

Activity of Elvitegravir, a Once-Daily Integrase Inhibitor, against Resistant HIV Type 1: Results of a Phase 2, Randomized, Controlled, Dose-Ranging Clinical Trial

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Background. This phase 2, randomized, active-controlled, 48-week study assessed the noninferiority of the human immunodeficiency virus (HIV) integrase inhibitor elvitegravir to comparator ritonavir-boosted protease inhibitor (CPI/r) in treatment-experienced subjects.

Methods. Subjects had HIV RNA levels ≥ 1000 copies/mL and ≥ 1 protease resistance mutation. Subjects received nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs) with or without T-20 and either CPI/r or once-daily elvitegravir at a dose of 20 mg, 50 mg, or 125 mg (blinded to dose) with ritonavir. After week 8, the independent data monitoring committee stopped the elvitegravir 20 mg arm and allowed subjects in the elvitegravir 50 mg and 125 mg arms to add protease inhibitors. The primary end point was the time-weighted average change from baseline in HIV RNA level through week 24 (DAVG₂₄).

Results. A total of 278 subjects with a median of 11 protease and 3 thymidine analog mutations were randomized and treated. One-half of subjects received NRTIs without expected antiviral activity. Compared with the DAVG₂₄ for the CPI/r arm ($-1.19 \log_{10}$ copies/mL), the elvitegravir 50 mg arm was noninferior ($-1.44 \log_{10}$ copies/mL), and the elvitegravir 125 mg arm was superior ($-1.66 \log_{10}$ copies/mL; $P = .021$). Efficacy was impacted by activity of background agents. There was no relationship between elvitegravir dosage and adverse events.

Conclusions. Elvitegravir was well-tolerated and produced rapid virologic suppression that was durable with active background therapy.

Trial registration. ClinicalTrials.gov identifier number: NCT00298350.

Elvitegravir (GS-9137) is a potent inhibitor of the strand-transfer step of integration mediated by human immunodeficiency virus type 1 (HIV-1) integrase [1].

In vitro, the 90% effective concentration is 1.2 nM in HIV-infected peripheral blood mononuclear cells [1]. Because it blocks the function of the integrase enzyme, elvitegravir is active against HIV-1 strains that are resistant to nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) [1]. In preclinical animal studies, no dose-limiting toxicity was observed. Co-administration with 100 mg of ritonavir boosted the systemic exposures of elvitegravir by ~20-fold and provided trough concentrations that were well-suited for reliable once-daily administration [2, 3]. Increasing the dose of ritonavir did not increase the exposure of elvitegravir further [4].

In a small monotherapy study of elvitegravir involving treatment-naïve and treatment-experienced subjects, all dosages that were evaluated produced signif-

Received 30 May 2009; accepted 29 September 2009; electronically published 10 February 2010.

Potential conflicts of interest: A.Z. has received grant support from Gilead Sciences and is on the National Advisory Board for Gilead Sciences; D.B. has received compensation for conducting clinical trials sponsored by Gilead Sciences and is a stockholder; H.L. has received grant support from Gilead Sciences; L.Z., S.C., J.E., B.K., and A.C. are employees and stockholders of Gilead Sciences.

Presented in part: Conference on Retroviruses and Opportunistic Infections 2007; Interscience Conference on Antimicrobial Agents and Chemotherapy 2007.

Financial support: Gilead Sciences.

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The Journal of Infectious Diseases 2010;201:814–822

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0022-1899/2010/20106-0004\$15.00

DOI: 10.1086/650698

icant decreases in HIV RNA level [3]. In particular, all 6 subjects who were treated once daily with elvitegravir at a dose of 50 mg and ritonavir at a dose of 100 mg experienced reductions in HIV RNA level of at least 1.5 log₁₀ copies/mL over a 10-day period. In this cohort of subjects, the mean reduction in HIV RNA level was -2.0 log₁₀ copies/mL. Elvitegravir was well-tolerated in this study.

We conducted this study to evaluate 3 dosages of elvitegravir administered with ritonavir in treatment-experienced, HIV-infected subjects to define further the safety and efficacy of elvitegravir.

METHODS

Study design. Study GS-US-183–105 was a prospective, randomized, partially blinded (ie, blinded to dosage of elvitegravir), active-controlled, dose-ranging, 48-week, phase 2 study conducted in the United States. Because the pharmacokinetic interactions between elvitegravir and ritonavir-boosted PIs had not been studied at the time that this study was initiated, the study did not permit the co-administration of these agents at the outset. This study was originally designed to assess the noninferiority of ritonavir-boosted elvitegravir (elvitegravir at a dosage of 20 mg, 50 mg, or 125 mg per day, with each dose boosted with 100 mg of ritonavir) versus ritonavir-boosted comparator PIs (CPI/r), both in combination with optimized background therapy (OBT) in HIV-1-infected treatment-experienced subjects. Institutional review boards approved the study protocol and informed consent form; each subject gave written informed consent.

