_{24}$ and $C_{max}$ for rifabutin and 25-O-desacetyl rifabutin. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($AUC_{inf}$, $\lambda_z$, and $t_{1/2}$) were evaluated for validity on a profile-by-profile basis by the pharmacokineticist.

Differences between the primary pharmacokinetic parameters for Treatments A and B or B and C were calculated using SAS® (SAS Institute, Cary, North Carolina, USA) following natural log transformation. PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 70-143%.

## Trial Results

***Bioanalytical methods***

Concentrations of EVG and ritonavir in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511 v7) by Gilead Sciences, Inc. (Durham, North Carolina, USA). Frozen plasma samples were received between 7 and 13 Nov 2007 and stored at -80˚C. Analysis was performed between 15 Nov 2007 and 8 Jan 2008. The first day of sample collection was 28 Oct 2007, so the maximum sample storage time was 73 days, which is within the validated long-term frozen stability duration (at -80˚C) of 268 days.

Concentrations of rifabutin and 25-O-desacetyl rifabutin in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0212) by (b) (4) . Frozen plasma samples were received between 7 Nov and 11 Dec 2007 and stored at -20˚C. Analysis was performed between 12 Dec 2007 and 9 Jan 2007. The first day of sample collection was 28 Oct 2007, so the maximum sample storage time was 74 days, which is within the validated long-term frozen stability duration (at -20˚C) of 76 days.

The EVG calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750.0, and 7500 ng/mL. For ritonavir, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15, 750, and 4000 ng/mL. For rifabutin and 25-O-desacetyl rifabutin, the calibration standards ranged from 1-1000 ng/mL and the QC concentrations were 1, 3, 50, 200, and 800 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for EVG, ritonavir, rifabutin, and 25-O-desacetyl rifabutin in human plasma** (source: Study Report Table 5-3)

| | Elvitegravir | Ritonavir | Rifabutin | 25-O-desacetyl Rifabutin |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20 to 10,000 | 5 to 5,000 | 1 to 1,000 ng/mL | 1 to 1,000 ng/mL |
| LLQ[a] (ng/mL) | 20 | 5 | 1 ng/mL | 1 ng/mL |
| Inter-Assay Precision Range[b] | 2.1% to 6.3% | 8.0% to 11.6% | 4.2% to 9.4% | 3.8% to 9.3% |
| Inter-Assay Accuracy Range[c] | −13.0% to −2.4% | −2.0% to 9.4% | −4.3% to 3.9% | −6.7% to 5.0% |
| Stability in Frozen Matrix (days) | 268 | 268 | 76 | 76 |

a LLQ, lower limit of quantitation
b Relative standard deviation
c Difference from nominal concentrations
Source: Appendix 10

***Trial population***

A total of 23 healthy adult subjects were enrolled in the study and received study drug; 18 subjects completed the study. Three subjects withdrew for safety or tolerability reasons (one for Grade 3 lymphopenia and Grade 4 neutropenia, one for moderate influenza-like illness, and one for mild nausea and headache, all during during administration of EVG/r plus rifabutin), one withdrew consent, and one was withdrawn by the investigator due a protocol violation (positive test for methamphetamines). Of the safety analysis set (n=23), the majority of subjects were white (60.9%); the remainder were Asian (17.4%), or of other ancestry (21.7%). Subjects were predominantly male (60.9%). Subjects had a mean age of 29 years (range: 18 to 44 years).

***Results of pharmacokinetic analyses***

In this study, the steady-state pharmacokinetics of elvitegravir/r, rifabutin, and 25-O-desacetyl rifabutin were compared following coadministration of EVG/r and dose-reduced rifabutin versus administration of EVG/r or rifabutin alone.

The mean concentration-time profiles of EVG were similar after coadministration of EVG/r plus rifabutin compared to EVG/r alone. The steady-state pharmacokinetic parameters for EVG are displayed in Table 2. Statistical comparisons of $C_{max}$, $C_{tau}$, and $AUC_{tau}$ demonstrated no significant changes in EVG exposures as defined by the associated 90% confidence intervals that fell within the predefined no-effect bounds of 70-143% (see Table 3).

**Table 2: Summary of steady-state EVG PK parameters after administration of EVG/r alone or with rifabutin** (PK analysis set; source: Study Report Table 7-1)

| Elvitegravir Plasma PK Parameters | Elvitegravir/r (N = 19) | Elvitegravir/r + Rifabutin (N = 19) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 2947.6 (20.4%) | 2698.3 (22.6%) |
| $AUC_{tau}$ (ng*h/mL) Mean (%CV) | 33452.5 (24.8%) | 31760.1 (24.5%) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 613.8 (40.2%) | 605.1 (55.4%) |
| $T_{max}$ (h) Median (Q1, Q3) | 4.00 (3.50,4.00) | 4.00 (3.00,4.00) |
| $T_{½}$ (h)[a] Median (Q1, Q3) | 9.74 (8.01,11.94) | 9.52 (8.25,11.23) |
| $T_{last}$ (h) Median (Q1, Q3) | 24.00 (24.00,24.00) | 24.00 (24.00,24.00) |

Note: Subjects 1007, 1009, 1010, and 1014 did not have evaluable PK for either treatment pair and were excluded from each PK analysis set. Subject 1019 had evaluable PK for the elvitegravir/r treatment pair but not rifabutin and was excluded from this PK analysis set.

a n = 18 (elvitegravir/r + rifabutin). Elimination $T_{½}$ could not be estimated for Subject 1016

Programming Details: PKSR\Version2\prog\t_pkparm.sas v8.2 Output file: t_pkparm_evg.out 09MAY2008:14:33

Source: Section 11.1, Table 5.1

**Table 3: Statistical comparisons of steady-state EVG PK parameters after administration of EVG/r alone or with rifabutin** (PK analysis set; source: Study Report Table 7-2)

| Test Versus Reference Comparison of Elvitegravir Plasma PK Parameters | Geometric Least-Squares Means | | | |
|---|---|---|---|---|
| | Test: Elvitegravir/r + Rifabutin (N = 19) | Reference: Elvitegravir/r (N = 19) | Geometric Least-Squares Mean Ratio | 90% Confidence Interval |
| $AUC_{tau}$ (ng*h/mL) | 30926.97 | 32354.39 | 95.59 | (89.67,101.90) |
| $C_{max}$ (ng/mL) | 2640.08 | 2871.68 | 91.94 | (84.16,100.43) |
| $C_{tau}$ (ng/mL) | 534.06 | 566.31 | 94.31 | (81.94,108.54) |

Note: Geometric Least-Squares Mean from PROC MIXED model.

Programming Details: PKSR\Version2\prog\t_ratios_macro.sas v8.2 Output file: t_ratios_macro.out 09MAY2008:14:33

Source: Section 11.1, Table 6.1

The mean concentration-time profiles of ritonavir were similar after coadministration of EVG/r plus rifabutin compared to EVG/r alone. Statistical comparisons demonstrated no significant changes in ritonavir $AUC_{tau}$ as defined by the associated 90% confidence intervals that fell within the predefined no-effect bounds of 70-143% (see Table 4). The upper bounds of the 90% CI for ritonavir $C_{max}$ and $C_{tau}$ fell slightly above the no-effect bounds (see Table 4), but these increases did not affect the extent to which ritonavir boosted EVG exposures.

**Table 4: Statistical comparisons of ritonavir PK parameters after administration of EVG/r alone or with rifabutin** (PK analysis set; source: Study Report Table 7-4)

| Test Versus Reference Comparison of Ritonavir Plasma PK Parameters | Geometric Least-Squares Means | | | |
|---|---|---|---|---|
| | Test: Elvitegravir/r + Rifabutin (N = 19) | Reference: Elvitegravir/r (N = 19) | Geometric Least-Squares Mean Ratio | 90% Confidence Interval |
| $AUC_{tau}$ (ng*h/mL) | 6163.77 | 4951.62 | 124.5 | (109.10,142.02) |
| $C_{max}$ (ng/mL) | 810.69 | 672.82 | 120.5 | (101.00,143.74) |
| $C_{tau}$ (ng/mL) | 41.91 | 37.19 | 112.7 | (85.42,148.70) |

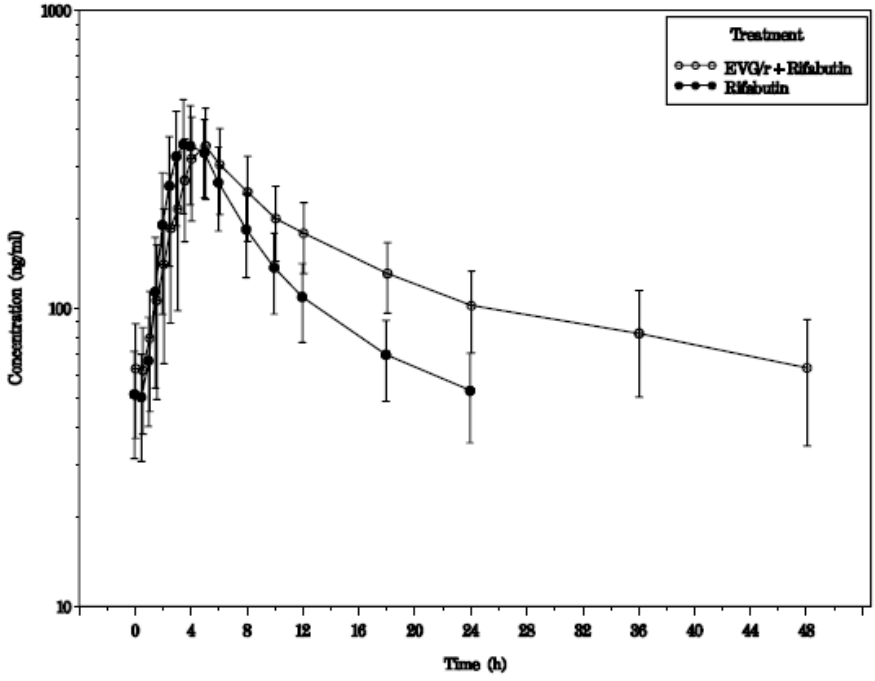
Note: Geometric Least-Squares Mean from PROC MIXED model.

Programming Details: PKSR\Version2\prog\t_ratios_macro.sas v8.2 Output file: t_ratios_macro.out 09MAY2008:14:33

Source: Section 11.1, Table 6.1

Rifabutin steady-state concentration-time profiles are displayed in Figure 1; rifabutin PK parameters are listed in Table 5. While $C_{max}$ and $C_{tau}$ were similar after rifabutin alone compared to dose-adjusted rifabutin with EVG/r, rifabutin $T_{max}$ was delayed slightly (3.75 h vs. 5.00 h) and $t_{1/2}$ increased by slightly more than two-fold (10.43 h vs. 24.4 h) following coadministration with EVG/r. Rifabutin $AUC_{tau}$ values were similar between the two treatments after adjustment for dosing interval differences.

**Figure 1: Steady-state rifabutin plasma concentrations after administration of rifabutin alone or with EVG/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-3)




Note: Subjects 1007, 1009, 1010, and 1014 did not have evaluable PK for either treatment pair and were excluded from each PK analysis set. Subject 1019 had evaluable PK for the elvitegravir/r treatment pair but not rifabutin and was excluded from this PK analysis set.

Source: Section 11.1, Figure 1.3

**Table 5: Summary of steady-state rifabutin PK parameters after administration of rifabutin alone or with EVG/r** (PK analysis set; source: Study Report Table 7-5)

| Rifabutin Plasma PK Parameters | Elvitegravir/r + Rifabutin (N = 18) | Rifabutin (N = 18) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 372.8 (31.8%) | 402.7 (31.2%) |
| $AUC_{tau}$ (ng*h/mL) Mean (%CV) | 6238.3 (27.9%) | 6637.3 (26.8%) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 63.2 (45.3%) | 53.0 (33.2%) |
| $T_{max}$ (h) Median (Q1, Q3) | 5.00 (4.00,5.00) | 3.75 (3.50,5.00) |
| $T_{½}$ (h) Median (Q1, Q3) | 24.40 (19.41,39.09) | 10.43 (8.80,11.94) |
| $T_{last}$ (h) Median (Q1, Q3) | 48.00 (48.00,48.00) | 24.00 (24.00,24.00) |

Note: Subject 1007, 1009, 1010, and 1014 did not have evaluable PK for either treatment pair and were excluded from each PK analysis set.

Subject 1019 had evaluable PK for the elvitegravir/r treatment pair but not rifabutin and was excluded from this PK analysis set.

Note: For rifabutin and 25-O-desacetyl rifabutin, $AUC_{tau}$ represents $AUC_{0-48}$ for elvitegravir/r + rifabutin and doubled $AUC_{0-24}$ for rifabutin.

Programming Details: PKSR\Version2\prog\t_pkparm.sas v8.2 Output file: t_pkparm_rbt.out 09MAY2008:14:33

Source: Section 11.1, Table 5.3

Statistical comparisons demonstrated no significant changes in rifabutin $C_{max}$, $C_{tau}$, or $AUC_{tau}$ as defined by the associated 90% confidence intervals that fell within the predefined no-effect bounds of 70-143% (see Table 6).

**Table 6: Statistical comparisons of rifabutin PK parameters after administration of rifabutin alone or with EVG/r** (PK analysis set; source: Study Report Table 7-6)

| Test Versus Reference Comparison of Rifabutin Plasma PK Parameters | Geometric Least-Squares Means | | Geometric Least-Squares Mean Ratio | 90% Confidence Interval |
|---|---|---|---|---|
| | Test: Elvitegravir/r + Rifabutin (N = 18) | Reference: Rifabutin (N = 18) | | |
| $AUC_{tau}$ (ng*h/mL) | 6017.19 | 6421.55 | 93.70 | (85.62,102.55) |
| $C_{max}$ (ng/mL) | 353.83 | 386.00 | 91.67 | (82.69,101.61) |
| $C_{tau}$ (ng/mL) | 58.39 | 50.38 | 115.9 | (102.33,131.26) |

Note: Geometric Least-Squares Mean from PROC MIXED model.

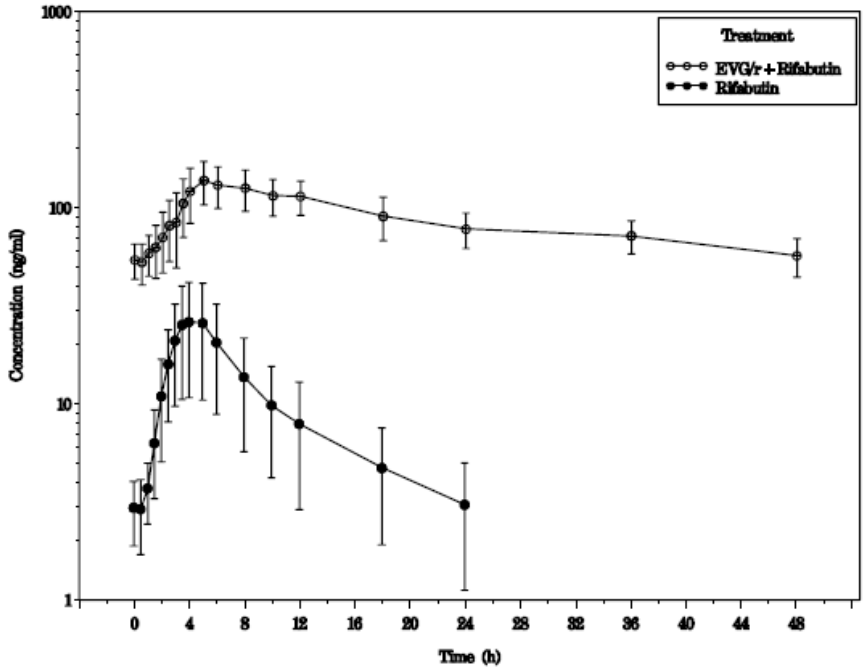
Note: For rifabutin and 25-O-desacetyl rifabutin, $AUC_{tau}$ represents $AUC_{0-48}$ for elvitegravir/r + rifabutin and doubled $AUC_{0-24}$ for rifabutin.

Programming Details: PKSR\Version2\prog\t_ratios_macro.sas v8.2 Output file: t_ratios_macro.out 09MAY2008:14:33

Source: Section 11.1, Table 6.1

25-O-desacetyl rifabutin steady-state concentration-time profiles are displayed in Figure 2 and corresponding PK parameters are listed in Table 7. Compared to administration of rifabutin alone, coadministration of dose-adjusted rifabutin and EVG/r resulted in a slight delay in 25-O-desacetyl rifabutin $T_{max}$ (4.00 h vs. 5.00 h) and a nearly five-fold increase in $t_{1/2}$ (8.08 h vs. 39.16 h). There were also significant increases in the $C_{max}$, $C_{tau}$, and $AUC_{tau}$ values for 25-O-desacetyl rifabutin following coadministration of dose-adjusted rifabutin and EVG/r compared to administration of rifabutin alone.

**Figure 2: Steady-state 25-O-desacetyl rifabutin plasma concentrations after administration of rifabutin alone or with EVG/r** (mean ± SD; PK analysis set; source: Study Report Figure 7-4)




Note: Subjects 1007, 1009, 1010, and 1014 did not have evaluable PK for either treatment pair and were excluded from each PK analysis set. Subject 1019 had evaluable PK for the elvitegravir/r treatment pair but not rifabutin and was excluded from this PK analysis set.

Source: Section 11.1, Figure 1.4

**Table 7: Summary of steady-state 25-O-desacetyl rifabutin PK parameters after administration of rifabutin alone or with EVG/r** (PK analysis set; source: Study Report Table 7-7)

| 25-O-desacetyl Rifabutin Plasma PK Parameters | Elvitegravir/r + Rifabutin (N = 18) | Rifabutin (N = 18) |
|---|---|---|
| $C_{max}$ (ng/mL) Mean (%CV) | 144.2 (24.9%) | 29.1 (52.2%) |
| $AUC_{tau}$ (ng*h/mL) Mean (%CV) | 4066.8 (18.6%) | 468.0 (53.5%) |
| $C_{tau}$ (ng/mL)[a] Mean (%CV) | 56.9 (22.3%) | 3.1 (63.4%) |
| $T_{max}$ (h) Median (Q1, Q3) | 5.00 (5.00,6.00) | 4.00 (3.50,5.00) |
| $T_{½}$ (h) Median (Q1, Q3) | 39.16 (33.35,52.23) | 8.08 (7.07,9.03) |
| $T_{last}$ (h) Median (Q1, Q3) | 48.00 (48.00,48.00) | 24.00 (24.00,24.00) |

Note: Subject 1007, 1009, 1010, and 1014 did not have evaluable PK for either treatment pair and were excluded from each PK analysis set. Subject 1019 had evaluable PK for the elvitegravir/r treatment pair but not rifabutin and was excluded from this PK analysis set.