At screening, treatment-experienced adult subjects 18–65 years of age were to have a plasma HIV RNA level ≥ 1000 copies/mL and documented presence of at least 1 protease gene mutation as defined by the International AIDS Society–USA 2005 Guidelines. Subjects received a stable drug regimen from at least 30 days prior to screening to the baseline visit. Subjects had to meet the following inclusion criteria: estimated glomerular filtration rate by the Cockcroft-Gault method ≥ 60 milliliters per min, hepatic aminotransferase levels ≤ 2.5 times the upper limit of normal, absolute neutrophil count ≥ 1000 cells/mm³, platelet count $\geq 50,000$ platelets/mm³, hemoglobin level ≥ 8.0 g/dL, and serum amylase level < 1.5 times the upper limit of normal. No minimum CD4 cell count was stipulated.

Subjects were excluded if they had received a diagnosis of a new AIDS-defining condition within 30 days before entry into the study (other than on the basis of CD4 cell count), had been treated previously with an HIV integrase inhibitor, were experiencing ascites or encephalopathy, were pregnant or breastfeeding, were receiving ongoing therapy with a disallowed medication, had received a diagnosis of malignancy other than cutaneous Kaposi sarcoma or basal cell carcinoma, were being treated with parenteral antibiotics or systemic antifungal ther-

apy, or expected to live < 1 year. All subjects were asked to use effective contraceptive methods while receiving study drugs and for 30 days after the last dose of study drugs.

Subjects were randomized (1:1:1:1) to receive a CPI/r in an open-label manner or elvitegravir at a dosage of 20 mg, 50 mg, or 125 mg (double blinded to dose) administered once-daily with 100 mg of ritonavir and food. Randomization was stratified by whether T-20 was to be used, regardless of whether it was being used for the first time. Randomization was implemented via an interactive voice response system managed by Covance (Princeton, NJ). Originally, the background antiretroviral regimen was to be composed of at least 2 NRTIs with or without T-20 (enfuvirtide) but not PIs.

Clinical and laboratory evaluations were conducted at the screening visit, before the baseline visit, at the baseline visit after which administration of study drugs was begun, at weeks 2 and 4, and then every 4 weeks through the 48 weeks of the study or at 30 days after early discontinuation. Adverse events, concomitant medications, and pill counts were assessed and a physical examination was performed at each visit. At each visit, plasma HIV RNA level and CD4 cell counts were determined and hematological and plasma chemistry profiles and urinalysis were performed. A fasting lipid panel was performed at weeks 16, 32, and 48.

Laboratory tests were conducted by Covance Laboratories, and Phenosense GT resistance analyses [5] were conducted by Monogram Biosciences (South San Francisco, CA). The study was designed and the data were analyzed by Gilead Sciences (Foster City, CA). The authors had access to the data and analyses, contributed to the writing and editing, and approved the final manuscript.

Statistical analyses. The primary objective of the study was to assess noninferiority of elvitegravir relative to CPI/r, both in combination with a background antiretroviral regimen, with use of the time-weighted average change in log₁₀ HIV-1 RNA levels from baseline through week 24 (DAVG₂₄). The secondary objectives were to assess noninferiority of elvitegravir relative to CPI/r, both in combination with a background antiretroviral regimen, at week 48 with use of DAVG₄₈ and to evaluate the safety and tolerability of the 2 types of regimens. The computation method for DAVG [6] was refined to use the difference between the time-weighted average of HIV RNA levels from first post-baseline (rather than baseline [6]) visit to week 24 (7 visits) or week 48 (13 visits) and the baseline HIV RNA level.

Intention-to-treat (ITT) analyses included all data for randomized subjects who received at least 1 dose of study drug. Per-protocol analyses also included all randomized subjects who received at least 1 dose of study drug, but data collected after any change in randomized treatment, including addition of a PI to an elvitegravir-containing regimen, were excluded. Treatment differences in DAVG between groups and the asso-

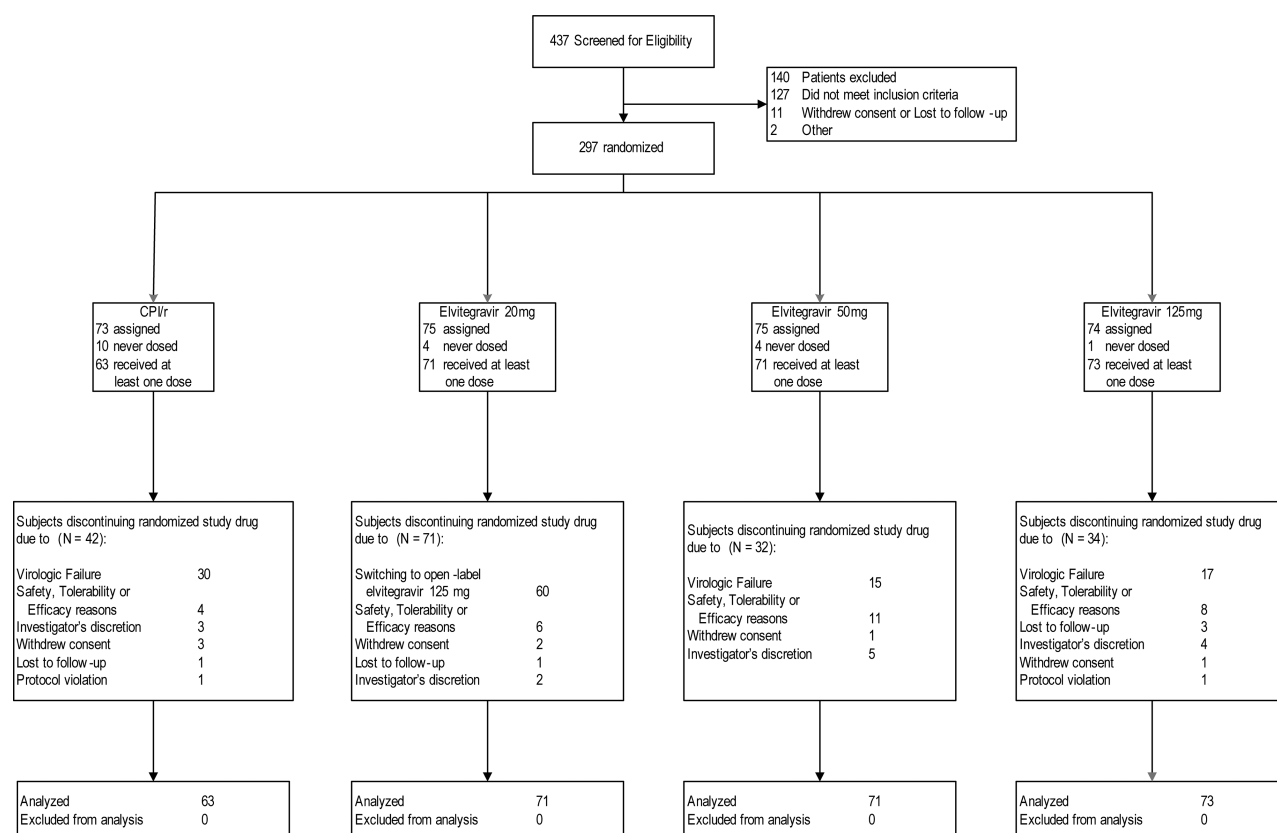


Figure 1. Disposition and baseline characteristics of subjects.

ciated 95% confidence intervals (95% CIs) were constructed using an analysis of variance model. Fisher's exact test was conducted to test differences in proportions. Benjamini and Hochberg's false discovery rate controlling procedure was applied to adjust for multiplicity for the primary outcome measure.

Safety analyses included data collected through 30 days after discontinuation of study drugs in all patients who received at least 1 dose of study drugs. The severity of adverse events and laboratory abnormalities was graded according to the modified Common Toxicity Criteria of the National Institutes of Allergy and Infectious Diseases.

The Genotypic Sensitivity Score (GSS) was calculated for the NRTIs in the optimized background therapy of each subject. Subjects with HIV reverse-transcriptase mutations associated with resistance [7] were assigned a GSS score of 0 for that drug. The baseline GSS was summarized and used in stratified analyses.

Assuming a common standard deviation of 0.75 log₁₀ copies/mL and no difference in least-squares means between the CPI/r group and any of the 3 GS-9137/r groups, a planned sample size of 50 subjects in each of the 4 treatment groups provides 80% power to establish noninferiority with an upper limit of HIV-1 RNA of 0.5 log₁₀ copies/mL for 95% CIs.

RESULTS

Beginning on 21 February 2006, 297 subjects were randomized to the 4 treatment arms at 72 sites in the United States and Puerto Rico; a total of 278 subjects received study drugs. All visits for the 48-week study were completed by July 2007. The disposition of the subjects in the 4 treatment arms are shown in Figure 1. The baseline characteristics of the 278 subjects and their background regimens were similar across the treatment arms (Table 1). Subjects were generally highly treatment-experienced, with a median of 11 protease resistance mutations and 3 thymidine analog mutations per subject. Three-quarters of subjects in the CPI/r arm received a newer-generation PI starting at baseline: 49% received darunavir, and 27% received tipranavir. The incidences and reasons for patients discontinuing the study were also similar across treatment arms, although 10 subjects in the CPI/r arm never received a dosage after learning their treatment assignment.