Note: For rifabutin and 25-O-desacetyl rifabutin, $AUC_{tau}$ represents $AUC_{0-48}$ for elvitegravir/r + rifabutin and doubled $AUC_{0-24}$ for rifabutin.

Programming Details: PKSR\Version2\prog\t_pkparm.sas v8.2 Output file: t_pkparm_25o.out 09MAY2008:14:33

a n = 17 as $C_{tau}$ was BLQ for Subject 1023

Source: Section 11.1, Table 5.4

Statistical comparisons demonstrated significant increases in 25-O-desacetyl rifabutin exposures, with the 90% CI values for $C_{max}$, $C_{tau}$, and $AUC_{tau}$ that fell above the predefined no-effect bounds of 70-143% (see Table 8). In addition, the antimycobacterial activity was shown to be increased by 50% (data not shown). This corresponding increase in activity is expected due to the molar equipotency of rifabutin and 25-O-desacetyl rifabutin.

**Table 8: Statistical comparisons of 25-O-desacetyl rifabutin PK parameters after administration of rifabutin alone or with EVG/r** (PK analysis set; source: Study Report Table 7-8)

| Test Versus Reference Comparison of 25-O-desacetyl rifabutin Plasma PK Parameters | Geometric Least-Squares Means | | | |
|---|---|---|---|---|
| | Test: Elvitegravir/r + Rifabutin (N = 18) | Reference: Rifabutin (N = 18) | Geometric Least-Squares Mean Ratio | 90% Confidence Interval |
| $AUC_{tau}$ (ng*h/mL) | 3992.64 | 419.78 | 951.1 | (809.49,1117.54) |
| $C_{max}$ (ng/mL) | 139.95 | 25.93 | 539.7 | (466.11,624.82) |
| $C_{tau}$ (ng/mL) | 55.42 | 2.86 | 1936 | (1584.52,2365.32) |

Note: Geometric Least-Squares Mean from PROC MIXED model.

Note: For rifabutin and 25-O-desacetyl rifabutin, $AUC_{tau}$ represents $AUC_{0-48}$ for elvitegravir/r + rifabutin and doubled $AUC_{0-24}$ for rifabutin.

Programming Details: PKSR\Version2\prog\t_ratios_macro.sas v8.2 Output file: t_ratios_macro.out 09MAY2008:14:33

Source: Section 11.1, Table 6.1

***Results of safety analysis***

Coadministration of EVG/r and rifabutin resulted in more than twice as many adverse events compared to administration of EVG/r or rifabutin alone. Headache and nausea were the most frequently reported AEs associated with study drug. One subject discontinued the study due to AEs related to administration of EVG/r with rifabutin (Grade 3 lymphopenia and Grade 4 neutropenia). Two other subjects discontinued the study during EVG/r plus rifabutin treatment because of AEs that were not related to study drug: one experienced moderate influenza-like illness and one experienced mild nausea and headache. There were no serious adverse events or deaths during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of elvitegravir, ritonavir, rifabutin, and 25-O-desacetyl rifabutin following administration of EVG/r 300/100 mg QD, rifabutin 300 mg QD, or coadministration of EVG/r 300/100 mg QD and rifabutin 150 mg QOD.

Upon coadministration of EVG/r and dose-adjusted rifabutin, slight increases in ritonavir $C_{max}$ and $C_{tau}$ were observed; however, elvitegravir exposures remained unchanged, demonstrating an absence of clinical significance. No dose adjustment for elvitegravir or ritonavir is necessary when EVG/r 300/100 mg QD is coadministered with rifabutin 150 mg QOD.

Coadministration of EVG/r and dose-adjusted rifabutin resulted in significant increases in rifabutin and 25-O-desacetyl rifabutin exposures, as well as a corresponding increase in antimycobacterial activity, compared to administration of rifabutin alone. The proposed language regarding rifabutin included in the draft package insert for NDA 203093 submitted by the Applicant states, "Increased monitoring for rifabutin-associated adverse events is warranted." Per the approved Mycobutin® label, rifabutin is generally well-tolerated (16% of subjects receiving rifabutin discontinued therapy due to AEs compared to 8% of subjects receiving placebo). Primary reasons for discontinuation were rash (4% of treated patients), gastrointestinal intolerance (3%), and neutropenia (2%). Rifabutin has also been linked to thrombocytopenia in rare cases. According to Dr. Seong Jang, the clinical pharmacology reviewer for Mycobutin®, the incidence of adverse events expected following coadministration of rifabutin 150 mg QOD and EVG/r 300/100 mg is acceptable based on the exposures observed in the current study. Given these data, this reviewer concurs with the Applicant that no further rifabutin dose adjustments are required.

**Trial GS-US-183-0145**
**A Multicenter, Randomized, Double-Blind, Double-Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) Versus Raltegravir (RAL) Each Administered with a Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults**

**Trial Period**
19 June 2008 to 24 Feb 2011
Final report date: 17 Aug 2011 (for 48 week analysis; submitted to IND 72,177)

**Trial Sites**
86 sites in the USA (range: 0-16 subjects randomized)
75 total sites in Spain, Canada, Australia, France, Germany, Italy, Portugal, Puerto Rico, Belgium, Mexico, the United Kingdom, and the Netherlands (range: 3-6 subjects randomized)

**Trial Rationale**
Elvitegravir (EVG, GS-9137) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection; the intended patient population in the proposed indication is treatment-experienced HIV-1 infected adults. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). Ritonavir (RTV) is an HIV PI indicated for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV infection. Coadministration of ARVs that are cytochrome P450 (CYP) isoform 3A substrates with the potent CYP3A inhibitor RTV increases the systemic exposure of the substrate drugs. This study was designed to evaluate the safety, tolerability, and efficacy of RTV-boosted elvitegravir (elvitegravir/r) compared to raltegravir, which is also an HIV-1 integrase inhibitor (INSTI), each administered with a background regimen containing a ritonavir-boosted PI and a second drug, in treatment-experienced patients failing any line of HIV-1 therapy.

**Trial Objectives**
The primary objective of the trial was to:

- assess noninferiority of a regimen containing ritonavir-boosted elvitegravir versus raltegravir, each administered with a background regimen in HIV-1 infected, antiretroviral treatment-experienced adult subjects as determined by the proportion of subjects achieving and maintaining confirmed HIV-1 ribonucleic acid (RNA) <50 copies/mL through Week 48

The secondary objectives of the trial were to:

- evaluate the efficacy, safety, and tolerability of the two treatment regimens through 96 weeks of treatment
- evaluate the long-term safety, tolerability, and efficacy of EVG administered with a background regimen

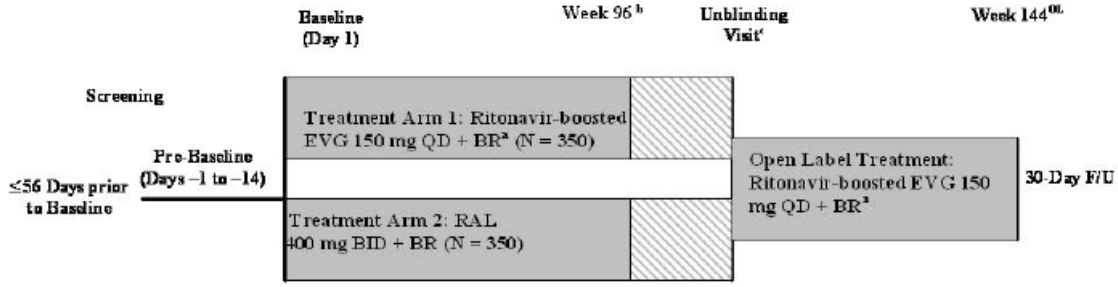
The first secondary objective was addressed in a separate study report, which was not reviewed. The second secondary objective was assessed in an open-label extension phase after the unblinding visit. This objective was not discussed in the current clinical study report and was therefore not reviewed.

## Trial Design

This was a randomized, double-blind, active-controlled, multiple-dose, multicenter, 96-week study (including a pharmacokinetic substudy at Week 2 in a subset of subjects at selected sites) with optional enrollment in a subsequent 144-week open-label extension phase. The background ARV regimens were selected by the investigator before study randomization based on each subject's ARV history and viral resistance profile. The background ARV regimen (BR) consisted of a ritonavir-boosted PI (PI/r) and a second agent. Randomization was stratified by HIV-1 RNA level at screening (≤100,000 vs. >100,000 copies/mL), the class of the second agent (NRTI vs. another class), and geographic location (US and Puerto Rico vs. Europe, Australia, Canada, and Mexico). Due to pharmacokinetic interactions, the dose of EVG was reduced from 150 mg QD to 85 mg QD if the BR contained ritonavir-boosted ATV or LPV.

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Figure 7-1)




a EVG 85 mg if subject was taking atazanavir (ATV)/r or lopinavir (LPV)/r as part of BR; all other subjects received EVG 150 mg

b Subjects will continue to attend visits every 8 weeks following Week 96 until Week 144, and every 12 weeks thereafter until treatment assignments have been unblinded.

c Subjects will continue to attend visits every 12 weeks following the Unblinding Visit throughout the open-label extension phase of the study until Week 144 or until EVG becomes commercially available (whichever occurs first). Subjects who permanently discontinued study drugs were asked to return to the clinic 30 days after completion of the Early Study Drugs Discontinuation Visit for the 30 Day Follow-Up Visit.

## Key Inclusion and Exclusion Criteria

Subjects were treatment-experienced HIV-1-infected males and females between the ages of 18 and 65 years, inclusive, with plasma HIV-1 RNA levels ≥ 1000 copies/mL and documented resistance (as defined by the IAS-USA 2005 Guidelines) to two or more

classes of antiretroviral drugs, or at least six months experience prior to screening with two or more classes of antiretroviral drugs. Subjects must have been on a stable ARV regimen for at least 30 days prior to screening, and must have remained on that regimen until the baseline visit. The ARV regimen had to contain a fully active ritonavir-boosted PI and an allowed second agent (see Table 1). Subjects had to have a normal ECG and adequate renal function as defined by estimated creatinine clearance ≥ 60 mL/min. Screening laboratory evaluations must have fallen within normal ranges.

**Table 1: Allowed components of background regimen** (source: Study Table 7-2)

| Fully-Active Ritonavir-Boosted Protease Inhibitor[a, b] | Second Agent[b, c] | Third Agent[g] (M184V/I present on screening genotype) |
|---|---|---|
| Atazanavir/r (ATV/r)[d]<br>Darunavir/r (DRV/r) | Any single approved NRTI | Emtricitabine (FTC)<br>Lamivudine (3TC) |
| Fosamprenavir/r (FPV/r)<br>Lopinavir/r (LPV/r)[d]<br>Tipranavir/r (TPV/r) | Enfuvirtide[e] (T-20)<br>Etravirine[h]<br>Maraviroc[f, h] | — |

a PIs must have been fully-active, defined by phenotypic susceptibility. For phenotypic susceptibility, the fold change must have been below the lower clinical or biological cutoff for that drug.

b Components of the BR were prescribed by the investigator as indicated in the prescribing information, including the ritonavir dose as indicated for use with the selected PI. The sponsor provided Viread® (tenofovir disoproxil fumarate) for those subjects who were prescribed Viread as part of their BR.

c Except at study centers in Spain, the second agent may or may not have been fully active. In Spain, the second agent was to be fully active.

d Due to known pharmacokinetic interactions, subjects who were taking ATV/r or LPV/r as part of their BR received elvitegravir 85 mg if randomized to Treatment Group 1.

e Subject must have been naive to enfuvirtide (< 10 days use prior to baseline) for the drug to have been considered fully active.

f Trofile™ assay was not provided by the sponsor.

g If, and only if, the M184V/I reverse transcriptase mutation was present on the screening genotype report and an NRTI was used as the second agent, then either emtricitabine (Emtriva®, FTC) or lamivudine (Epivir®, 3TC) may have been added as a third agent in the BR. The fixed-dose combination therapies Combivir®, Truvada®, or Epzicom®/Kivexa® may have been prescribed as the combined second and third agents of the BR only if the M184V/I reverse transcriptase mutation was detected at screening.

h Subjects who were receiving etravirine or maraviroc through the expanded access programs were eligible for this study.

Potential subjects were excluded from enrollment if they had a new AIDS-defining condition diagnosed within 30 days of baseline. Exclusion criteria also included previous exposure to any HIV-1 integrase inhibitor, the use of alcohol or other substances in a way that could interfere with study compliance, a malignancy other than cutaneous Kaposi sarcoma or basal cell carcinoma, or an active, serious infection requiring parenteral antibiotic or antifungal therapy within 30 days of baseline.

Potential subjects were excluded for the use of specified medications from the following drug classes within 30 days of the baseline visit (refer to the table in section 7.3.2 of the study report for details): sedatives/hypnotics, GI motility agents, neuroleptic drugs, ergot derivatives, immunosuppressants, antibacterials, calcium channel blockers, antiarrythmics, antimycobacterials, antihistamines, anticonvulsants, herbal supplements, systemic chemotherapeutic (antineoplastic) agents, immunomodulators, medications not

to be taken with RTV, systemic corticosteroids, HMG-CoA reductase inhibitors (statins), antifungals, anticoagulants, opiates, and phosphodiesterase-5 inhibitors.

**Rationale for Dose Selection**

Background regimens contained one of the following: atazanavir/r (ATV/r) 300/100 mg QD, darunavir/r (DRV/r) 600/100 mg BID, fosamprenavir/r (FPV/r) 700/100 mg BID, lopinavir/r (LPV/r) 400/100 mg BID, or tipranavir/r (TPV/r) 500/200 mg BID. These doses are those approved in the US for treatment-experienced people with HIV-1 infection. Elvitegravir was administered at doses of 85 mg QD (in combination with ATV/r or LPV/r) or 150 mg QD (in combination with DRV/r, FPV/r, or TPV/r) based on results from previously conducted drug-drug interaction studies (GS-US-183-0147 [ATV/r] and GS-US-183-0116 [LPV/r]).

**Investigational Product**

Film-coated tablets containing 85 or 150 mg of elvitegravir were manufactured by (b) (4); Lots AJ0704D1, AJ0705D1, AJ0802C1, AJ1001C1 for EVG 85 mg and Lots AJ0704E1, AJ0705E1, AJ0802D1, AJ1001D1 for EVG 150 mg). Film-coated raltegravir tablets (RAL, Isentress®) were manufactured by Merck & Co., Inc. (Allentown, Pennsylvania, USA; Lots BA0702A1, BA0801A1, BA0901A1, BA0903A1, BA1001A1, BA1101A1). The Applicant also provided commercial tenofovir disoproxil fumarate (TDF, Viread®) for subjects who were prescribed this drug as part of their background regimen. All other components of the background ARV regimens were dispensed in open-label fashion as prescribed by the investigator, and administered according to the prescribing information for each particular product.

**Drug Administration**

Elvitegravir was administered orally with the fully active PI/r of the background regimen once daily with food, at approximately the same time each day. Subjects in the pharmacokinetic substudy arrived at the clinic after an 8 h fast and were given a standardized breakfast. Five minutes after completion of the meal, their assigned dose of elvitegravir/r was administered with 240 mL of water under staff supervision. Subjects also received their ARV regimens according to their dosing schedule. Food was restricted until after the 4 h blood draw, and water was restricted from 1 h before until 2 h after dosing.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, subjects were instructed not to use any drug with antiretroviral activity that was not part of their prescribed CPI or ARV regimens. The following were also prohibited 2 h before and 2 h after any dose of elvitegravir/r: antacids containing calcium, magnesium, or aluminum; sucralfate; and vitamin or mineral supplements containing calcium, iron, or zinc.

**Sample Collection**

Predose blood samples (20 to 24 h following the previous dose of EVG) were collected for the analysis of elvitegravir, its metabolites GS-9202 and GS-9200, and RTV plasma during Weeks 2, 12, 16, 24, and 48. At Week 4, blood samples were collected predose and immediately after dosing, 1 and 4 h postdose, and an optional sample 2, 3, and/or 4 h postdose. In addition, a single blood sample was collected at Weeks 8, 20, 32, and 40, without regard to time since the previous EVG dose.

Blood was collected for quantification of HIV-1 RNA in plasma at the screening and baseline (Day 1), and 30-day follow-up visits, as well as at the end of Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and every 8 weeks thereafter until study discontinuation.

## Analytical Plan

*Pharmacokinetic data*

The pharmacokinetic parameters $AUC_{tau}$, $C_{max}$, $T_{max}$, $C_{tau}$, $C_{last}$, $T_{last}$, $C_{trough}$, $\lambda_z$, and $t_{1/2}$ were estimated for EVG, GS-9200 (M4), GS-9202 (M1), and RTV in plasma. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2)}$ were reported when the pharmacokineticist deemed the data evaluable after examination.

## Trial Results

***Bioanalytical methods***

Concentrations of EVG, its metabolites GS-9200 and GS-9202, and RTV in plasma samples were determined using LC-MS/MS by (b) (4) . Frozen plasma samples were received between 17 Mar 2009 and 23 Feb 2011 and stored at -70˚C. Analysis was performed 16 Jun 2009 and 3 Mar 2011. Analyzed samples were collected between 5 Aug 2008 and 7 Dec 2010, so the maximum storage sample time was 815 days, which is within the validated long-term frozen stability duration of 834 days at -70˚C for all compounds assayed. The LC-MS/MS method (b) (4) 60-0811 was used to analyze all compounds.