On 6 October 2006, the independent data monitoring committee reviewed the week 8 data. On the basis of the recommendations of the committee, the protocol was amended. The elvitegravir 20 mg arm was discontinued, because that arm was

Table 1. Baseline Characteristics of Subjects

Variable	CPI/r (n = 63)	Elvitegravir, by dosage		
		20 mg per day (n = 71)	50 mg per day (n = 71)	125 mg per day (n = 73)
Age, median years	44	44	44	44
Male sex	54 (86)	70 (99)	63 (89)	62 (85)
Race or ethnic group, %				
White	86	68	66	73
Black	10	30	31	19
HIV RNA level				
Median log ₁₀ copies/mL	4.58	4.77	4.45	4.92
>100,000 copies/mL	17 (27)	25 (35)	30 (42)	29 (40)
CD4 cell count				
Median cells/mm ³	106	143	210	99
<50 cells/mm ³	17 (27)	24 (34)	16 (23)	22 (30)
Co-infection				
Hepatitis B virus	3 (5)	2 (3)	3 (4)	2 (3)
Hepatitis C virus	6 (10)	6 (9)	0	5 (7)
Protease inhibitor mutations, median no. of mutations per subject	11	11	10	11
Thymidine analog mutations, median no. of mutations per subject	3	3	3	3
Genotypic Sensitivity Score of 0 for NRTIs	32 (51)	35 (49)	34 (49)	35 (48)
First use of T-20	11 (17)	11 (15)	17 (24)	17 (23)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CPI/r, comparator ritonavir-boosted protease inhibitor; HIV, human immunodeficiency virus; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitor.

associated with higher rates of virologic failure. Subjects taking elvitegravir at a dosage of 20 mg per day were unblinded and offered open-label elvitegravir at a dosage of 125 mg per day with their background regimen. In addition, the use of ritonavir-boosted darunavir or tipranavir with elvitegravir was permitted because of data that demonstrated the lack of drug-drug interactions. If subjects receiving elvitegravir were also given darunavir or tipranavir, the ritonavir dosage was adjusted to 100 mg twice per day or 200 mg twice per day, respectively.

The noninferiority design of this trial is impacted following the allowance of PIs in the elvitegravir arms. In the elvitegravir

50 mg and 125 mg arms, only 4 subjects added a PI before the week 16 visit (2 subjects in each arm). Therefore, the week 16 data provide the latest time point at which to compare elvitegravir arms to the CPI/r arms with minimal confounding effect of added PIs. Before the week 24 visit, 15 (10%) of 144 subjects in the elvitegravir 50 mg and 125 mg arms had added a boosted PI.

Efficacy. In an intent-to-treat (ITT) analysis of the primary end point, the DAVG₂₄ for the elvitegravir 50 mg and 125 mg arms met the criteria for noninferiority, compared with the CPI arm (Table 2). Furthermore, the DAVG₂₄ for the elvitegravir

Table 2. Time-Weighted Average Change in HIV RNA (DAVG) at Weeks 16, 24, and 48

Variable	CPI/r	Ritonavir-boosted elvitegravir, by dosage	
		50 mg per day	125 mg per day
DAVG ₁₆ ITT, log ₁₀ copies/mL	−1.15	−1.51	−1.68
Difference vs CPI/r (95% CI)		−0.30 (−0.66 to 0.05)	−0.48 (−0.83 to −0.13) ^a
DAVG ₂₄ ITT, log ₁₀ copies/mL	−1.19	−1.44	−1.66
Difference vs CPI/r (95% CI)		−0.19 (−0.54 to 0.17)	−0.42 (−0.77 to −0.06) ^b
DAVG ₄₈ PP, log ₁₀ copies/mL	−1.08	−1.37	−1.52
Difference vs CPI/r (95%CI)		−0.22 (−0.59 to 0.14)	−0.39 (−0.75 to −0.02) ^c

NOTE. CI, confidence interval; CPI/r, comparator ritonavir-boosted protease inhibitor; HIV, human immunodeficiency virus; ITT, intent-to-treat analysis; PP, per protocol analysis.

^a *P* = .008 vs CPI/r.

^b *P* = .021 vs CPI/r.

^c *P* = .037 vs CPI/r.