The EVG calibration standards ranged from 20-10,000 ng/mL and the quality control (QC) concentrations were 20.0, 50.0, 750, and 7500 ng/mL. For GS-9200, the calibration standards ranged from 17.5-875.5 ng/mL and the QC concentrations were 17.5, 43.8, 131.35, and 656.2 ng/mL. For GS-9202, the calibration standards ranged from 20-750 ng/mL and the QC concentrations were 20.0, 50.0, 150, and 750 ng/mL. For RTV, the calibration standards ranged from 5 to 5000 ng/mL and the QC concentrations were 5.0, 15.0, 750, and 4000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 2) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 2: Bioanalytical assay validation for EVG, GS-9200, GS-9202, and RTV in human plasma** (source: Study Report Table 7-8)

| Parameter | Elvitegravir | GS-9200 | GS-9202 | Ritonavir |
|---|---|---|---|---|
| Linear range (ng/mL) | 20–10,000 | 17.5–875.5 | 20–1,000 | 5–5,000 |
| LLQ[a] (ng/mL) | 20 | 17.5 | 20 | 5 |
| Interassay precision range[a] | 3.3–5.5 | 4.1–12.1 | 3.8–4.8 | 3.1–14.6 |
| Interassay accuracy range[b] | -0.4–9.2 | 1.4–7.8 | 0.4–8.1 | -3.7–7.6 |
| Stability in frozen matrix (days) | 585 Days at -70°C | 585 Days at -70°C | 585 Days at -70°C | 585 Days at -70°C |

LLQ = lower limit of quantitation
a Relative standard deviation
b Difference from nominal concentrations
Source: Appendix 16.1.10.

***Trial population***

A total of 724 subjects were randomized in the study: 361 to the EVG arm and 363 to the RAL arm. Twelve subjects were never dosed; the remaining 712 subjects received at least one dose of study drug and were included in the intent-to-treat and safety analysis sets. Two hundred thirty-four subjects (32.9%) discontinued study drug prematurely: 58 (29 EVG, 29 RAL) because of subject noncompliance; 51 (24 EVG, 25 RAL) were lost to follow-up; 33 (21 EVG, 12 RAL) withdrew consent; 31 (15 EVG, 16 RAL) for lack of efficacy, 24 (11 EVG, 13 RAL) for protocol violations; 23 (9 EVG, 14 RAL) because of adverse events; eight due to death (8 RAL); six at the discretion of the investigator (2 EVG, 4 RAL); and two due to pregnancy (2 EVG).

The majority of subjects in the intent-to-treat (ITT) analysis set (n=702) were white (62.3%) and male (82.1%), with a mean age of 45 years (range: 19-78 years). There were no statistically significant differences between treatment groups. As specified in the protocol, all subjects received a ritonavir-boosted PI, with darunavir being most commonly prescribed, followed by lopinavir and atazanavir. The second agent in the BR was an NRTI for the majority of subjects (80%), followed by an NNRTI (15%) and the CCR5 entry inhibitor maraviroc (6%).

***Results of pharmacokinetic analyses***

A total of 31 subjects had evaluable pharmacokinetic data from the intensive pharmacokinetic substudy conducted in Week 2 (PK Substudy Analysis Set). The pharmacokinetics of EVG, GS-9200, and ritonavir in plasma were assessed; however, in the presence of ritonavir, plasma concentrations of the CYP3A metabolite GS-9202 were below the limit of quantitation, precluding the evaluation of GS-9202 pharmacokinetics in this study.

In addition to the intensive PK substudy, EVG trough concentrations were calculated at Weeks 2, 4, 12, 16, 24, and 48.

The steady-state PK parameters for EVG after 2 weeks of treatment are listed in Table 3. Mean $AUC_{tau}$ and $C_{max}$ values were similar following administration of EVG 85 mg

compared to EVG 150 mg, while $C_{tau}$ was higher with the 85 mg dose compared to the 150 dose. EVG exposures were comparable to those observed in previous studies.

**Table 3: Summary of elvitegravir pharmacokinetic parameters at Week 2** (PK Substudy Analysis Set; source: Study Report Table 10-1)

| EVG PK Parameter[a] | EVG Dose: 85 mg (n = 12) | EVG Dose: 150 mg (n = 19) |
|---|---|---|
| $AUC_{tau}$ (ng•h/mL), Mean (%CV) | 21918.1 (56.4) | 20298.1 (51.5) |
| $C_{max}$ (ng/mL), Mean (%CV) | 1514.4 (49.7) | 1721.5 (43.3) |
| $C_{tau}$ (ng/mL), Mean (%CV) | 759.6 (73.3) | 378.2 (67.4) |
| $T_{max}$ (h), Median (Q1, Q3) | 4.75 (1.50, 9.09) | 3.00 (1.17, 4.50) |
| $T_{½}$ (h), Median (Q1, Q3)[b] | 13.72 (8.69, 17.20) | 8.67 (7.10, 13.75) |

%CV, percentage coefficient of variation
a Values below lower limit of quantitation were treated as 0 for summary statistics.
b Number of subjects for this parameter was 11.
Source: Section 15.1, Table 47.1

The steady-state PK parameters for GS-9200 (the glucuronidated metabolite of EVG) after 2 weeks of EVG administration are listed in Table 4. Mean plasma concentrations of the GS-9200 metabolite were lower after administration of EVG 85 mg compared to EVG 150 mg; this is likely due to inhibition of glucuronidation by ATV/r and LPV/r, with which the 85 mg dose was administered. The ratios of the mean $AUC_{tau}$ values for GS-9200 compared to elvitegravir were 10.8% and 21.2% for the EVG 85 mg and 150 mg treatment arms, respectively, and are consistent with values observed in previous clinical trials.

**Table 4: Summary of GS-9200 pharmacokinetic parameters at Week 2** (PK Substudy Analysis Set; source: Study Report Table 10-2)

| GS-9200 PK Parameter[a] | EVG Dose: 85 mg (n = 12) | EVG Dose: 150 mg (n = 19) |
|---|---|---|
| $AUC_{tau}$ (ng•h/mL), Mean (%CV) | 2066.2 (70.3) | 3685.7 (33.4) |
| $C_{max}$ (ng/mL), Mean (%CV) | 158.0 (63.8) | 354.8 (31.2) |
| $C_{tau}$ (ng/mL), Mean (%CV) | 60.5 (73.2) | 68.7 (71.1) |
| $T_{max}$ (h), Median (Q1, Q3) | 3.75 (2.10, 5.00) | 2.08 (2.00, 4.00) |
| $T_{½}$ (h), Median (Q1, Q3) | 10.91 (4.78, 12.45) | 8.87 (6.48, 11.98) |

%CV, percentage coefficient of variation
a Values below lower limit of quantitation were treated as 0 for summary statistics.
Source: Section 15.1, Table 47.3

Plasma concentrations of GS-9202 (the hydroxylated metabolite of EVG) were below the lower limit of quantitation at nearly all the sampling timepoints, preventing evaulation of its phamacokinetics.

Mean steady-state RTV plasma concentrations following administration of RTV 100 mg QD or BID in combination with a PI and EVG were consistent with historical data (data not shown).

Mean EVG trough concentrations were calculated across study visits between Weeks 2 and 48 (see Table 5). Mean trough concentrations were slightly lower in the EVG 150 mg dose group compared to the EVG 85 mg dose group; interindividual variability was slightly higher in the 150 mg group. Despite minor differences, mean EVG trough concentrations remained at least 6.9-fold above the $IC_{95}$ target across both treatment arms between Weeks 2 and 48.

***Summary of efficacy analysis***

Efficacy data are summarized through Week 48. EVG administered once daily was noninferior to RAL given twice daily when administered in combination with a PI/r (59.0% of subjects receiving EVG achieved and maintained HIV-1 RNA <50 copies/week at Week 48, compared to 57.8% of subjects in the RAL group using a TLOVR analysis). Response rates were generally similar between the EVG and RAL treatment arms; the largest difference was observed in females, with response rates of 45.8% and 58.2% in the EVG and RAL treatment arms, respectively.

***Summary of safety analysis***

The incidence of treatment-related adverse events was similar between the treatment groups (22.6% and 20.1% in the EVG and RAL arms, respectively). The most frequently reported AEs related to study drug were diarrhea, nausea, and headache, all of which occurred at rates of less than 10% in both treatment groups. Nine and 15 subjects receiving EVG and RAL, respectively, discontinued study drug due to AEs. There were two deaths in the EVG group (neither related to study drug) and eight in the RAL group (three related to study drug: hemolytic anemia, possible acute coronary event, and cardiac arrest). Overall, the safety profile of EVG was similar to that of RAL, with the exceptions of the deaths and elevations in ALT and AST in the RAL treatment group.

**Trial Summary**

In this study, the steady-state pharmacokinetics of EVG following administration of EVG 85 mg (in combination with ATV/r or LPV/r) or 150 mg (in combination with FPV/r, TPV/r, or DRV/r) were evaluated. Mean EVG $AUC_{tau}$ and $C_{max}$ values were comparable following 85 and 150 mg EVG and were similar to historical values. EVG trough concentrations remained well above the protein binding-adjusted $IC_{95}$ value from Week 2 through Week 48.

The results of this study demonstrated noninferiority of elvitegravir once-daily compared to raltegravir twice-daily in treatment-experienced HIV-1 infected adults. Review of the pharmacokinetic data supports the proposed elvitegravir dose reduction from 150 mg QD to 85 mg QD when EVG is administered in combination with lopinavir/r or atazanavir/r; no further dose adjustments are needed.

**Trial GS-US-183-0147**
**A Phase 1, Multiple-Dose Pharmacokinetic Drug Interaction Study of Elvitegravir and Atazanavir**

**Trial Period**
11 Oct to 30 Nov 2007
Final report date: 12 Sept 2008 (submitted to IND 72,177)

**Trial Site**
SeaView Research, Miami, Florida, USA

**Trial Rationale**
Elvitegravir (EVG, GS-9137) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). In clinical practice, elvitegravir may be coadministered with the PI atazanavir (trade name Reyataz®) boosted by the HIV PI ritonavir (RTV). Elvitegravir and atazanavir are both substrates of CYP3A; when given in combination with ritonavir, exposures are elevated due to the inhibition of CYP3A activity by ritonavir. A previous study demonstrated that that coadministration of ATV/r 300/100 mg and EVG 200 mg resulted in a two-fold increase in EVG exposures compared to administration of EVG/r 200/100 mg alone (GS-US-183-0108); a follow-up study demonstrated that EVG exposures were similar following coadministration of EVG 85 mg plus ATV/r 300/100 mg compared to administration of EVG/r 150/100 mg alone. The current study was conducted to characterize the mechanism of the interaction between EVG and ATV in the absence of RTV, as well as to determine the effects of EVG in combination with RTV or ATV on the pharmacokinetics of the CYP3A probe midazolam (MDZ).

**Trial Objectives**
The primary objective of the trial was to:

- evaluate the pharmacokinetics of EVG when coadministered with ATV relative to coadministration with RTV

The secondary objective of the trial was to:

- evaluate the effect of ATV and RTV, each in combination with EVG, on CYP3A enzyme activity using MDZ as the probe substrate
- evaluate the safety of EVG when coadministered with RTV or ATV

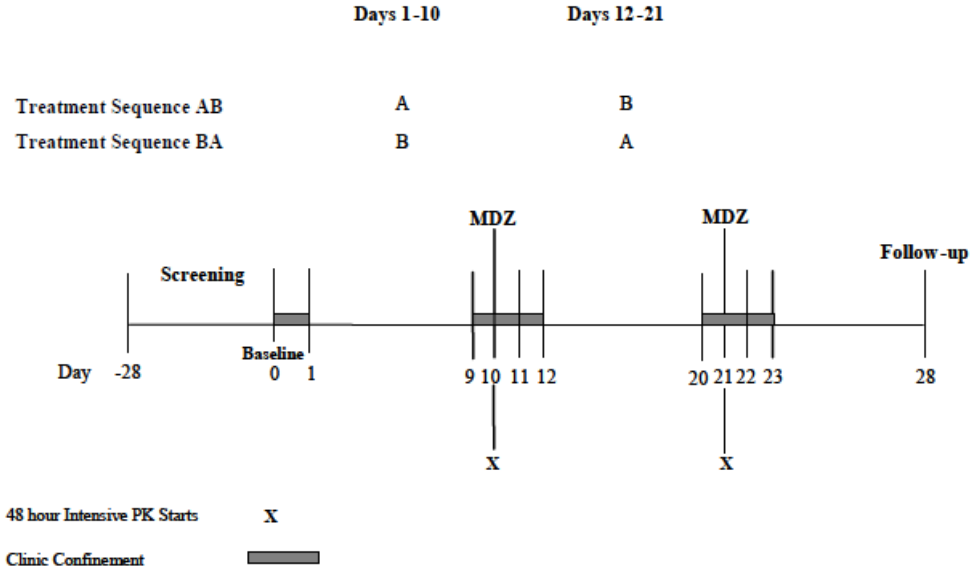
**Trial Design**
This was an open-label, multiple-dose, drug interaction study. There were two treatment periods, each lasting 10 days, followed by a follow-up visit seven days after the last dose

of study drug. A single dose of midazolam was administered on the last day of each treatment period.

Treatment A elvitegravir/r 300/100 mg QD
Treatment B elvitegravir 300 mg plus atazanavir 400 mg QD
Midazolam 5 mg single dose

Subjects were randomized to one of two treatment sequences: AB or BA. The study schema for both sequences is shown in Figure 1.

**Figure 1: Study schema** (source: Study Report Figure 5-1)




**Treatment A:** EVG (1 × 300-mg tablet) plus RTV (1 × 100-mg capsule), once daily coadministered in the morning.
**Treatment B**: EVG (1 × 300-mg tablet) plus ATV (2 × 200-mg capsules), once daily coadministered in the morning.
**MDZ:** A single dose of 5 mg oral syrup administered along with the assigned study treatment on Day 10 and Day 21.
Source: Appendix 1

### Drug Administration

All study drugs were taken in an open-label fashion with 240 mL of water and within 5 minutes of consuming a meal at approximately the same time every morning. Standardized morning meals (400 kcal and 13 g of fat) were provided at the clinic on Days 10 and 21. On mornings of intensive PK sampling days (Days 10 and 21), water was restricted beginning 1 h before until 2 h after dosing, and subjects fasted after drug administration until after the 4 h postdose blood draw.

### Rationale for Dose Selection

The EVG/r dose of 300/100 mg QD (which is expected to be similar to EVG/r 250/100 mg QD of the previous elvitegravir formulation based on a bioequivalence study) was selected for this study because it is the higher of two EVG doses proposed for evaluation

in Phase 3 studies. The RTV dose of 100 mg is used as a boosting agent (once- or twice-daily); this dose has been shown to increase elvitegravir exposures and no additional inhibitory effect on CYP3A was observed at doses up to 400 mg BID.

The ATV dose of 400 mg QD was selected for this study because it is the same unboosted dose that is currently marketed for treatment-naïve adults infected with HIV-1.

The MDZ dose of 5 mg selected for this study is substantially lower than the maximum 20 mg dose used for sedative purposes. The 5 mg dose is frequently administered in pharmacokinetic studies in which MDZ is used as a CYP3A probe substrate.

**Investigational Product**

Tablets containing 300 mg of elvitegravir were manufactured by Gilead Sciences, Inc. (Foster City, California, USA; Lot AJ0702F1). Soft gelatin capsules containing 100 mg RTV (Norvir®) were manufactured by Abbott Laboratories (Abbott Park, Illinois, USA; Lot 526392E21). Capsules containing 150 mg of atazanavir (Reyataz®) were manufactured by Bristol-Myers Squibb Co. (New York, New York, USA; Lots 7E3099A and 7E3102A). Midazolam hydrochloride syrup containing 2 mg/mL midazolam was manufactured by Roxane Laboratories (Columbus, Ohio, USA; Lot 658337A).

**Key Inclusion and Exclusion Criteria**

Subjects were healthy nonsmoking males and females between the ages of 19 and 45 years, inclusive, with a creatinine clearance of at least 80 mL/min. Potential subjects were excluded if they were pregnant or lactating, or if they had taken any prescription or over-the-counter medication (including herbal products, and with the exception of vitamins, acetaminophen, ibuprofen, and hormonal contraceptives) within 30 days prior to study drug dosing.

Potential subjects were excluded if they had received nephrotoxic drugs or potential competitors of renal excretion, hepatotoxic drugs, systemic steroids, immunosuppressants, or chemotherapeutic agents within 3 months prior to study screening.

**Concomitant Medications**

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, food or beverages containing caffeine, xanthine, or soda were not permitted starting 48 h before study drug administration and during all confinement periods. Antacids or vitamin or mineral supplements containing calcium, magnesium, iron, or zinc were not permitted for the duration of the study. Alcohol was not permitted for the duration of the study. Consumption of certain citrus fruits and fruit and vegetable juices was restricted during the study.

**Sample Collection**

Blood was collected for the analysis of elvitegravir, its metabolites M1 (GS-9202, formed via CYP3A) and M4 (the glucuronide metabolite GS-9200), ritonavir, atazanavir, and/or

midazolam and 1'-hydroxymidazolam were collected on the specified study days at the times (in hours post-dose) listed below:

| | |
|---|---|
| Days 10 and 21 | 0:00 (predose), 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 4:30, 5:00, 6:00, 8:00, 10:00, 12:00, 18:00, 24:00, 32:00, 36:00, and 48:00 |

## Analytical Plan

*Pharmacokinetic data*

The primary pharmacokinetic parameters evaluated in this study were $C_{max,}$ $C_{tau}$, and $AUC_{tau}$ for elvitegravir. In addition, $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{1/2}$, $C_{tau}$, and $AUC_{tau}$ were calculated for elvitegravir, its metabolites M1 and M4, ritonavir, and atazanavir; $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{inf}$, $\%AUC_{exp}$, $V_z/F$, and CL/F were estimated for midazolam and its metabolite 1'-OH midazolam. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin®, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2}$) were reported when the pharmacokineticist deemed the data evaluable after examination.

Differences in EVG PK between treatments were calculated using mixed-effects statistical models (SAS® PROC MIXED software, v8.2; SAS Institute, Inc., Cary, North Carolina, USA). PK parameters were considered unaltered if the 90% CI values were within the lack of interaction boundaries of 60-167%. The effects of ATV and RTV on MDZ PK were evaluated using similar statistical methods.