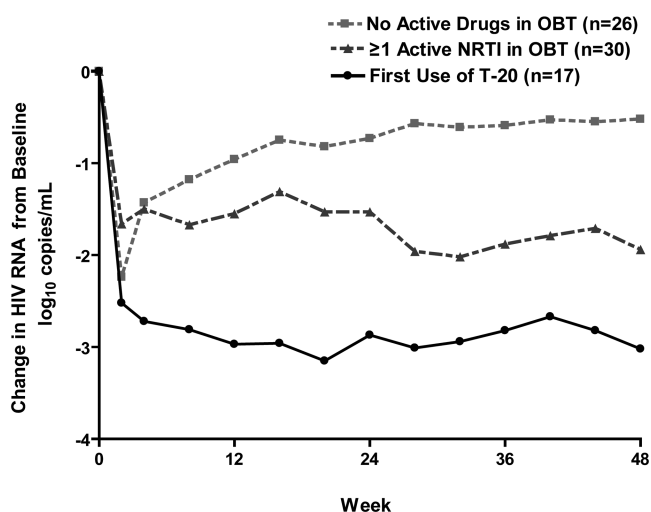


Figure 2. Mean change from baseline in human immunodeficiency virus (HIV) RNA for subjects who received elvitegravir (125 mg), showing impact of activity of optimized background therapy (OBT) by type of drugs. Subjects shown with ≥ 1 active nucleoside reverse-transcriptase inhibitor (NRTI) in OBT did not have concomitant first use of T-20. Data after subjects added a protease inhibitor are excluded.

125 mg arm was statistically superior ($P = .021$), compared with the $DAVG_{24}$ for the CPI arm. This difference in efficacy was also evident at week 16, when the $DAVG_{16}$ for the elvitegravir 50 mg arm was noninferior to that of the CPI arm, and the $DAVG_{16}$ for the elvitegravir 125 mg group was statistically superior ($P = .008$), compared with that of the CPI arm (Table 2). A per protocol analysis, performed to minimize the impact of changes in randomized treatment, showed that the $DAVG_{48}$ for the elvitegravir 50 mg arm was noninferior to that of the CPI arm. The $DAVG_{48}$ for the elvitegravir 125 mg arm was statistically superior to that of the CPI arm ($P = .037$; Table 2).

Subjects given elvitegravir 50 mg or 125 mg had a 2-week virologic response similar to that observed in the monotherapy study and greater than that observed for patients given CPI/r. At week 2, the mean change in HIV RNA level from baseline was $-1.08 \log_{10}$ copies/mL for the CPI/r arm, compared with $-1.79 \log_{10}$ copies/mL for the elvitegravir 50 mg arm (ITT analysis, $P < .001$) and $-2.07 \log_{10}$ copies/mL for the elvitegravir 125 mg arm ($P < .001$). The difference in mean change from baseline in HIV RNA level between the elvitegravir 50 mg and 125 mg arms did not reach statistical significance ($P = .067$).

The 3 treatment arms also showed differences in the proportion of subjects who ever achieved reductions in HIV RNA of at least a 1 or 2 $\log_{10}$ copies/mL from baseline prior to the addition of a boosted PI. Over 90% of subjects who received elvitegravir 50 mg or 125 mg achieved reductions in HIV RNA of at least 1 $\log_{10}$ copies/mL by week 24, compared with 62% of subjects who received CPI/r (per-protocol analysis, 91% vs

62% [$P < .001$] and 92% vs 62% [$P < .001$], respectively). Similarly, more subjects in the elvitegravir 125 mg arm than in the CPI/r arm achieved reductions in HIV RNA of at least 2 $\log_{10}$ copies/mL (76% vs 53%; $P = .009$); the elvitegravir 50 mg arm, however, compared with the CPI/r arm, did not have significantly more subjects attain this level of suppression (69% vs 53%; $P = .092$). Subjects with HIV RNA levels $>100,000$ copies/mL at baseline and those with HIV RNA levels $\leq 100,000$ copies/mL at baseline experienced similar $DAVG_{24}$ in all treatment arms. Thus, the response rates for the elvitegravir 125 mg group were superior to those for the CPI/r arm, whereas the response rates for the elvitegravir 50 mg group were non-inferior to those for the CPI/r arm.

Effect of the activity of the OBT. The activity of the optimized background therapy significantly impacted the durability and magnitude of the response to elvitegravir 125 mg (Figure 2). Subjects with no active background agents (GSS equal to 0 and not using T-20 for the first time; $n = 26$) had a mean change from baseline in HIV RNA level of $-2.24 \log_{10}$ copies/mL at week 2, but this effect was not durable; at week 24, the mean change from baseline in HIV RNA level was $-0.73 \log_{10}$ copies/mL. Compared with subjects who had no active agents in their OBT, subjects who received at least 1 active NRTI (GSS ≥ 1 and not using T-20 for the first time; $n = 30$) with elvitegravir at a dosage of 125 mg had greater reductions in HIV RNA level at week 24 of $-1.53 \log_{10}$ copies/mL ($P = .048$; per-protocol analysis). Subjects who received elvitegravir 125 mg with another fully-active, new-class agent (ie, first use of T-20; $n = 17$), experienced significantly greater reductions in HIV RNA at week 24 ($-2.87 \log_{10}$ copies/mL) than did