## Trial Results

***Bioanalytical methods***

Concentrations of EVG, GS-9200, GS-9202, and RTV in plasma samples were determined using LC-MS/MS (Method M-GS-9137-16511V7) by Gilead Sciences Bioanalytical Laboratory (Durham, North Carolina, USA). Frozen plasma samples were received between 6 and 16 Nov 2007 and stored at -80˚C. Analysis was performed between 17 Nov and 19 Dec 2007. The first day of sample collection was 23 Oct 2007, so the maximum sample storage time was 57 days, which is within the validated long-term frozen stability duration (at -80˚C) of 268 days for EVG, GS-9200, GS-9202, and RTV.

Concentrations of ATV in plasma samples were determined using LC-MS/MS (Method [(b) (4)]06-204) by [(b) (4)]. Frozen plasma samples were received between 6 and 16 Nov 2007 and stored at -20˚C. Analyses were completed by 20 Dec 2007. The first day of sample collection was 23 Oct 2007, so the maximum sample storage time was 57 days, which is within the validated long-term frozen stability duration (at -70˚C) of 96 days.

Concentrations of MDZ and 1'-OH MDZ in plasma samples were determined using LC-MS/MS (Method (b) (4) 42-0624) by (b) (4) . Frozen plasma samples were received between 6 and 16 Nov 2007 and stored at -20˚C. Analyses were completed by 10 Dec 2007. The first day of sample collection was 2 Nov 2007, so the maximum sample storage time was 38 days, which is within the validated long-term frozen stability duration (at -70˚C) of 135 days.

The EVG calibration standards ranged from 20-10000 ng/mL and the quality control (QC) concentrations were 50.0, 750, and 7500 ng/mL. For GS-9200 and GS-9202 calibration standards ranged from 20-1000 ng/mL and the QC concentrations were 50.0, 150, and 750 ng/mL. For RTV, the calibration standards ranged from 5-5000 ng/mL and the QC concentrations were 15.0, 750, and 4000 ng/mL. For ATV, the calibration standards ranged from 10-5000 ng/mL and the QC concentrations were 30.0, 2000, and 4000 ng/mL. For MDZ and 1'-OH MDZ, the calibration standards ranged from 0.1-100 ng/mL and the QC concentrations were 0.1, 0.3, 5, 30, and 75 ng/mL. All inter-assay accuracy and precision estimates (displayed in Tables 1 and 2 for parent and metabolite compounds, respectively) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for EVG, RTV, ATV, and MDZ in human plasma** (source: Study Report Table 5-4)

| | Elvitegravir | Ritonavir | Atazanavir | Midazolam |
|---|---|---|---|---|
| Linear Range (ng/mL) | 20.0 to 10,000.0 | 5.0 to 5000.0 | 10.0 to 5000.0 | 0.1 to 100.0 |
| LLQ (ng/mL) | 20.0 | 5.0 | 10.0 | 0.1 |
| Inter-Assay Precision Range[a] | 2.1% to 6.3% | 8.0% to 11.6% | 2.3% to 3.0% | 2.4% to 7.1% |
| Inter-Assay Accuracy Range[b] | −13.0% to −2.4% | −2.0% to 9.4% | −5.7% to −1.5% | −2.7% to −1.0% |
| Stability in Frozen Matrix (days) | 268 | 268 | 96 | 135 |

LLQ = lower limit of quantitation

a Relative standard deviation

b Difference from nominal concentrations

Source: Appendix 10

**Table 2: Bioanalytical assay validation for GS-9200, GS-9202, and 1'-OH MDZ in human plasma** (source: Study Report Table 5-5)

| | GS-9200 | GS-9202 | 1-OH MDZ |
|---|---|---|---|
| Linear Range (ng/mL) | 20.0 to 1000.0 | 20.0 to 1000.0 | 0.1 to 100.0 |
| LLQ (ng/mL) | 20.0 | 20.0 | 0.1 |
| Inter-Assay Precision Range[a] | 4.7% to 14.7% | 3.5% to 10.9% | 3.0% to 8.2% |
| Inter-Assay Accuracy Range[b] | −4.5% to 1.5% | −5.1% to −3.3% | −3.0% to −1.3% |
| Stability in Frozen Matrix (days) | 268 | 268 | 135 |

LLQ = lower limit of quantitation
a Relative standard deviation
b Difference from nominal concentrations
Source: Appendix 10

***Trial population***

A total of 18 healthy adult subjects were enrolled in the study, received study drug, and were included in the safety analysis set; 15 subjects completed the study. Three subjects discontinued the study early: one subject was lost to follow-up, one subject had increased blood CPK related to administration of EVG/ATV, and one subject had drug eruption related to administration of EVG/ATV. Of the safety analysis set (n=18), the majority of subjects were white (88.9%); the remainder were black (11.1%). Half of the subjects were female (50%). Subjects had a mean age of 35 years (range: 18 to 45 years).

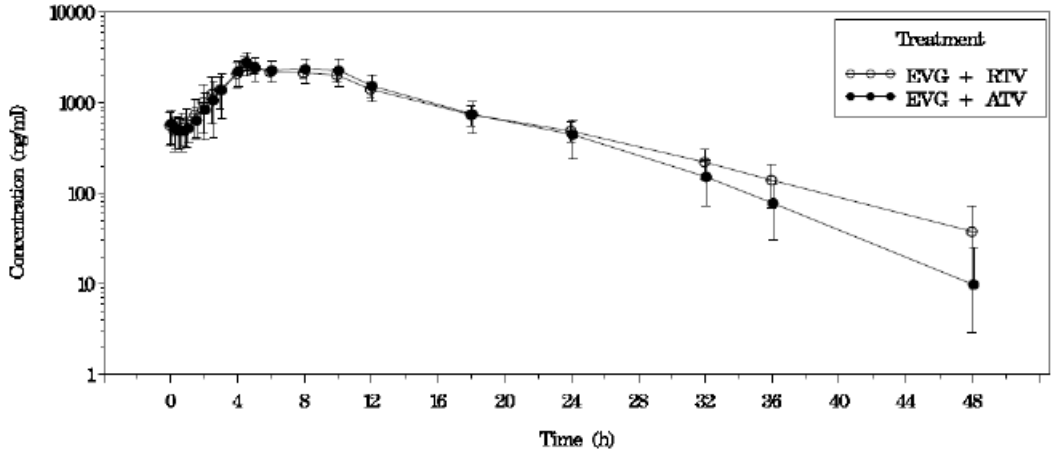
***Results of pharmacokinetic analyses***

In this study, elvitegravir, its metabolite M4 (GS-9200), midazolam, and 1'-OH midazolam exposures were compared following administration of EVG/r and EVG/ATV.

Predose EVG and ATV concentrations were substantially lower than the mean in one subject (2848-1004), suggesting potential noncompliance with study drug dosing. Statistical analyses were performed with and without this subject; only the latter are reviewed here.

The steady-state concentration-time profiles of EVG following EVG/r and EVG/ATV administration are shown in Figure 2. For the first 24 h post-dose, mean EVG plasma concentrations were similar between the two treatments; thereafter, EVG concentrations were modestly lower in the EVG/ATV treatment arm. The steady-state EVG PK parameters are displayed in Table 2. Statistical comparisons of $C_{max}$, $C_{tau}$, and $AUC_{tau}$ (excluding Subject 2848-1004) demonstrated no significant changes in EVG exposures as defined by the associated 90% confidence intervals that fell within the predefined no-effect bounds of 60-167% (see Table 3).

**Figure 2: Steady-state elvitegravir plasma concentrations after coadministration of elvitegravir with ritonavir or atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-1)




EVG + ATV = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)
EVG + RTV = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)
Values presented as mean ± standard deviation. The PK analysis set includes 15 subjects.
Source: Section 11.1, Table 4.1, Figure 1.1

**Table 2: Summary of steady-state elvitegravir PK parameters after coadministration of elvitegravir with ritonavir or atazanavir** (PK analysis set; source: Study Report Table 7-1)

| EVG PK Parameter | EVG/ATV (N = 15) | EVG/r (N = 15) |
|---|---|---|
| $C_{max}$ (ng/mL), Mean (% CV) | 2912.5 (27.6) | 2770.6 (16.6) |
| $C_{tau}$ (ng/mL), Mean (% CV) | 443.3 (45.6) | 484.6 (25.6) |
| $AUC_{tau}$ (ng•h/mL), Mean (% CV) | 31834.6 (29.3) | 30657.0 (15.7) |
| $T_{max}$ (h), Median (Q1, Q3) | 4.50 (4.50, 10.00) | 4.50 (4.50, 4.50) |
| $T_{½}$ (h), Median (Q1, Q3) | 5.18 (4.56, 5.73) | 6.28 (5.80, 7.66) |

EVG/ATV = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)
EVG/r = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)
CV = coefficient of variation, h = hour(s), Q1 = first quartile, Q3 = third quartile
Source: Section 11.1 Table 5.1; Appendix 14, Listing 21.1

**Table 3: Statistical comparisons of elvitegravir PK parameters after coadministration of elvitegravir with ritonavir or atazanavir** (PK analysis set; source: Study Report Table 7-2)

| EVG PK Parameter | Geometric Least Squares Means[a] | | Geometric Least Squares Mean Ratio Test/Reference(%) | 90% CI |
|---|---|---|---|---|
| | EVG/ATV (N = 15) | EVG/r (N = 15) | | |
| $C_{max}$ (ng/mL) | 2794.71 | 2736.85 | 102.11 | 89.87, 116.03 |
| $C_{tau}$ (ng/mL) | 372.91 | 473.47 | 78.76 | 58.19, 106.60 |
| $AUC_{tau}$ (ng•h/mL) | 30115.37 | 30477.63 | 98.81 | 84.02, 116.21 |
| **EVG PK Parameter (excluding Subject 2848-1004)[b]** | **EVG/ATV (N = 14)** | **EVG/r (N = 14)** | **Geometric Least Squares Mean Ratio Test/Reference(%)** | **90% CI** |
| $C_{max}$ (ng/mL) | 2973.87 | 2744.78 | 108.35 | 99.01, 118.56 |
| $C_{tau}$ (ng/mL) | 439.51 | 488.96 | 89.89 | 71.43, 113.12 |
| $AUC_{tau}$ (ng•h/mL) | 32531.39 | 30479.40 | 106.73 | 95.60, 119.17 |

Test (EVG/ATV) = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)

Reference (EVG/r) = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)

CI = confidence interval, h = hour(s)

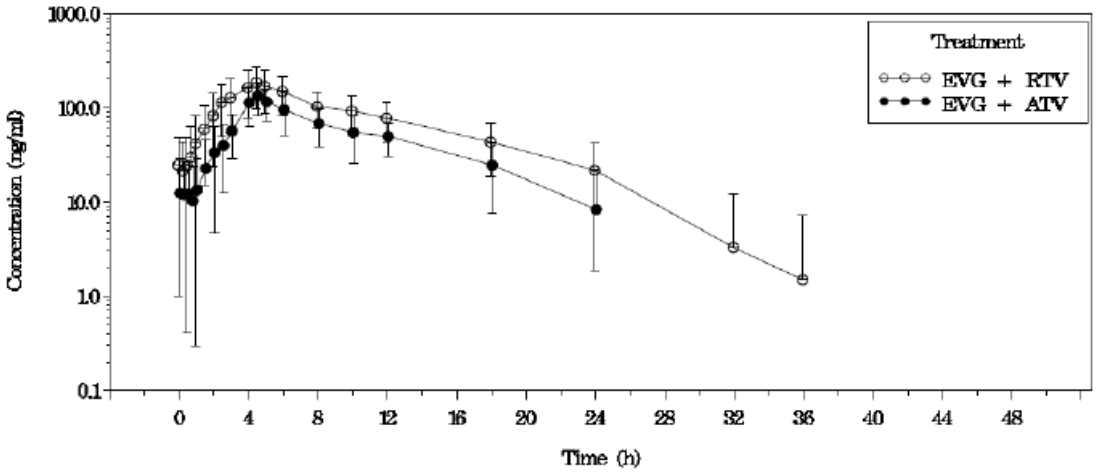
a Geometric least squares means were obtained by PROC MIXED model.

b Following the 10-day dosing period, Subject 2848-1004 displayed below-quantifiable predose levels of ATV and substantially lower predose concentration of EVG (62.9 ng/mL) compared to the mean (586.1 ng/mL), suggesting potential noncompliance with study drug dosing. Therefore, statistical analyses were performed both with and without this subject.

Source: Section 11.1, Table 6.1, 6.2; Appendix 14, Listing 22.1, 22.2

The mean plasma concentrations of the EVG glucuronide metabolite M4 (GS-9200) were modestly lower following administration of EVG/ATV compared to those observed following administration of EVG/r (see Figure 3). After excluding Subject 2848-1004, the 90% CIs for M4 $C_{max}$ were within the prespecified no-effect boundaries of 60-167%, but the lower bounds of the 90% CIs for M4 $C_{tau}$ and $AUC_{tau}$ fell below 60% (see Table 4), indicating decreased M4 exposures with EVG/ATV relative to EVG/r. The mean M4:elvitegravir ratio was lower after EVG/ATV administration compared to after EVG/r (2.7% vs. 4.4%, respectively), reflecting the inhibitory effects of ATV on EVG glucuronidation (i.e. UGT1A1/3).

**Figure 3: Steady-state M4 plasma concentrations after coadministration of elvitegravir with ritonavir or atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-2)




Treatment A = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)

Treatment B = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)

Values presented as mean ± standard deviation. The PK analysis set includes 15 subjects. Subjects 2848-1002, 2848-1009, and 2848-1017 did not have evaluable profiles for each treatment pair and were excluded from the analysis set.

Source: Section 11.1, Table 4.2, Figure 1.2

**Table 4: Statistical comparisons of M4 PK parameters after coadministration of elvitegravir with ritonavir or atazanavir** (PK analysis set; source: Study Report Table 7-4)

| GS-9200 PK Parameter | Geometric Least Squares Means[a] | | Geometric Least Squares Mean Ratio Test/Reference (%) | 90% CI |
|---|---|---|---|---|
| | EVG/ATV (N = 15) | EVG/r (N = 15) | | |
| $C_{max}$ (ng/mL) | 136.13 | 182.60 | 74.55 | 64.61, 86.01 |
| $C_{tau}$ (ng/mL)[b] | 23.80 | 35.12 | 67.76 | 50.51, 90.92 |
| $AUC_{tau}$ (ng•h/mL) | 1066.08 | 1702.38 | 62.62 | 54.69, 71.71 |
| **GS-9200 PK Parameter (excluding Subject 2848-1004)[c]** | **EVG/ATV (N = 14)** | **EVG/r (N = 14)** | **Geometric Least Squares Mean Ratio Test/Reference (%)** | **90% CI** |
| $C_{max}$ (ng/mL) | 138.12 | 178.59 | 77.34 | 67.12, 89.11 |
| $C_{tau}$ (ng/mL)[b] | 23.80 | 35.12 | 67.76 | 50.51, 90.92 |
| $AUC_{tau}$ (ng•h/mL) | 1108.81 | 1681.78 | 65.93 | 58.74, 74.00 |

Test (EVG/ATV) = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)

Reference (EVG/r) = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)

CI = confidence interval, h = hour(s)

a Geometric least squares means were obtained by PROC MIXED model.

b EVG/ATV N = 5, EVG/r N = 9

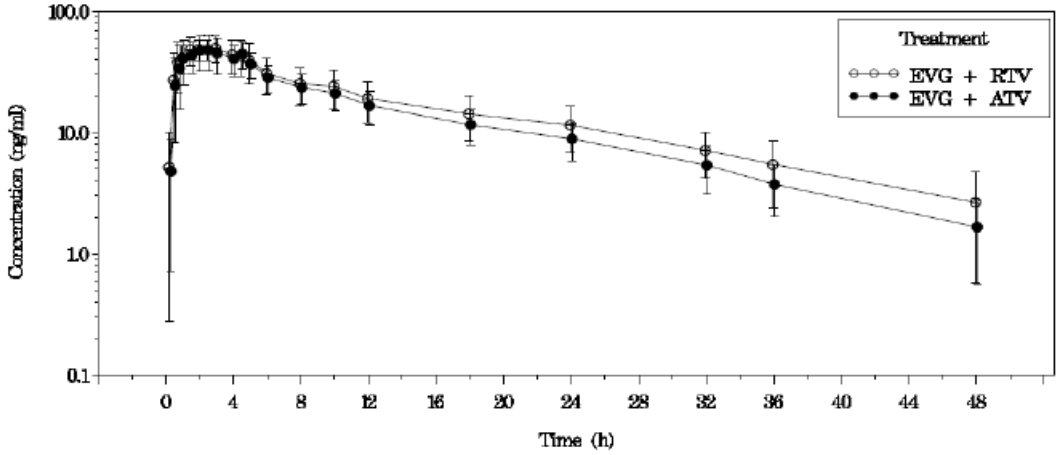
c Following the 10-day dosing period, Subject 2848-1004 displayed below-quantifiable predose levels of ATV and substantially lower predose concentration of EVG (62.9 ng/mL) compared to the mean (586.1 ng/mL), suggesting potential noncompliance with study drug dosing. Therefore, statistical analyses were performed both with and without this subject.

Source: Section 11.1, Table 6.1, 6.2; Appendix 14, Listing 22.1, 22.2

Mean plasma concentrations of the hydroxylation metabolite M1 (GS-9202) were too low to provide substantive pharmacokinetic data for any of the treatments examined.

The concentration-time profiles of MDZ following a single dose of MDZ and multiple doses of EVG/r or EVG/ATV are shown in Figure 4. Mean MDZ plasma concentrations were similar between the two treatments, although MDZ concentrations were slightly lower in the EVG/ATV treatment arm. Statistical comparisons of single-dose MDZ PK parameters are displayed in Table 5. After exclusion of Subject 2848-1004, the geometric least square mean MDZ $AUC_{0\text{-last}}$ and $AUC_{inf}$ values were approximately 9-10% lower after coadministration of MDZ with EVG/ATV relative to after coadministration of MDZ with EVG/r.