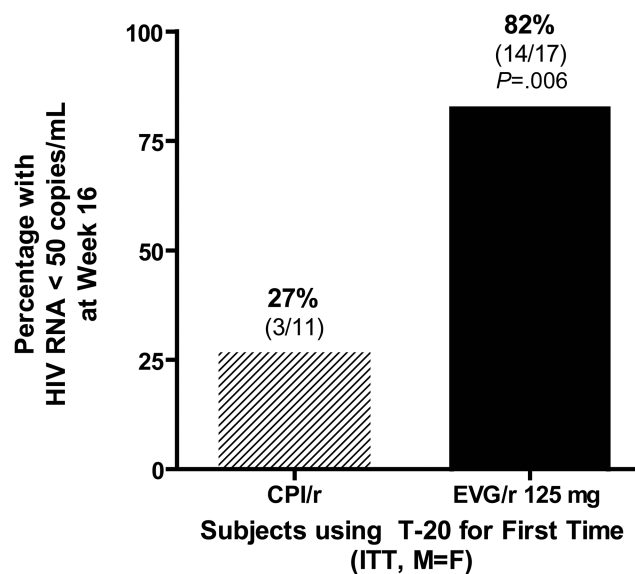


Figure 3. Proportions of subjects with human immunodeficiency virus (HIV) RNA level <50 copies/mL at week 16. ITT, intent to treat. CPI/r, comparator ritonavir-boosted protease inhibitor.

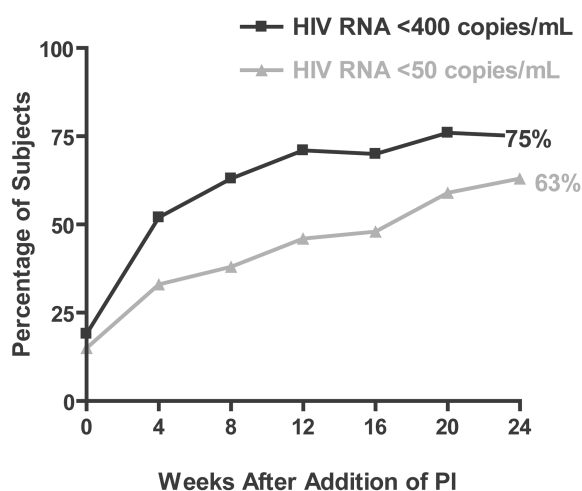


Figure 4. Percentage of subjects who received elvitegravir (125 mg) with virologic suppression after addition of a boosted protease inhibitor (PI). HIV, human immunodeficiency virus.

subjects with no active drugs in their OBT ($P < .001$) or subjects with at least 1 active NRTI in their OBT ($P = .008$). At week 48, the impact of the activity of background therapy on virologic response for these 3 subsets of subjects was similar to the effect observed at week 24 (Figure 2).

A contribution of T-20 to virologic response was also evident in the CPI/r arm. However, the mean change from baseline in HIV RNA level was significantly greater for subjects who received elvitegravir 125 mg with first use of T-20 than it was for those who received CPI/r with first use of T-20. This difference in response resulted in a statistically significant difference in $DAVG_{24}$ ($-1.68 \log_{10}$ copies/mL for CPI/r with new T-20 use vs $-2.85 \log_{10}$ copies/mL for elvitegravir 125 mg with

new T-20 use; $P = .004$; ITT analysis). Furthermore, this difference of $1 \log_{10}$ copies/mL persisted through week 48. The $DAVG_{48}$ for subjects who received CPI/r with new T-20 use was $-1.75 \log_{10}$ copies/mL, compared with $-2.77 \log_{10}$ copies/mL for subjects in the elvitegravir 125 mg arm with new T-20 use ($P = .008$). The effect of active background therapy is also seen in the proportions of subjects with HIV RNA levels <50 copies/mL at week 16 (Figure 3). Thus, the greater response seen with elvitegravir at a dosage of 125 mg in combination with T-20 is not solely attributable to T-20.

Subjects in the elvitegravir 125 mg arm who added boosted darunavir or tipranavir ($n = 27$) to their regimen achieved additional clinically significant reductions in HIV RNA level. The mean change from the HIV RNA value prior to the addition of the boosted PI was $-1.29 \log_{10}$ copies/mL 24 weeks after addition of the boosted PI. In addition, the proportion of subjects with HIV RNA levels <400 copies/mL or <50 copies/mL increased steadily over 24 weeks after the addition of a PI to the regimen (Figure 4).