**Figure 4: Plasma concentrations of MDZ after coadministration of MDZ and elvitegravir with ritonavir or atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-5)




EVG + ATV (EVG/ATV) = 300 mg EVG plus 400 mg ATV administered once daily (in the morning)
EVG + RTV (EVG/r) = 300 mg EVG plus 100 mg RTV administered once daily (in the morning)
Values presented as mean ± standard deviation. The PK analysis set includes 15 subjects. Subjects 2848-1002, 2848-1009, and 2848-1017 did not have evaluable profiles for each treatment pair and were excluded from the analysis set.
Source: Section 11.1, Table 4.6, Figure 1.6

**Table 5: Statistical comparisons of MDZ PK parameters after coadministration of MDZ and elvitegravir with ritonavir or atazanavir** (PK analysis set; source: Study Report Table 7-6)

| MDZ PK Parameter | Geometric Least Squares Means[a] | | Geometric Least Squares Mean Ratio Test/Reference (%) | 90% CI |
|---|---|---|---|---|
| | MDZ + EVG/ATV (N = 15) | MDZ + EVG/r (N = 15) | | |
| $AUC_{0\text{-last}}$ (ng•h/mL) | 580.31 | 690.08 | 84.09 | 71.03, 99.56 |
| $AUC_{inf}$ (ng•h/mL) | 604.16 | 734.54 | 82.25 | 69.47, 97.38 |
| $C_{max}$ (ng/mL) | 52.31 | 56.87 | 91.99 | 79.34, 106.66 |
| **MDZ PK Parameter (excluding Subject 2848-1004)[b]** | **MDZ + EVG/ATV (N = 14)** | **MDZ + EVG/r (N = 14)** | **Geometric Least Squares Mean Ratio Test/Reference (%)** | **90% CI** |
| $AUC_{0\text{-last}}$ (ng•h/mL) | 635.87 | 692.91 | 91.77 | 83.33, 101.07 |
| $AUC_{inf}$ (ng•h/mL) | 663.96 | 741.50 | 89.54 | 80.75, 99.29 |
| $C_{max}$ (ng/mL) | 56.06 | 56.73 | 98.82 | 89.63, 108.95 |

Test (MDZ + EVG/ATV) = 5 mg midazolam plus 300 mg EVG plus 400 mg ATV administered once daily (in the morning)
Reference (MDZ + EVG/r) = 5 mg midazolam plus 300 mg EVG plus 100 mg RTV administered once daily (in the morning)

CI = confidence interval, h = hour(s)

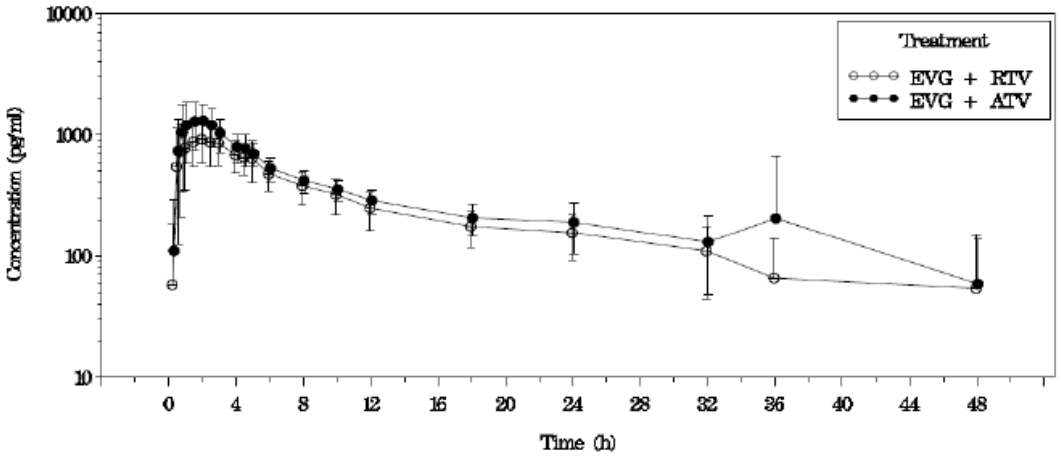
a Geometric least squares means were obtained by PROC MIXED model.

b Following the 10-day dosing period, Subject 2848-1004 displayed below-quantifiable predose levels of ATV and substantially lower predose concentration of EVG (62.9 ng/mL) compared to the mean (586.1 ng/mL), suggesting potential noncompliance with study drug dosing. Therefore, statistical analyses were performed both with and without this subject.

Source: Section 11.1, Table 6.1, 6.2; Appendix 14, Listing 22.1, 22.2

The concentration-time profiles of 1'-OH MDZ following a single dose of MDZ and multiple doses of EVG/r or EVG/ATV are shown in Figure 5. Mean 1'-OH MDZ plasma concentrations were similar between the two treatments, although 1'-OH MDZ concentrations were slightly higher in the EVG/ATV treatment arm. Statistical comparisons of 1'-OH MDZ PK parameters are displayed in Table 6. After exclusion of Subject 2848-1004, the GLSM values of 1'-OH MDZ $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{inf}$ were approximately 26-32% higher after coadministration of MDZ with EVG/ATV relative to after coadministration of MDZ with EVG/r. These data indicate that inhibition of CYP3A was slightly less in the presence of EVG/ATV compared to EVG/r.

**Figure 5: Plasma concentrations of 1'-OH MDZ after coadministration of MDZ and elvitegravir with ritonavir or atazanavir** (mean ± SD; PK analysis set; source: Study Report Figure 7-6)




Values presented as mean ± standard deviation. The PK analysis set includes 15 subjects. Subjects 2848-1002, 2848-1009, and 2848-1017 did not have evaluable profiles for each treatment pair and were excluded from the analysis set.

Source: Section 11.1, Table 4.7, Figure 1.7

**Table 6: Statistical comparisons of 1'-OH MDZ PK parameters after coadministration of MDZ and elvitegravir with ritonavir or atazanavir** (PK analysis set; source: Study Report Table 7-9)

| 1-OH MDZ PK Parameter | Geometric Least Squares Means[a] | | Geometric Least Squares Mean Ratio Test/Reference (%) | 90% CI |
|---|---|---|---|---|
| | MDZ + EVG/ATV (N = 15) | MDZ + EVG/r (N = 15) | | |
| $AUC_{0\text{-last}}$ (ng•h/mL) | 12.70 | 9.82 | 129.31 | 119.28, 140.18 |
| $AUC_{inf}$ (ng•h/mL)[b] | 16.48 | 12.62 | 130.62 | 111.43, 153.12 |
| $C_{max}$ (ng/mL) | 1.40 | 1.00 | 139.98 | 113.93, 172.00 |
| **1-OH MDZ PK Parameter (excluding Subject 2848-1004)[c]** | **MDZ + EVG/ATV (N = 14)** | **MDZ + EVG/r (N = 14)** | **Geometric Least Squares Mean Ratio Test/Reference (%)** | **90% CI** |
| $AUC_{0\text{-last}}$ (ng•h/mL) | 12.74 | 10.04 | 126.90 | 116.97, 137.67 |
| $AUC_{inf}$ (ng•h/mL)[d] | 16.72 | 12.71 | 131.50 | 111.89, 154.53 |
| $C_{max}$ (ng/mL) | 1.32 | 1.05 | 126.23 | 111.23, 143.24 |

Test (MDZ + EVG/ATV) = 5 mg midazolam plus 300 mg EVG plus 400 mg ATV administered once daily (in the morning)

Reference (MDZ + EVG/r) = 5 mg midazolam plus 300 mg EVG plus 100 mg RTV administered once daily (in the morning)

CI = confidence interval, h = hour(s)

a Geometric least squares means were obtained by PROC MIXED model.

b EVG/ATV N = 11, EVG/r N = 11

c Following the 10-day dosing period, Subject 2848-1004 displayed below-quantifiable predose levels of ATV and substantially lower predose concentration of EVG (62.9 ng/mL) compared to the mean (586.1 ng/mL), suggesting potential noncompliance with study drug dosing. Therefore, statistical analyses were performed both with and without this subject.

d EVG/ATV N = 10, EVG/r N = 11

Source: Section 11.1, Table 6.1, 6.2; Appendix 14, Listing 22.1, 22.2

***Results of safety analysis***

Coadministration of EVG/ATV was associated with a higher incidence of adverse events compared to administration of EVG/r; the only study drug-related adverse events reported in more than one subject were abdominal pain, diarrhea, dizziness, and drug eruption. There were two discontinuations due to adverse events, both in subjects receiving EVG/ATV: one subject discontinued due to moderate increases in blood CPK and one subject discontinued due to severe drug eruption. There were no deaths or discontinuations due to serious adverse events during this trial.

**Trial Summary**

This study was designed to compare the pharmacokinetics of elvitegravir, its glucuronide metabolite M4, midazolam, and its metabolite 1'-OH midazolam following administration of EVG/ATV 300/400 mg QD or EVG/r 300/100 mg, with or without a single 5 mg dose of the CYP3A probe drug MDZ.

Coadministration of EVG and ATV resulted in similar EVG exposures compared to administration of EVG/r. M4 exposures ($AUC_{tau}$) were approximately 37% lower in the presence of ATV. MDZ $AUC_{0\text{-last}}$ and $AUC_{inf}$ were approximately 8-10% lower and 1'-OH MDZ $AUC_{0\text{-last}}$ and $AUC_{inf}$ were approximately 26-32% higher following administration of EVG/ATV relative to EVG/r. In total, these data indicate that the two-fold increase EVG exposures observed in Study GS-US-183-0108 after coadministration of ATV/r 300/100 mg and EVG 200 mg relative to administration of EVG/r 200/100 mg were likely due to inhibition by ATV of EVG metabolism via UGT1A1/3 rather than CYP3A. Although these results provide a mechanistic explanation for the need to dose adjust, they have no bearing on the Applicant's selection of the reduced dose of EVG 85 mg QD when coadministered with ATV/r 300/100 mg QD.

**Trial 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**

**Trial Period**
21 Aug 2008 to 2 Jul 2010
Final report date: 6 Dec 2010 (submitted to IND 72,177)

**Trial Sites**
10 sites in the United States, United Kingdom, and Canada

**Trial Rationale**
Elvitegravir (EVG, GS-9137) is an inhibitor of the human immunodeficiency virus (HIV) integrase, currently under development for the treatment of HIV infection; the intended patient population in the proposed indication is treatment-experienced HIV-1 infected adults. Results from *in vitro* studies have demonstrated potent anti-HIV activity, including activity against viruses that are resistant to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PI). Ritonavir (RTV) is an HIV PI indicated for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV infection. Coadministration of ARVs that are cytochrome P450 (CYP) isoform 3A substrates with the potent CYP3A inhibitor RTV increases the systemic exposure of the substrate drugs. This study was designed to evaluate the pharmacokinetics and safety of elvitegravir administered with a background regimen containing a ritonavir-boosted PI in treatment-experienced adolescent subjects with HIV-1 infection using the proposed adult doses, with an optional 48-week treatment phase to evaluate efficacy.

**Trial Objectives**
The primary objective of the trial was to:

- evaluate the steady-state pharmacokinetics and confirm the dose of RTV-boosted elvitegravir (EVG/r) in HIV-1 infected ARV treatment-experienced adolescent subjects

The secondary objective of the trial was to:

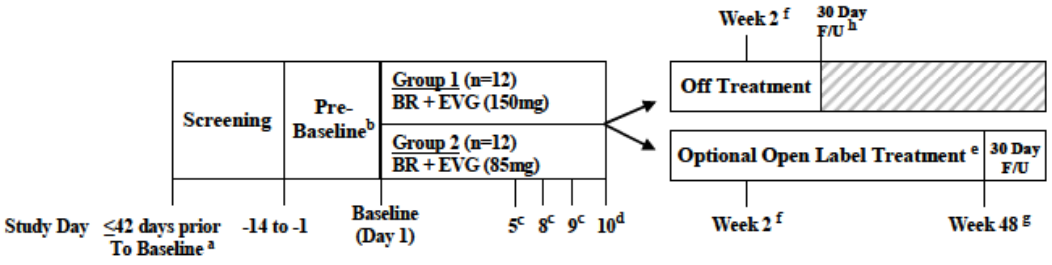
- evaluate the safety and tolerability of EVG/r in HIV-1 infected ARV treatment-experienced adolescents

**Trial Design**
This was a nonrandomized, open-label, multiple-dose, multicenter, 10-day pharmacokinetic study with optional enrollment in a subsequent 48-week extension phase for subjects with HIV-1 RNA >1000 copies/mL at Screening. The background ARV regimens were selected by the investigator before study randomization based on each

subject's ARV history and viral resistance profile. The background ARV regimen (BR) contained one of the following ritonavir-boosted PIs (PI/r): lopinavir/r (LPV/r), atazanavir/r (ATV/r), darunavir/r (DRV/r), fosamprenavir/r (FPV/r), and tipranavir/r (TPV/r). Due to pharmacokinetic interactions, the dose of EVG was reduced from 150 mg QD to 85 mg QD if the BR contained ritonavir-boosted ATV or LPV.

The study schema is shown in Figure 1.

**Figure 1: Study schema** (source: Study Figure 7-1)




BR = background regimen, EVG = elvitegravir, F/U = follow-up.

a The screening window was extended up to 47 days for subjects who required repeat testing of viral genotype/phenotype.

b Pre-baseline visit was to be performed 1 to 14 days prior to the baseline visit to ensure that the BR was identified and all components of the BR were prescribed and available. This visit could occur either in the clinic or by telephone.

c Subjects were contacted on Days 5, 8, and 9 for assessment of AEs, concomitant medications, and adherence to the EVG + BR dosing schedule during the 10-day period leading up to intensive PK evaluation.

d The Day 10 visit was to occur on the protocol-specified visit date based on the baseline (Day 1) visit. For the purposes of scheduling, the Day 10 visit may have been performed within +4 days of the protocol-specified visit date. Beginning on the morning of Day 10 visit, blood samples were collected at predose (0), and 2, 4, 4.5, 5, 8, and 10–12 hours postdose (with predose also serving as t = 24) to assess EVG pharmacokinetics and confirm the doses of EVG for adolescent subjects. Subjects were instructed that the Day 10 dose of EVG + BR components must not be taken before coming to the clinic for the Day 10 assessments.

e After completing the 10-day PK evaluation subjects who had HIV-1 RNA >1000 copies/mL at screening had the option to receive open-label EVG through 48 weeks in this study. Upon completion of the 10-day PK evaluation phase, appropriateness of the dosage level relative to that in adults for the subjects enrolled was assessed. Individual subjects with EVG exposures outside of the established adult range (such as less than 2.5th adult percentile) during the 10-day PK evaluation could undergo dose adjustment as appropriate during the optional treatment phase. If dose adjustment was performed, additional PK evaluations may have been repeated as appropriate.

f A Week 2 visit (4 days post-Day 10 PK assessments) was performed for all subjects.

g Subjects who completed 48 weeks of study treatment in Study GS-US-183-0152 were offered open-label EVG in a separate rollover protocol until either EVG received marketing approval or EVG development was terminated by Gilead Sciences, Inc.

h After completion of the Week 2 visit, subjects not participating in the optional treatment phase were asked to return for a 30-day follow-up visit (30 days post-Day 10 PK assessments).

### Key Inclusion and Exclusion Criteria

Subjects were treatment-experienced HIV-1-infected males and females 12 to <18 years of age with plasma HIV-1 RNA levels ≥1000 or <400 copies/mL and documented resistance (as defined by the IAS-USA Guidelines) to one or more class of antiretroviral drugs, or at least six months experience prior to screening with two or more classes of antiretroviral drugs. Subjects must have been on a stable ARV regimen (or off ARV therapy completely) for at least 30 days prior to screening, and must have remained on that regimen until the baseline visit. Subjects had to have a normal ECG and adequate renal function as defined by estimated glomerular filtration rate (using the Schwartz

formula) of ≥ 60 mL/min. Screening laboratory evaluations must have fallen within normal ranges.

Potential subjects were excluded from enrollment if they had a new AIDS-defining condition diagnosed within 30 days of baseline. Exclusion criteria also included previous exposure to any HIV-1 integrase inhibitor, the use of alcohol or other substances in a way that could interfere with study compliance, a malignancy other than cutaneous Kaposi sarcoma or basal cell carcinoma, or an active, serious infection requiring parenteral antibiotic or antifungal therapy within 30 days of baseline.

Potential subjects were excluded for the use of specified medications from the following drug classes within 30 days of the baseline visit (refer to the table in section 7.4.7 of the study report for details): sedatives/hypnotics, GI motility agents, neuroleptic drugs, ergot derivatives, immunosuppressants, antibacterials, calcium channel blockers, antiarrythmics, antimycobacterials, antihistamines, anticonvulsants, herbal supplements, systemic chemotherapeutic (antineoplastic) agents, immunomodulators, medications not to be taken with RTV, systemic corticosteroids, HMG-CoA reductase inhibitors (statins), antifungals, anticoagulants, opiates, and phosphodiesterase-5 inhibitors.

**Rationale for Dose Selection**

Background regimens contained one of the following: atazanavir/r (ATV/r) 300/100 mg QD, darunavir/r (DRV/r) 600/100 mg BID, fosamprenavir/r (FPV/r) 700/100 mg BID, lopinavir/r (LPV/r) 400/100 mg BID, or tipranavir/r (TPV/r) 500/200 mg BID. These doses are those approved in the US for treatment-experienced people with HIV-1 infection.

Elvitegravir shares some similarities with PIs in terms of clearance mechanisms (i.e. CYP3A-mediated oxidation and UGT-mediated glucuronidation). In general, doses of RTV-boosted PIs are the same in adults and adolescents. Therefore, the proposed adult doses of elvitegravir were used in this adolescent study. The elvitegravir dose of 150 mg QD (in combination with DRV/r, FPV/r, or TPV/r) was chosen based on a relative bioavailability study (GS-US-183-0105) demonstrating bioequivalent exposures to 125 mg of an earlier elvitegravir formulation, which was shown to have substantial antiviral activity in Phase 1 and 2 studies. The elvitegravir dose of 85 mg QD (in combination with ATV/r or LPV/r) was chosen based on results from previously conducted drug-drug interaction studies (GS-US-183-0147 [ATV/r] and GS-US-183-0116 [LPV/r]).