CD4 cells and efficacy. Similar mean changes in CD4 cell counts were observed across all treatment arms at week 24 (mean increases of 53, 53, and 57 CD4 cells/mm³ for the CPI/r and elvitegravir 50 mg and 125 mg arms, respectively; ITT analysis). Likewise, there were no differences in mean CD4 cell count increases at week 48 (increases of 68, 49, and 83 cells/mm³ for the CPI/r and elvitegravir 50 mg and 125 mg arms, respectively). Subjects in the elvitegravir 125 mg arm with ≥ 50 CD4 cells/mm³ at baseline achieved greater virologic suppression than did subjects with <50 CD4 cells/mm³ ($DAVG_{24}$ -1.9 vs -1.0 ; $P = .005$).

Safety. The occurrence of treatment-emergent adverse events, related adverse events, grade 3 or 4 adverse events, deaths, serious

Table 3. Treatment-Emergent Adverse Events Reported by at Least 10% of Subjects through Week 48

Variable	No. (%) of subjects with adverse event, by treatment group			
	CPI/r (<i>n</i> = 63)	Elvitegravir, by dosage		
		20 mg per day (<i>n</i> = 71)	50 mg per day (<i>n</i> = 71)	125 mg per day (<i>n</i> = 73)
Any treatment-emergent adverse event	59 (94)	63 (89)	67 (94)	72 (99)
Diarrhoea	18 (29)	9 (13)	18 (25)	14 (19)
Constipation	1 (2)	3 (4)	4 (6)	9 (12)
Nausea	12 (19)	11 (16)	12 (17)	12 (16)
Vomiting	3 (5)	5 (7)	5 (7)	9 (12)
Fatigue	8 (13)	12 (17)	9 (13)	14 (19)
Pyrexia	4 (6)	4 (6)	4 (6)	7 (10)
Injection Site Reaction	9 (14)	12 (17)	9 (13)	9 (12)
Upper Respiratory Tract Infection	7 (11)	15 (21)	13 (18)	20 (27)
Sinusitis	4 (6)	7 (10)	8 (11)	5 (7)
Headaches	4 (6)	8 (11)	8 (11)	11 (15)
Cough	3 (5)	4 (6)	5 (7)	8 (11)

NOTE. CPI/r, comparator ritonavir-boosted protease inhibitor.

adverse events, and adverse events leading to study drug discontinuation was similar across the treatment groups. The most common treatment-emergent adverse events were diarrhea and nausea (Table 3). There was no association of a type of adverse event with the elvitegravir arms, compared with the CPI/r arm, and there was no dose-dependent increase in a type of adverse event in the elvitegravir arms.

The incidences of grade 3 or 4 laboratory toxicity were similar across treatment groups (32%, 42%, 28%, and 34% in the CPI/r and elvitegravir 20 mg, 50 mg, and 125 mg groups, respectively). In each treatment group, 1 subject had grade 3 or 4 elevation of aspartate transaminase or alanine transaminase levels. Grade 3 or 4 elevations in cholesterol level were observed in 1, 4, 2, and 1 subject in the CPI/r and elvitegravir 20 mg, 50 mg, and 125 mg arms, respectively. Grade 3 or 4 values for triglyceride levels were seen in 4, 5, 3, and 4 subjects in the CPI/r and elvitegravir 20 mg, 50 mg, and 125 mg groups, respectively.

Through week 48, a similar percentage of subjects had experienced serious adverse events across all treatment groups. Three serious adverse events across all treatment groups were assessed as related or possibly related to study drugs by the investigator: syncope in a subject randomized to the elvitegravir 50 mg group, significant hypersensitivity reaction in a subject with a history of multiple drug allergies randomized to the elvitegravir 20 mg group, and right eye hyphaema in a subject randomized to CPI/r.

The incidences of all malignancies, including basal cell carcinoma, were similar in the CPI/r arm (3.2%) and in all 3 elvitegravir arms combined (3.7%). Among subjects randomized to the elvitegravir 125 mg arm, only 1 subject (1 [1%] of 73) received a neoplasm diagnosis by week 48; this subject developed a basal cell carcinoma.

None of the 3 deaths (due to *Pneumocystis* pneumonia, B cell lymphoma, and cardiorespiratory failure in subjects who were in the elvitegravir 20 mg, 20 mg, and 50 mg arms, respectively) in this study were considered to be related to study drug.

DISCUSSION

In this dose-ranging, randomized study, the $DAVG_{24}$ for regimens containing elvitegravir 50 mg or 125 mg was noninferior to the $DAVG_{24}$ for regimens containing a boosted PI, thereby fulfilling the primary objective. Moreover, the $DAVG_{24}$ for the elvitegravir 125 mg group was statistically superior to that for the CPI/r arm. Implementation of the recommendations of the independent data monitoring committee to maximize patient safety and antiviral efficacy, however, limited the interpretation of the results at this time point. Because only 3 subjects in the elvitegravir arms added a boosted PI before week 16—and generally for a short time before week 16—measures of

efficacy at week 16 provide a clearer view of the antiviral potency of elvitegravir.