**Investigational Product**

Film-coated tablets containing 85 or 150 mg of elvitegravir were manufactured by Gilead Sciences, Inc. (Foster City, California, USA; Lots AJ0704D1 and AJ0802C1 for EVG 85 mg and Lots AJ0704E1 and AJ0705E1 for EVG 150 mg). All components of the background ARV regimens (including ritonavir) were dispensed in open-label fashion as prescribed by the investigator, and administered according to the prescribing information for each particular product.

### Drug Administration

Elvitegravir was administered orally with the fully active PI/r of the background regimen once daily with food, at approximately the same time each day. Study drugs were self-administered at home on Days 1 through 9. On Day 10, subjects arrived at the clinic after an 8 h fast and were given a standardized breakfast. Five minutes after completion of the meal, their assigned dose of elvitegravir/r was administered with 240 mL of water under staff supervision. Subjects also received their ARV regimens according to their dosing schedule. Food was restricted until after the 4 h blood draw, and water was restricted from 1 h before until 2 h after dosing.

### Concomitant Medications

In addition to the medications detailed in the "Key Inclusion and Exclusion Criteria" section above, subjects were instructed not to use any drug with antiretroviral activity that was not part of their prescribed CPI or ARV regimens. The following were also prohibited 2 h before and 2 h after any dose of elvitegravir/r: antacids containing calcium, magnesium, or aluminum; sucralfate; and vitamin or mineral supplements containing calcium, iron, or zinc.

### Sample Collection

Blood samples were collected for the analysis of elvitegravir, its metabolites GS-9202 and GS-9200, and RTV in plasma on Day 10 before administration of study drug and 2, 4, 4.5, 5, 8, 10 to 12 h, and 24 h after dosing.

### Analytical Plan

*Pharmacokinetic data*

The pharmacokinetic parameters $AUC_{tau}$, $C_{max}$, $T_{max}$, $C_{tau}$, $C_{last}$, $T_{last}$, $\lambda_z$, and $t_{1/2}$ were estimated for EVG, GS-9200 (M4), GS-9202 (M1), and RTV in plasma. All pharmacokinetic parameters were estimated using a nonlinear model derived using standard noncompartmental methods (WinNonlin® Professional Edition, Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters that depend on an accurate estimation of the terminal elimination phase ($\lambda_z$ and $t_{1/2)}$ were reported when the pharmacokineticist deemed the data evaluable after examination. An analysis of variance model (ANOVA) was fitted to the natural logarithmic transformation of the EVG AUCtau data to determine if systemic EVG exposures were similar in adolescents and adults, using 90% confidence interval (CI) no effect boundaries of 70% to 143%.

### Trial Results

***Bioanalytical methods***

Concentrations of EVG, its metabolites GS-9200 and GS-9202, and RTV in plasma samples were determined using LC-MS/MS by (b) (4) . Frozen plasma samples were received between 14 Nov 2008 and 16 Sep 2010 and stored at -70˚C. Analysis was performed 2 Dec 2008 and 22 Sep 2010. Samples were collected between 14 Oct 2008 and 25 Jun 2010, so the maximum storage sample time was 655 days, which is within the validated long-term frozen

stability duration of 834 days at -70˚C for all compounds assayed. The LC-MS/MS method (b) (4) 60-0811 was used to analyze all compounds.

The EVG calibration standards ranged from 20-10,000 ng/mL and the quality control (QC) concentrations were 20.0, 50.0, 750, and 7500 ng/mL. For GS-9200, the calibration standards ranged from 17.5-875.5 ng/mL and the QC concentrations were 17.5, 43.8, 131.35, and 656.2 ng/mL. For GS-9202, the calibration standards ranged from 20-750 ng/mL and the QC concentrations were 20.0, 50.0, 150, and 750 ng/mL. For RTV, the calibration standards ranged from 5 to 5000 ng/mL and the QC concentrations were 5.0, 15.0, 750, and 4000 ng/mL. All inter-assay accuracy and precision estimates (displayed in Table 1) were within the acceptable range (≤20% deviation from nominal at the LLoQ concentration, and ≤15% from nominal at all other concentrations).

**Table 1: Bioanalytical assay validation for EVG, GS-9200, GS-9202, and RTV in human plasma** (source: Study Report Table 7-4)

| Parameter | EVG | GS-9200 Metabolite M4 | GS-9202 Metabolite M1 | RTV |
|---|---|---|---|---|
| Linear range (ng/mL) | 20 to 10,000 | 17.5 to 875.5 | 20 to 1000 | 5 to 5000 |
| LLQ(ng/mL) | 20 | 17.5 | 20 | 5 |
| Interassay precision range (%CV) | 3.3 to 5.5% CV | 4.1 to 12.1% CV | 3.8 to 4.8% CV | 3.1 to 14.6% CV |
| Interassay accuracy range (%) | –0.4 to 9.2% RE | 1.4 to 7.8% RE | 0.4 to 8.1% RE | –3.7 to 7.6% RE |
| Stability in frozen matrix (days at –70 °C) | 585 | 585 | 585 | 585 |

CV = coefficient of variation, LLQ = lower limit of quantitation, RE = Relative Error
Source: Appendix 16.1.9

***Trial population***

A total of 25 subjects were randomized in the study and received study treatment: 14 were enrolled in the EVG 85 mg treatment group, and 11 were enrolled in the EVG 150 mg treatment group. Two subjects (8%) discontinued study drug on Day 1 due to adverse events (AEs). Three subjects in the EVG 85 mg treatment group and eight subjects in the EVG 150 mg treatment group were eligible for the optional 48-week treatment phase; three and six subjects from the EVG 85 and 150 mg treatment groups, respectively, enrolled in the optional treatment phase.

The majority of subjects in the intent-to-treat (ITT) analysis set (n=25) were African American (72%; 28% were white) and male (52%), with a mean age of 15 years (range: 12-17 years). Four subjects in the EVG 85 mg treatment group and one subject in the 150 mg treatment group was 12 to <15 years old; the remainder were 15 to <18 years of age.

***Results of pharmacokinetic analyses***

A total of 23 subjects had evaluable pharmacokinetic data: 14 for EVG 85 mg and 11 for EVG 150 mg. The pharmacokinetics of EVG, GS-9200, and ritonavir in plasma were assessed; however, in the presence of ritonavir, plasma concentrations of the CYP3A metabolite GS-9202 were below the limit of quantitation, precluding the evaluation of GS-9202 pharmacokinetics in this study.

The mean EVG concentration-time profiles on Day 10 are displayed in Figure 2 and the steady-state PK parameters for EVG after 10 days of treatment are listed in Table 2. Mean $AUC_{tau}$ and $C_{max}$ values were similar following administration of EVG 85 mg compared to EVG 150 mg. $C_{tau}$ (estimated using $C_0$ as a surrogate) was higher in subjects in the EVG 85 mg treatment group compared to the 150 mg treatment group (EVG 85 mg $C_{tau}$: 627.0 ng/mL; EVG 150 mg $C_{tau}$: 324.5 ng/mL), which was consistent with EVG pharmacokinetics in adults in Study GS-US-183-0145 (EVG 85 mg $C_{tau}$: 759.6 ng/mL; EVG 150 mg $C_{tau}$: 378.2 ng/mL).

**Figure 2: Day 10 mean (SD) EVG plasma concentration-time profiles by treatment** (semi-logarithmic scale, EVG PK Analysis Set; source: Study Report Figure 10-1)

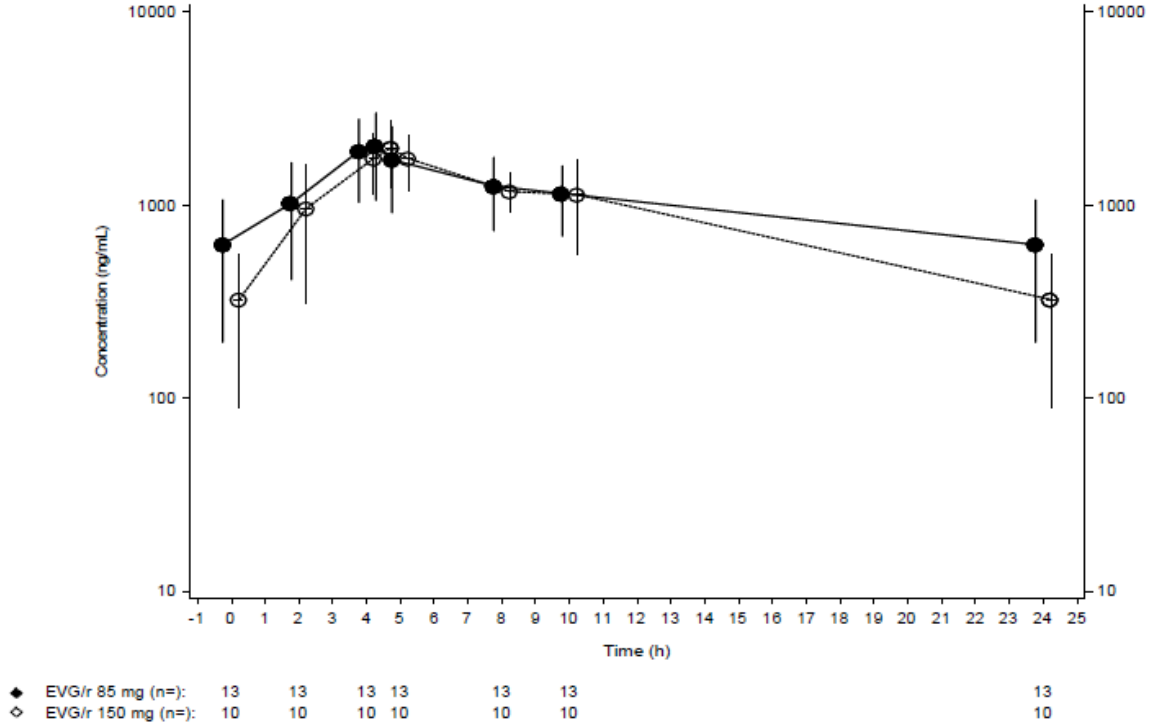



**Table 2: Summary of elvitegravir pharmacokinetic parameters on Day 10** (EVG PK Analysis Set; source: Study Report Table 10-1)

| | BR + EVG 85 mg (n = 13)[a] | BR + EVG 150 mg (n = 10)[b] |
|---|---|---|
| **EVG PK Parameter** | | |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 25,299.2 (44.7) | 21,199.7 (35.7) |
| $C_{max}$ (ng/mL) Mean (%CV) | 2142.3 (44.6) | 2067.0 (35.8) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 627.0 (68.9) | 324.5 (72.5) |
| $T_{max}$ (h) Median (Q1, Q3) | 4.50 (4.25, 4.67) | 4.50 (4.02, 4.50) |
| $T_{1/2}$ (h) Median (Q1, Q3) | 14.42 (11.99, 18.18) | 7.65 (5.52, 10.76) |

CV = coefficient of variation, PK = pharmacokinetic, Q1 = first quartile, Q3 = third quartile
a Subject 4335-5010 did not have intensive PK evaluation due to early termination and was excluded from summaries.
b Subject 4335-5009 did not have intensive PK evaluation due to early termination and was excluded from summaries.
Source: Section 15.1.1, Table 34.1

Statistical comparisons of EVG PK in adults and adolescents are displayed in Table 3. The primary exposure endpoint was EVG $AUC_{tau}$. The 90% confidence intervals (CI) associated with the ratios of the geometric least square means (GLSM) for EVG $AUC_{tau}$ were within the protocol-defined no-effect bounds of 80-143% for the EVG 150 mg treatment group, but the upper bound of the 90% CI for $AUC_{tau}$ rose above 143% for the EVG 85 mg treatment group, indicating a statistically significant increase in EVG exposure in adolescents relative to adults. However, these exposure differences are not considered to be clinically relevant based on the EVG exposure-safety relationship.

Note that Table 10-2 in the Clinical Study Report contains the means of EVG $AUC_{tau}$ and $C_{tau}$ in the "Test GLS Mean Adolescent Subjects EVG 85 mg" column rather than the GLSM, although the GLSM ratios are correct as shown in the Clinical Study Report.

**Table 3: Statistical comparison of EVG pharmacokinetic parameters for adolescent (Test) versus adult (Reference) subjects** (EVG PK Analysis set; source: Study Report Table 10-2)

| EVG PK Parameter | Test GLSM Adolescent Subjects[a] EVG 85 mg | Test GLSM Adolescent Subjects[b] EVG 150 mg | Reference GLSM Adult Subjects | Adolescent vs. Adult GLSM Ratios as % (90% CI) | | |
|---|---|---|---|---|---|---|
| | | | | Adolescent Subjects EVG 85 mg | Adolescent Subjects EVG 150 mg | Adolescent Subjects[c] Combined |
| | n=13 | n=10 | n=24 HIV-1 infected[d] | n=13 | n=10 | n=23 |
| $AUC_{tau}$ (ng·h/mL) | 23130.4 | 19970.04 | 17742.86 | 130.35 (102.98, 165.04) | 112.55 (89.53, 141.50) | 122.30 (101.83, 146.88) |
| $C_{tau}$ (ng/mL) | 500.6 | 251.83 | 225.38 | 222.11 (145.24, 339.66) | 111.74 (69.02, 180.89) | 164.76 (113.01, 240.19) |
| $C_{max}$ (ng/mL) | 1987.8 | 1944.15 | 1519.50 | 130.82 (105.17, 162.72) | 127.95 (101.11, 161.90) | 129.56 (108.49, 154.72) |
| | – | n=10 | n=42 healthy[e] | – | n=10 | – |

| | | | | | | |
|---|---|---|---|---|---|---|
| $AUC_{tau}$ (ng·h/mL) | 23130.4 | 19970.04 | 21374.97 | – | 93.43 (75.81, 115.14) | – |

CI = confidence interval, GLSM = geometric least squares mean, PK = pharmacokinetic
GLSM were obtained using a mixed-effects model. The model included treatment as a fixed effect and subject as a random effect.
[a]Data for infected adolescents came from Study GS-US-183-0152 (Treatment Group 2: BR + EVG 85 mg).
[b]Data for infected adolescents came from Study GS-US-183-0152 (Treatment Group 2: BR + EVG 150 mg).
[c]Data for infected adolescents came from Study GS-US-183-0152 (Treatment Group 1: BR + EVG 85 mg and Treatment Group 2: BR + EVG 150 mg, combined).
[d]Data for infected adults came from Study GS-US-236-0104 (Treatment Arm 1: EVG 150 mg) and Study GS-US-183-0105 (Treatment Arm 4: EVG 125 mg) combined. The Phase 2 EVG 125-mg dose/formulation has previously been shown to provide bioequivalent EVG exposures to the Phase 3 150-mg dose/formulation in a multiple-dose clinical study (GS-US-183-0140).
[e]Data for healthy adults came from Study GS-US-183-0140 (Treatment B: EVG 150 mg) and Study GS-US-183-0146 (Treatment A: EVG 150 mg) combined.
Source Section 15.1, Table 35, Table 36

The steady-state PK parameters for GS-9200 (the glucuronidated metabolite of EVG) after 2 weeks of EVG administration are listed in Table 4. Similar to the findings in adults, the mean plasma concentrations of the GS-9200 metabolite were lower after administration of EVG 85 mg compared to EVG 150 mg in adolescents. This is likely due to inhibition of glucuronidation by ATV/r and LPV/r, with which the 85 mg dose was administered. The ratios of the mean $AUC_{tau}$ values for GS-9200 compared to elvitegravir were 8.3% and 10.3% for the EVG 85 mg and 150 mg treatment arms, respectively, and are consistent with values observed in previous clinical trials conducted in adults.

**Table 4: Summary of GS-9200 pharmacokinetic parameters at Day 10** (EVG PK Analysis Set; source: Study Report Table 10-3)

| | BR + EVG 85 mg (n = 9)[a] | BR + EVG 150 mg (n = 10)[b] |
|---|---|---|
| **GS-9200 PK Parameter** | | |
| $AUC_{tau}$ (ng•h/mL) Mean (%CV) | 1728.1 (31.3) | 2306.3 (57.1)[c] |
| $C_{max}$ (ng/mL) Mean (%CV) | 144.4 (22.2) | 215.9 (52.5) |
| $C_{tau}$ (ng/mL) Mean (%CV) | 34.6 (83.3) | 17.7 (140.6) |
| $T_{max}$ (h) Median (Q1, Q3) | 4.48 (4.00, 4.52) | 4.25 (3.97, 4.93) |

CV = coefficient of variation, PK = pharmacokinetic, Q1 = first quartile, Q3 = third quartile
a Subject 4335-5010 did not have intensive PK evaluation due to early termination and was excluded from summaries. GS-9200 concentrations were not analyzed for Subjects 2877-5001, 2877-5002, 2877-5003, and 2877-5004.
b Subject 4335-5009 did not have intensive PK evaluation due to early termination and was excluded from summaries.
c n = 8; AUC was not calculated for Subjects 0609-5024 and 2887-5019.
Source: Section 15.1, Table 34.3.

Mean steady-state RTV plasma concentrations following administration of RTV 100 mg QD or BID in combination with a PI and EVG were consistent with historical data (data not shown).

***Summary of efficacy analysis***

Efficacy data are summarized through Week 48. At the end of the 10-day PK phase, all subjects who had HIV-1 RNA >1000 copies/mL at baseline had reductions in HIV-1 RNA (median: -1.84 $log_{10}$ copies/mL, range: -2.41 to -1.39 $log_{10}$ copies/mL). All nine

subjects who enrolled in the optional 48-week treatment phase (eligibility criteria included HIV-1 RNA >1000 copies/mL at Screening) had reductions in HIV-1 RNA at Week 48 (median change from baseline: -1.75 $\log_{10}$ copies/mL, range: -2.69 to -0.40 $\log_{10}$ copies/mL).

***Summary of safety analysis***

During the PK phase, the incidence of treatment-emergent adverse events was similar between the treatment groups (71.4% and 72.7% in the EVG 85 mg and 150 mg arms, respectively). The most frequently reported AEs were nausea (24%) and dizziness (12%). One subject in each treatment arm discontinued study drug due to AEs (treatment-related nausea, vomiting, dizziness, and chills). There were no deaths or study drug-related serious AEs. No relationship was observed between AE incidence and EVG dose.