The $DAVG_{16}$ for the elvitegravir 125 mg group was also statistically superior to that of the CPI/r arm. Overall, elvitegravir at a dose of 125 mg provided slightly better efficacy than elvitegravir at a dose of 50 mg. Subjects who received elvitegravir at a dose of 125 mg experienced an average decrease in HIV RNA level of $>2 \log_{10}$ copies/mL at week 2. The durability of this response, however, was impacted by the activity of the other drugs in the background regimen. Unlike subjects in the studies of raltegravir [8], subjects in this study did not receive a boosted PI in their background regimen from the outset. Thus, the activity of this restricted background regimen could be readily determined on the basis of genotypic analysis of NRTI mutations and whether the subject had used T-20 previously in a failing regimen. Subjects who received elvitegravir at a dose of 125 mg with 1 other potent, fully active, new-class agent (namely, first use of T-20) experienced significant and durable virologic suppression, even in the absence of additional background antiviral activity from NRTIs. Thus, similar to other antiretroviral agents, a maximal and durable response with elvitegravir is seen when this drug is used in combination with other active agents in highly treatment-experienced subjects [9–12], and use as functional monotherapy can lead to early virologic rebound, as has been described elsewhere for lamivudine and efavirenz [13, 14].

Subjects in the elvitegravir 125 mg arm who added boosted darunavir or tipranavir to their regimen had additional virologic suppression (Figure 3). The increased suppression leading to undetectable HIV RNA levels in the majority of these subjects attests to the efficacy of these PIs when added sequentially to elvitegravir. Concomitant use of elvitegravir with an active, boosted PI and another agent would be anticipated to provide similar, if not improved, virological suppression.

There are several limitations to this study. Following the recommendations of the independent data monitoring committee, the closure of the 20 mg arm prevents meaningful analysis of the results from this arm. Also, the addition of boosted PIs to the regimens of many subjects in the other elvitegravir arms makes the comparison of efficacy with that of the active comparator beyond week 16 more challenging. Nevertheless, by evaluating all data at week 16 and excluding data after subjects added a boosted PI to their regimen (Figure 2), the efficacy of elvitegravir 125 mg is clear.

Elvitegravir was well-tolerated at all doses used in this study. No association with any treatment-emergent adverse event was observed in the elvitegravir arms, compared with the CPI/r group. In addition, there was no relationship of any adverse event with increasing doses of elvitegravir, including depression and malignancies [15].

In summary, once-daily administration of elvitegravir was

well-tolerated and produced rapid virologic suppression that was durable when the drug was administered with active background therapy. This study clearly demonstrates the importance of using at least 1 fully active drug to support the potent antiviral activity of an integrase inhibitor, such as elvitegravir, in producing a durable virologic response. Elvitegravir is currently being evaluated in a phase 3 program.

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References

1. Matsuzaki Y, Watanabe W, Yamataka K, et al. JTK-303/GS-9137, a novel small molecule inhibitor of HIV-1 integrase: anti-HIV activity profile and pharmacokinetics in animals [abstract 508]. In: Program and abstracts of the Conference on Retroviruses and Opportunistic Infections, Denver, CO, 5–8 February 2006. **2006**.
2. Mathias A, Jain A, Hui J, Kearney BP. Pharmacokinetic characterization of GS-9137, an HIV integrase inhibitor dosed with ritonavir [abstract 85]. In: Program and abstracts of the 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, Portugal, 20 April 2006. **2006**.
3. DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naïve and treatment-experienced patients. *J Acquir Immune Defic Syndr* **2006**; 43:1–5.
4. Mathias A, West S, Hui J, Kearney B. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther* **2009**; 85(1):64–70.
5. Petropoulos CJ, Parkin NT, Limoli KL, et al. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. *Antimicrob Agents Chemother* **2000**; 44:920–928.
6. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* **2002**; 16:1257–1263.
7. HIV French Resistance Web page. <http://www.hivfrenchresistance.org>. Accessed 19 January 2007.
8. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* **2008**; 359:339–354.
9. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* **2007**; 369:1169–1178.
10. Lazzarin A, Campbell T, Clotet B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* **2007**; 370:39–48.
11. Madrugá JV, Cahn P, Grinsztejn B, et al. Efficacy and safety of TMC125

- (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* **2007**;370:29–38.
12. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med* **2008**;359:355–365.
 13. Schuurman R, Nijhuis M, van Leeuwen R, et al. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *J Infect Dis* **1995**;171:1411–1419.
 14. Bachelier LT, Anton ED, Kudish P, et al. Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy. *Antimicrob Agents Chemother* **2000**;44:2475–2484.
 15. Harris M, Larsen G, Montaner J. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS* **2008**;22:1890–1892.