**Trial Summary**

In this study, the steady-state pharmacokinetics of EVG following administration of EVG 85 mg (in combination with ATV/r or LPV/r) or 150 mg (in combination with FPV/r, TPV/r, or DRV/r) were evaluated in adolescent subjects from 12 to <18 years of age. Mean EVG $AUC_{tau}$ values were comparable following 85 and 150 mg EVG and were similar to the values observed in HIV-1 infected adults (Study GS-US-183-0145). The results of this study demonstrate that elvitegravir once-daily is well tolerated in adolescents and that the proposed adult doses of 85 and 150 mg QD are appropriate for adolescents 12 to less than 18 years of age.

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/s/

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LESLIE W CHINN
04/01/2013

DHANANJAY D MARATHE
04/01/2013

JEFFRY FLORIAN
04/01/2013

ISLAM R YOUNIS
04/01/2013

| BIOPHARMACEUTICS REVIEW<br>Office of New Drug Quality Assessment | | | |
|---|---|---|---|
| **Application No.:** | NDA 203-093 | **Reviewer:** Kareen Riviere, Ph.D. | |
| **Submission Date:** | 6/27/2012; 10/5/2012; 1/8/2013 | | |
| **Division:** | DAVP | **Secondary Reviewer:** Sandra Suarez Sharp, Ph.D. | |
| **Applicant:** | Gilead Sciences, Inc. | **Supervisor:** Richard Lostritto, Ph.D. | |
| **Trade Name:** | Vitekta (elvitegravir) tablets | **Date Assigned:** | 7/11/2012 |
| **Generic Name:** | elvitegravir | **Date of Review:** | 3/21/2013 |
| **Indication:** | In combination with other antiretroviral agents for the treatment of HIV-1 infection in ARV treatment-experienced adults | **Type of Submission:** Original 505(b)(1) New Drug Application | |
| **Formulation/strengths:** | IR Tablets/ 85mg and 150mg | | |
| **Route of Administration:** | Oral | | |

**REVIEW SUMMARY:**

This submission is a 505(b)(1) New Drug Application for Vitekta (elvitegravir) tablets, 85 mg and 150 mg. The proposed indication for elvitegravir (EVG) tablets is for the once daily use as a part of an antiretroviral (ARV) regimen that includes a ritonavir-boosted protease inhibitor and other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method as well as the proposed dissolution acceptance criterion. This submission has Quality by Design elements for the drug substance and product manufacturing.

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion, as well as the role of dissolution as a response parameter in the selection of the design space for the drug product's manufacturing process.

**A. Dissolution Method**

The proposed dissolution method for the 85 mg and 150 mg strengths is shown below.

For 85 mg Tablet

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| II | 75 rpm | 700 mL | 37°C | 0.01N HCl (pH2) w/ 2% polysorbate 80 |

For 150 mg Tablet

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| II | 75 rpm | 1000 mL | 37°C | 0.01N HCl (pH2) w/ 2% polysorbate 80 |

Note that the only difference between these two methods is the volume of the medium. The dissolution method conditions for both strengths are adequately justified. Additionally, the proposed dissolution method has adequate discriminating power. Thus, the proposed dissolution methods are acceptable.

**B. Dissolution Acceptance Criterion**

The proposed acceptance criterion for both strengths is shown below.

| Acceptance Criterion |
|---|
| Q = (b)(4)% at 45 min |

The proposed dissolution acceptance criterion did not reflect adequately the *in vitro* performance of the drug product. In an IR letter to the Applicant dated December 12, 2012, the ONDQA Biopharmaceutics Team recommended a dissolution acceptance criterion of Q = (b)(4)% at 45 minutes based on the mean in-vitro dissolution profiles for all strengths at release. In a submission dated January 8, 2013, the Applicant accepted the Agency's recommendation.

**C. Information to Support the Approval of the Lower Strength**

The Applicant conducted one pivotal Phase 3 efficacy and safety study with the 85 mg and 150 mg strengths that also included pharmacokinetics assessment. Additionally, the Phase 3 formulation is the same as the proposed commercial formulation.

**D. Role of Dissolution in the Development of the Design Space for the Manufacturing Process**

The manufacturing process for the proposed commercial EVG tablets involves (b) (4)

Design of experiments (DoE) were performed to establish a design space for the drug product's manufacturing process. (b) (4)

Dissolution was studied in the DoEs as a response variable. During the review cycle, the ONDQA review team requested that the Applicant provide dissolution profiles comparison with *f2* (similarity factor) statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies to determine whether batches manufactured throughout the proposed design space would result in products that are bioequivalent. In a submission dated January 8, 2013, the Applicant provided *f2* values for dissolution profiles of EVG tablets manufactured with parameters representing the design space. (b) (4)

The ONDQA Biopharmaceutics Team deems the proposed design space (see table below) for elvitegravir tablets acceptable.

| Process | Parameter | Range | Target |
|---|---|---|---|
| (b) (4) | | | |

It is noted however, (b) (4)

(b) (4)

(refer to Figure 13).

**RECOMMENDATION:**

1. Vitekta (elvitegravir) 85 mg and 150 mg strength IR tablets are recommended for approval from a Biopharmaceutics standpoint.
    - The following dissolution method and acceptance criterion were agreed upon for both strengths (refer to the submission dated January 8, 2013):
        i. Dissolution method for 85 mg Tablet: Apparatus II, 75 rpm agitation rate, 700 mL media volume, 37 °C, 0.01N HCl w/ 2% polysorbate 80.
        ii. Dissolution method for 150 mg Tablet: Apparatus II, 75 rpm agitation rate, 1000 mL media volume, 37 °C, 0.01N HCl w/ 2% polysorbate 80.
        iii. Dissolution acceptance criterion: Q = (b) (4)% at 45 minutes.

**Kareen Riviere, Ph.D.**
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

**Sandra Suarez-Sharp, Ph.D.**
Secondary Signature
Office of New Drug Quality Assessment

cc: Dr. Angelica Dorantes, Dr. Richard Lostritto

# ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

## 1. Background

### Drug Substance

The structure of elvitegravir (EVG) is shown in Figure 1.

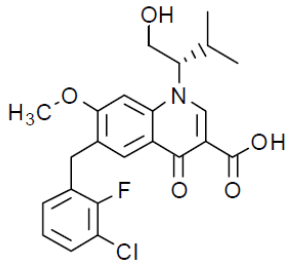



**Figure 1.** Chemical structure of elvitegravir

The Applicant states that EVG has a pKa of 6.6. According to the Applicant, EVG is a BCS Class 2 (low solubility, high permeability) compound. The aqueous solubility of EVG free acid reported by the Applicant is less than 0.5 µg/mL under acidic conditions (pH 5 and below) and observed a solubility enhancement under basic conditions to approximately 100 µg/mL at pH 10. The Applicant determined that the aqueous solubility of EVG can be greatly enhanced by the presence of nonionic, cationic, and anionic surfactants. EVG solubility was evaluated in different surfactant types and concentrations at pH 2.0, 4.5 and 6.8. The nonionic surfactants included polysorbate 20, polysorbate 80, and Cremophor EL. The ionic surfactants included sodium lauryl sulfate (SLS) and cetyltrimethylammonium bromide (CTAB). The solubility profile of elvitegravir in different buffer solutions with various surfactants is shown in Table 1.

**Table 1.** Solubility of Elvitegravir in Buffer Solution with Surfactants at Room Temperature

| Medium | Solubility mg/mL | | |
|---|---|---|---|
| | pH 2.0 | pH 4.5 | pH 6.8 |
| No surfactant | 0.0002 | 0.0002 | 0.0009 |
| Polysorbate 80, 1% w/v | 0.16 | 0.19 | 0.18 |
| **Polysorbate 80, 2% w/v[a]** | **0.36** | **0.41** | **0.35** |
| Polysorbate 80, 3% w/v | 0.46 | 0.46 | 0.48 |
| Polysorbate 20, 1% w/v | 0.11 | 0.12 | 0.14 |
| Polysorbate 20, 2% w/v | 0.22 | 0.27 | 0.26 |
| Polysorbate 20, 3% w/v | 0.31 | 0.35 | 0.35 |
| Cremophor EL, 1% w/v | 0.12 | 0.15 | 0.14 |
| Cremophor EL, 2% w/v | 0.25 | 0.30 | 0.24 |
| Cremophor EL, 3% w/v | 0.35 | 0.40 | 0.37 |
| CTAB, 0.25% w/v | 0.43 | 0.46 | 0.82 |
| CTAB, 0.5% w/v | 0.85 | 0.97 | 1.5 |
| CTAB, 0.75% w/v | 1.3 | 1.3 | 2.2 |
| SLS 0.25% w/v | 0.17 | 0.20 | 0.21 |
| SLS 0.5% w/v | 0.28 | 0.36 | 0.50 |
| SLS 1% w/v | 1.0 | 1.1 | 1.0 |

a Surfactant and pH selected for the dissolution medium

(b) (4)

***Reviewer's Assessment:***
***The data in Table 1 demonstrate that 1) EVG is not soluble in buffers in the physiological pH range and 2) surfactant is needed to enhance the solubility of EVG. The acceptability of the selected medium, pH, surfactant type, and surfactant concentration are discussed in Section 2 of this review.***

## Drug Product

The composition of the proposed product is shown in Table 2.

**Table 2.** Quantitative Composition of the Proposed 85 mg and 150 mg EVG Commercial Tablets

| | Clinical (mg/tablet) | Commercial (mg/tablet) | Clinical (mg/tablet) | Commercial (mg/tablet) |
|---|---|---|---|---|
| **Ingredient** | **85 mg** | | **150 mg** | |
| Elvitegravir | 85.0 | 85.0 | 150.0 | 150.0 |
| Microcrystalline Cellulose | (b) (4) | | | |
| Lactose Monohydrate | | | | |
| Sodium Lauryl Sulfate | | | | |
| Hydroxypropyl Cellulose | | | | |
| Croscarmellose Sodium | | | | |
| Magnesium Stearate | | | | |
| Subtotal | | | | |
| **Film-Coat** | | | | |
| (b) (4)[a] | | | | (b) (4) |
| Total Film-Coated Tablet Weight | 219.4 | 219.4 | 386.3 | 386.3 |

a (b) (4) contains indigo carmine (b) (4) aluminum lake (b) (4), polyethylene glycol, polyvinyl alcohol, talc (b) (4), titanium dioxide (b) (4), and yellow iron oxide (b) (4).
b Represents theoretical weight gain of (b) (4)% (range of (b) (4)%).

***Reviewer's Assessment:***
***The 85 mg and 150 mg strengths of the proposed product are*** (b) (4)

## 2. Dissolution Method

The proposed dissolution method for each strength is shown below.

Dissolution Method for 85 mg Tablet

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| II | 75 rpm | 700 mL | 37°C | 0.01N HCl (pH2) w/ 2% polysorbate 80 |

Dissolution Method for 150 mg Tablet

| USP Apparatus | Rotation Speed | Media Volume | Temp | Medium |
|---|---|---|---|---|
| II | 75 rpm | 1000 mL | 37°C | 0.01N HCl (pH2) w/ 2% polysorbate 80 |

**Selection of Dissolution Medium, pH, Surfactant, and Surfactant Concentration**

The Applicant conducted preliminary dissolution studies on a representative batch of 150 mg tablets (Lot RL-414034) to evaluate the effect of surfactant and pH on dissolution rate. The results are summarized in Table 3.

**Table 3.** Effect of pH and Surfactant on the Dissolution of EVG 150 mg Tablets (Lot RL-4140-34)

(b) (4)

(b) (4)

Figure 2 shows the effect of adding 2% polysorbate 80 on the dissolution of EVG in different pH medium.

**Figure 2.** Effect of pH on the Dissolution Profile of EVG 150 mg Tablets (Lot RL-4140-34) with and without 2% Polysorbate 80 (1000 mL media, Paddle, 75 rpm, n=3)


The Applicant selected to use 2% *w/v* polysorbate 80 in the dissolution medium because (b) (4)

***Reviewer's Assessment:***

(b) (4)

***Thus, the Applicant's selection of dissolution medium, pH, surfactant, and surfactant concentration is acceptable.***

**Selection of Medium Volume**

At a volume of 1000 mL and in 0.01 N HCl (pH 2.0) medium with 2.0% polysorbate 80, the 150 mg EVG tablets have a solubility of 0.36 mg/mL or 2.4 times the volume that is necessary to dissolve the 150 mg tablet.

The Applicant further evaluated the volume for the 85 mg tablets. Figure 3 shows the dissolution profile of 85 mg EVG tablets in a volume of (b) (4) 700 and 1000 mL. They stated that the volume with the lowest variability in dissolution data was 700 mL. This volume represents three times the volume necessary to dissolve the 85 mg tablet.

**Figure 3.** Effect of Medium Volume on the Dissolution Profile of EVG 85 mg Tablets
(Lot AJ1001C; Paddle, 75 rpm, n=3)


***Reviewer's Assessment:***
***The data in Figure 3 demonstrate that 700 mL volume for the 85 mg table provides a gradual release profile. Also, a 700 mL volume guarantees that sink conditions are met for the 85 mg tablet. The selection of 1000 mL provides sufficient sink conditions for the 150 mg tablet. Thus, the Applicant's medium volume selection for each strength is acceptable.***

**Selection of Apparatus and Rotation Speeds**

The Applicant stated that they chose to use the paddle apparatus for the dissolution method in order to establish (b) (4) for the size and shape of the tablets.

The Applicant investigated various paddle speeds ( (b) (4) 75 and (b) (4) rpm) for dissolution of EVG tablets (refer to Figure 4).

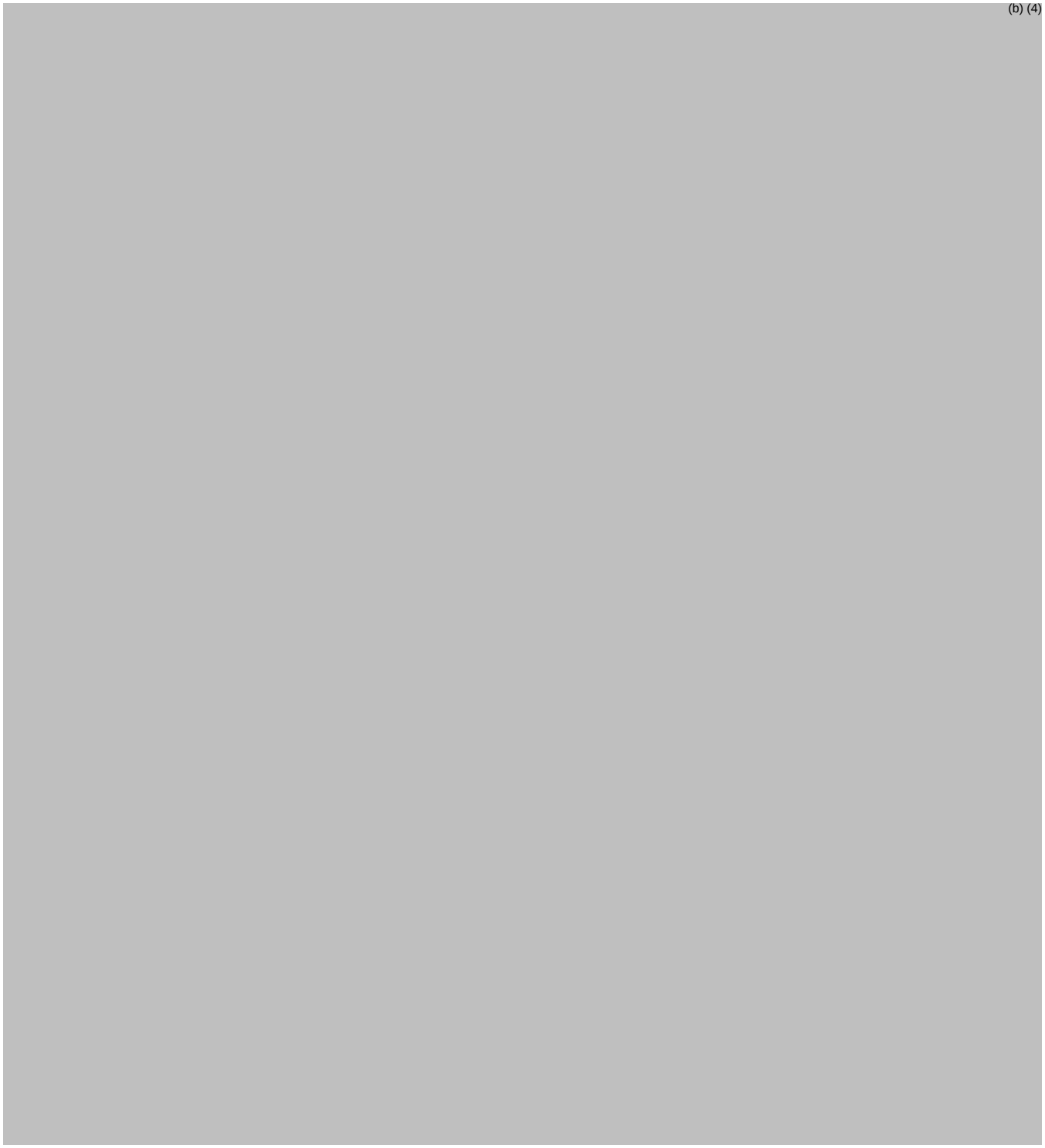
**Figure 4.** Effect of Paddle Speed on the Dissolution Profile of EVG 150 mg Tablets
(Lot AJ1001D; 1000 mL, Paddle, sinkers, (b) (4) n=12 for 75 rpm)


The Applicant stated that they observed lower recovery, higher variability, and coning at the (b) (4) rpm paddle speeds. They selected a paddle speed of 75 rpm because it was the minimum paddle speed that would achieve dissolution of EVG, while preventing coning and providing reproducible results.

***Reviewer's Assessment:***

***Apparatus 2 (paddle) is commonly used for tablet formulations. Therefore, the Applicant's selection of the paddle is acceptable. Figure 4 shows that the dissolution rate of EVG increased with paddle speed, as expected. All paddle speeds tested provided gradual release profiles. Since the Applicant observed higher variability and coning at (b) (4) rpm paddle speeds, their selection of the 75 rpm paddle speed is acceptable.***

(b) (4)



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***Overall, the proposed dissolution method conditions are acceptable and the proposed dissolution method has adequate discriminating ability. Thus, the proposed dissolution method is acceptable.***

### 3. Dissolution Acceptance Criterion

The proposed acceptance criterion is shown below.

| Acceptance Criterion |
|---|
| Q = (b) (4) % at 45 min |

The dissolution profiles for representative clinical batches and primary stability batches of the 85 mg and 150 mg elvitegravir tablets are shown in Figures 11 and 12.

**Figure 11.** Dissolution Profile of 85 mg EVG Tablets used in Clinical Studies
(700 mL, Paddle, 75 rpm, sinkers, n=12 forAJ1101E and AJ1101F, n=6 for remaining)


**Figure 12.** Dissolution Profile of 150 mg EVG Tablets used in Clinical Studies
(1000 mL, Paddle, 75 rpm, sinkers, n=12 forAJ1101H and AJ1101G, n=6 for remaining)


***Reviewer's Assessment:***
***Dissolution data from the clinical batches (Figures 11 and 12) demonstrate that the dissolution acceptance criterion should be revised to Q = (b) (4) % at 45 minutes.***

***The long term stability batches were tested with a different dissolution medium*** (b) (4) ***Therefore, the dissolution data from the long term stability batches did not factor into the selection of the dissolution acceptance criterion.***

***The following ONDQA Biopharmaceutics comments were conveyed to the Applicant on Dec 12, 2012.***

**FDA Comment**
Provide dissolution data for the long term stability batches tested with the proposed dissolution method.

**Applicant's Response (excerpt)**
A summary of the 48-month long term stability batches tested with the proposed dissolution method is listed, and the dissolution data are provided.

**Table 4.** Summary of Long-term Stability Batches Tested with the Proposed Dissolution Method

| Lot No. | Tablet Strength (mg) | Time Point, Storage Condition |
|---|---|---|
| AJ0702D1 | 85 | 48 months, 25 °C/60% RH |
| | | 48 months, 30°C/75% RH |
| **AJ0704D1** | **85** | **48 months, 25 °C/60% RH** |
| | | **48 months, 30°C/75% RH** |
| **AJ0705D2** | **85** | **48 months, 25 °C/60% RH** |
| | | **48 months, 30°C/75% RH** |
| AJ0702E1 | 150 | 48 months, 25 °C/60% RH |
| | | 48 months, 30°C/75% RH |
| **AJ0704E1** | **150** | **48 months, 25 °C/60% RH** |
| | | **48 months, 30°C/75% RH** |
| **AJ0705E2** | **150** | **48 months, 25 °C/60% RH** |
| | | **48 months, 30°C/75% RH** |

***In a submission dated January 8, 2013, the Applicant provided long term stability dissolution data at the 48 month time point only. Nonetheless, the CMC reviewer will consider this data when selecting the appropriate expiry for the proposed drug product (refer to Dr. Celia Cruz's CMC review).***

**FDA Comment**
The following dissolution acceptance criterion is recommended: Q = (b)(4)% at 45 minutes. This recommendation is based on the mean in-vitro dissolution profiles for all strengths at release. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product. Note that dissolution data from the long term stability studies were not factored in the selection of the dissolution acceptance criterion because the long term stability batches were not tested with the proposed dissolution method.

**Applicant's Response**
Gilead agrees to the recommended dissolution acceptance criterion of Q = (b)(4)% at 45 minutes. The specifications, GSPEC-199-01.00 and GSPEC-199-96.02 for elvitegravir tablets, 85 mg and GSPEC-200-01.00 and GSPEC-200-96.02 for elvitegravir tablets, 150 mg, have been revised with the recommended acceptance criterion for dissolution. Dissolution of the batches tested using the proposed dissolution method at release (Lots AJ1101E, AJ1101F, AJ1101G, and AJ1101H, provided in updated Sections 3.2.P.5.4 and 3.2.P.5.4 Access) and long-term stability (presented in Table 2 through Table 13) comply with the revised dissolution acceptance criterion of Q = (b)(4)% at 45 minutes. Sections 3.2.P.5.1 and 3.2.P.5.1 Access have been updated with the revised specification.

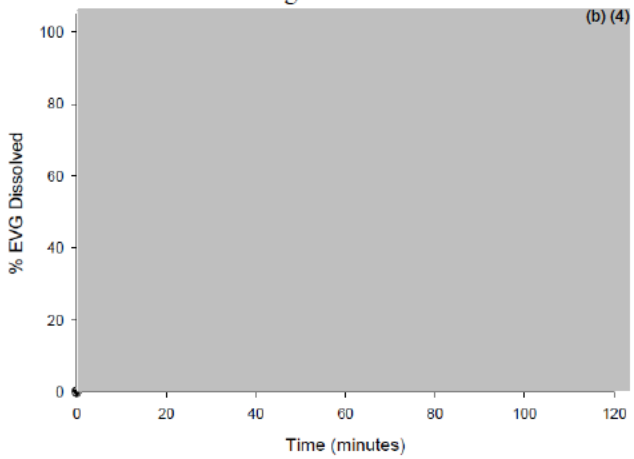
***In a submission dated January 8, 2013, the Applicant accepted to revise the dissolution acceptance criterion.***

## 4. Role of Dissolution in the Development of the Design Space for the Tablet Formulation

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Figure 16.** Dissolution Profile of 150 mg EVG Tablets as a Function of Tablet (b) (4)




***Reviewer's Assessment:***

***The Applicant did not perform f2 testing. Therefore, the following comments were conveyed in an IR letter dated December 12, 2012.***

**FDA Comment**

There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following data:

c. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figures 12 and 13 demonstrating that the proposed drug product manufactured with the (b) (4) values at the proposed ranges have similar dissolution rate compared to batches manufactured at target (b) (4) values.

**Applicant's Response (excerpt)**

The f2 (similarity factor) statistical testing for dissolution profiles of EVG tablets (Figures 12 and 13 in 3.2.P.2.3) using 10, 20, and 30 minutes time points are presented. The results of f2 statistical testing provide values greater than (b) (4) which demonstrate that tablets manufactured with (b) (4) within the ranges of (b) (4) kp for 85 mg tablets and (b) (4) kp for 150 mg tablets result in similar dissolution profiles.

***In a submission dated January 8, 2013, the Applicant submitted the f2 data in Table 10.***

**Table 10.** Similarity Factor (f2) of Dissolution Profiles of EVG Tablets Manufactured with Various Tablet (b) (4)

| Tablet Strength | Hardness (kp) | f2 |
|---|---|---|
| 85 mg | (b) (4) | |
| 150 mg | | |

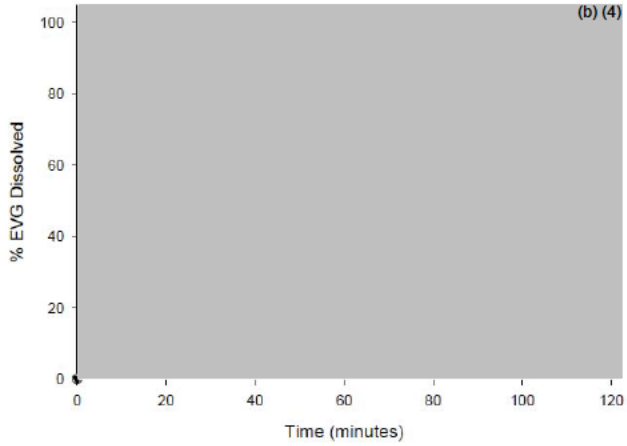
a 10, 20, and 30 minutes time points were used in f2 statistical testing.
b Target (b) (4) value for 85 mg tablets.
c Target value for 150 mg tablets.

***Table 10 demonstrates that tablets manufactured with (b) (4) within the ranges of (b) (4) kp for 85 mg tablets and (b) (4) kp for 150 mg tablets result in f2 similar dissolution profiles. Therefore, the proposed drug product manufactured with these (b) (4) values are expected to have equivalent clinical performance.***

**Film-coating Process**

The Applicant investigated the effect of final film-coat level on tablet dissolution (refer to Figure 14).

**Figure 17.** Dissolution Profile of EVG Tablets as a Function of Coating Level




***Reviewer's Assessment:***
***The Applicant did not perform f2 testing. Therefore, the following comments were conveyed in an IR letter dated December 12, 2012.***

**FDA Comment**
There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed design space would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following data

d. F2 statistical testing for the dissolution profiles comparisons in 3.2.P.2.3 Figure 14 demonstrating that the proposed drug product manufactured with the film coat weight gain at the proposed ranges have similar dissolution rate compared to batches manufactured at the target film coat weight gain value.

**Applicant's Response (excerpt)**
The f2 (similarity factor) statistical testing for dissolution profiles of EVG tablets (Figure 14 in 3.2.P.2.3) using 10, 20, 30, and 45 minutes time points are presented. The results of f2 statistical testing provides values greater than (b) (4) which demonstrate that the dissolution profiles of tablets with (b) (4)% weight gain are similar to that of (b) (4)% weight gain tablets. Thus, the range of weight gain of film-coat from (b) (4)% is satisfactory for the film-coating process.

***In a submission dated January 8, 2013, the Applicant submitted the f2 data in Table 11.***

**Table 11.** Similarity Factor (f2) of Dissolution Profiles of EVG Tablets with Weight Gain from Film Coating

| Tablet Weight Gain | f2 |
|---|---|
| | (b) (4) |

a 10, 20, 30, and 45 minutes time points were used in f2 statistical testing.
b Target film-coat weight gain

***Table 11 demonstrates that tablets with (b) (4) % and (b) (4) % weight gain are f2 similar to that of (b) (4) % weight gain tablets. Therefore, the proposed drug product manufactured with this range of coating weight gain values are expected to have equivalent clinical performance.***

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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KAREEN RIVIERE
03/21/2013

SANDRA SUAREZ
03/21/2013

# Office of Clinical Pharmacology
## New Drug Application Filing and Review Form

| **General information about the submission** | |
|---|---|
| NDA/BLA Number | 203093 (0000/0) |
| OCP Division | DCP4 |
| Medical Division | Division of Antiviral Products |
| OCP Reviewer | Leslie Chinn, Ph.D. |
| OCP Team Leader | Shirley Seo, Ph.D. (acting) |
| Pharmacometrics Reviewer | Dhananjay Maranthe, Ph.D. |
| Date of Submission | 27 June 2012 |
| OCP Review Estimated Due Date | 16 Mar 2013 |
| Medical Division Due Date | |
| PDUFA Due Date | 27 April 2013 |

| **General information about the drug/biologic** | |
|---|---|
| Brand Name | Vitekta |
| Generic Name | Elvitegravir |
| Drug Class | Integrase strand-transfer inhibitor (INSTI) |
| Indication(s) | Treatment of HIV-1 infection in ARV treatment-experienced adults, in combination with a ritonavir-boosted protease inhibitor (PI/r) and other ARV agents |
| Dosage Form | 85 and 150 mg elvitegravir tablets |
| Dosing Regimen | Elvitegravir 85 mg once daily coadministered with one of the following PI/r:<br>• atazanavir/ritonavir 300/100 mg once daily<br>• lopinavir/ritonavir 400/100 mg twice daily<br><br>Elvitegravir 150 mg once daily coadministered with one of the following PI/r:<br>• darunavir/ritonavir 600/100 mg twice daily<br>• fosamprenavir/ritonavir 700/100 mg twice daily<br>• tipranavir/ritonavir 500/200 mg twice daily |
| Route of administration | Oral |
| Sponsor | Gilead Sciences, Inc. |
| Priority Classification | Standard |

| **Clinical pharmacology and biopharmaceutics information** |
|---|

| Study Type | Incl. at Filing | No. of Studies Submitted | No. of Studies Reviewed (studies reviewed as part of Stribild NDA) | Critical Comments |
|---|---|---|---|---|
| Table of Contents<br>incl. reports, tables, data | ☒ | | | |
| Tabular Listing<br>incl. all human studies | ☒ | | | |
| Human PK Summary | ☒ | | | |
| Labeling | ☒ | | | |
| Reference Bioanalytical and Analytical Methods | ☒ | | | |
| **I. CLINICAL PHARMACOLOGY** | | | | |
| Mass Balance | ☒ | 1 | 1 | GS-US-183-0126<br>(ritonavir-boosted) |
| Isoenzyme Characterization | ☒ | 6 | 6 | JTK303-AD-015<br>JTK303-AD-016<br>JTK303-AD-017<br>JTK303-AD-018<br>JTK303-AD-024<br>AD-183-2034 |
| Blood/Plasma Ratio | ☒ | 1 | 1 | JTK303-AD-013 |
| Plasma Protein Binding | ☒ | 1 | 1 | JTK303-AD-014 |
| **Pharmacokinetics (e.g. Phase 1)** | | | | |
| *Healthy Volunteers* | | | | |
| Single Dose | ☐ | | | |
| Multiple Dose | ☒ | 2 | 2 | GS-US-183-0102<br>GS-US-183-0113 |
| *Patients* | | | | |
| Single Dose | ☐ | | | |
| Multiple Dose | ☒ | 2 | 1 | GS-US-183-0105<br>GS-US-183-0145 |
| *Dose Proportionality – Fasting/Non-Fasting* | | | | |
| Single Dose | ☐ | | | |
| Multiple Dose | ☐ | | | |
| *Drug-Drug Interaction Studies* | | | | |

| | | | | |
|---|---|---|---|---|
| In Vivo Effects on Primary Drug | ☒ | 16 | 2 | GS-US-183-0103<br>GS-US-183-0104<br>GS-US-183-0106<br>GS-US-183-0108<br>GS-US-183-0110<br>GS-US-183-0111<br>GS-US-183-0112<br>GS-US-183-0115<br>GS-US-183-0116<br>GS-US-183-0118<br>GS-US-183-0119<br>GS-US-183-0120<br>GS-US-183-0123<br>GS-US-183-0125<br>GS-US-183-0146<br>GS-US-183-0147 |
| In Vivo Effects of Primary Drug | ☐ | | | |
| In Vitro | ☒ | 6 | 6 | JTK303-AD-025<br>JTK303-AD-027<br>JTK303-AD-023<br>AD-183-2028<br>JTK303-AD-026<br>AD-183-2030 |
| *Special Populations* | | | | |
| Ethnicity | ☐ | | | |
| Gender | ☐ | | | |
| Pediatrics | ☒ | 1 | | GS-US-183-0152 |
| Geriatrics | ☐ | | | |
| Renal Impairment | ☒ | 1 | 1 | GS-US-216-0124 (cobicistat-boosted) |
| Hepatic Impairment | ☒ | 1 | 1 | GS-US-183-0133 (cobicistat-boosted) |
| *Pharmacodynamics* | | | | |
| Phase 2 | ☐ | | | |
| Phase 3 | ☐ | | | |
| *Pharmacokinetics/Pharmacodynamics* | | | | |
| Proof of Concept (Phase 1 or 2) | ☒ | 1 | 1 | GS-US-183-0101 |
| Clinical Trial (Phase 3) | ☐ | | | |
| *Population Analyses* | | | | |
| Data-rich | ☐ | | | |
| Data-sparse | ☐ | | | |
| **II. BIOPHARMACEUTICS** | | | | |

| | | | | |
|---|---|---|---|---|
| *Bioavailability* | | | | |
| Absolute Bioavailability | ☐ | | | |
| Relative Bioavailability (solution as reference) | ☒ | 1 | 1 | GS-US-183-0140 |
| Relative Bioavailability (alt. formulation as ref.) | ☐ | | | |
| *Bioequivalence* | | | | |
| Traditional Design (single/multiple dose) | ☐ | | | |
| Replicate Design (single/multiple dose) | ☐ | | | |
| *Food-Drug Interaction* | ☒ | 1 | 1 | GS-US-236-0105 (FDC) |
| *Biowaiver Request (based on BCS class)* | ☐ | | | |
| *Dissolution (alcohol-induced dose-dumping)* | ☐ | | | |
| **III. OTHER CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS** | | | | |
| *Genotype/Phenotype* | ☐ | | | |
| *Chronopharmacokinetics* | ☐ | | | |
| *Pediatric Development Plan* | ☒ | 1 | | PPSR |
| *Literature References* | ☐ | | | |
| **TOTAL NUMBER OF STUDIES** | | 41 | 25 | 16 to review |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | ☐ | ☐ | ☒ | Phase 3 formulation is identical to to-be-marketed products |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | ☒ | ☐ | ☐ | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | ☒ | ☐ | ☐ | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | ☒ | ☐ | ☐ | |
| 5 | Has a rationale for dose selection been submitted? | ☒ | ☐ | ☐ | |

| | | | | | |
|---|---|---|---|---|---|
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | ☒ | ☐ | ☐ | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | ☒ | ☐ | ☐ | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | ☒ | ☐ | ☐ | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | ☒ | ☐ | ☐ | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | ☐ | ☐ | ☒ | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | ☒ | ☐ | ☐ | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | ☒ | ☐ | ☐ | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | ☒ | ☐ | ☐ | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetics or pharmacodynamics? | ☒ | ☐ | ☐ | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | ☒ | ☐ | ☐ | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | ☒ | ☐ | ☐ | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | ☒ | ☐ | ☐ | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | ☒ | ☐ | ☐ | |
| 19 | Was the translation (of study reports or other study | ☒ | ☐ | ☐ | |

| | | | | | |
|---|---|---|---|---|---|
| | information) from another language needed and provided in this submission? | | | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

☒ **Yes** ☐ **No**

**If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.**

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

| | |
|---|---|
| Leslie Chinn, Ph.D. | 8 Aug 2012 |
| **Reviewing Clinical Pharmacologist** | **Date** |
| Shirley Seo, Ph.D. | 8 Aug 2012 |
| **Team Leader/Supervisor (Acting)** | **Date** |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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LESLIE W CHINN
08/14/2012

SHIRLEY K SEO
08/14/2012