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PHARMACOKINETIC/PHARMACODYNAMIC MODELING OF THE ANTIRETROVIRAL ACTIVITY OF THE CCR5 ANTAGONIST VICRIVIROC IN TREATMENT EXPERIENCED HIV-INFECTED SUBJECTS (ACTG PROTOCOL 5211)

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Abstract

Objective—This sub-study of ACTG Protocol 5211 explored the relationship between antiretroviral effect and plasma concentrations of vicriviroc, an investigational CCR5-antagonist for HIV infection. Eighty-six treatment-experienced subjects failing their current antiretroviral regimens were randomized to add vicriviroc 5, 10 or 15 mg QD or placebo for two weeks. Beyond week 2, subjects were changed to optimized background antiretroviral treatment while continuing vicriviroc or placebo. Plasma samples collected at weeks 2 and 8 were assayed for vicriviroc concentrations and combined with vicriviroc concentration data from 110 seronegatives enrolled in five phase 1 studies. An inhibitory Emax models was used to assess pharmacokinetic/pharmacodynamic relationships and recursive partitioning was applied to determine the breakpoint in vicriviroc PK parameters associated with virologic suppression.

Results—A two-compartment model was fitted to the drug concentration data. At Week 2, a higher vicriviroc C_{min} was associated with a greater mean drop in HIV RNA (viral load) and a higher percentage of subjects experiencing a $>1 \log_{10}$ copies/ml drop in viral load. In subjects with $C_{min} > 54$ ng/ml, the mean viral load decrease was $1.35 \log_{10}$ copies/ml, versus $0.76 \log_{10}$ with $C_{min} < 54$ ng/ml ($p=0.003$, Student's t-test). At this C_{min} breakpoint, 70% of subjects with the higher C_{min} had a $>1 \log$ drop in VL, compared to 44% with a lower C_{min} ($p=0.048$, Fisher's exact test). Similar results were seen with an AUC breakpoint of $1460 \text{ ng} \cdot \text{hr/mL}$. At Weeks 16 and 24, all vicriviroc-treated subjects experienced better viral load responses than placebo recipients, but there was no apparent relationship between PK and change in viral load among these vicriviroc-treated subjects.

Conclusions—There was a positive correlation between vicriviroc C_{min} , AUC, and viral load changes at Week 2 in treatment-experienced HIV-infected subjects receiving no other new active

antiretroviral drugs. This correlation did not persist beyond Week 16, probably because treatment response at that point also depended on having other active drugs in the regimen.

Introduction

The discovery that HIV uses the chemokine receptors CCR5 (R5 virus) and CXCR4 (X4 virus) as co-receptors for binding and entry during infection was a milestone in understanding HIV pathogenesis, and introduced a novel therapeutic target (1,2). Some viruses can use both receptors (dual tropic; 3), and subjects can harbor a mixture of pure R5 and dual-tropic or X4 viruses (mixed tropic). Variations in the V3-loop sequence of the viral envelope protein gp120 determine which chemokine receptor is utilized most efficiently (4). R5 viruses are the predominant transmitted form, and they are the variant that occur predominantly throughout the course of the disease (5). Emergence of dual or CXCR4-tropic virus is associated with a more precipitous decline in CD4 lymphocytes and accelerated progression to AIDS (6,7). The observation that individuals expressing a 32-base pair deletion in the CCR5 receptor gene produced a non-functional receptor and displayed either resistance to HIV infection (homozygotes) or slower progression to AIDS with infection (heterozygotes), suggested these receptors might be safe therapeutic targets for HIV infection (8,9).

Vicriviroc (1-[(4,6-dimethyl-5-pyrimidinyl)carbonyl]-4-[4-[2-methoxy-1(R)-4-(trifluoromethyl)phenyl]ethyl-3(S)-methyl-1-piperazinyl]-4-methylpiperidine), is a CCR5 antagonist with potent antiviral activity against a wide variety of R5 HIV-1 strains, with an IC₅₀ and IC₉₀ of 1.58 ng/ml and 10 ng/ml, respectively. It has activity against strains resistant to other antiretroviral drugs and displays synergy with other anti-HIV agents (10,11). In monotherapy studies, vicriviroc can produce up to a 1.6 log copies/ml decrease in HIV RNA by day 14 in ART-naïve individuals (12). As observed with other chemokine antagonists, this effect persists after discontinuation of the drug, suggesting sustained binding of the receptor.

Maintaining adequate plasma concentrations of antiretroviral drugs is absolutely essential to achieve efficacy and prevent emergence of drug-resistant mutants of the virus. Characterizing drug concentrations that optimize efficacy while minimizing toxicity and the risk of resistance is an essential step in determining regimens for large treatment trials (13). ACTG study 5211 was undertaken to evaluate the efficacy of vicriviroc in treatment-experienced subjects, and demonstrated that the drug produced potent virologic suppression over 24 weeks in combination with an optimized background regimen (14). Vicriviroc plasma concentrations were obtained during this study and we used population pharmacokinetic modeling to estimate individual plasma exposures of vicriviroc in this group. Furthermore, we sought to explore pharmacokinetic-pharmacodynamic relationships by evaluating the relationship between vicriviroc exposure and virologic response among study participants. These relationships were used to aid in the dose selection for Phase III clinical trials.

Methods

Study Design

ACTG 5211 (14) was a double-blind, randomized phase 2 study of vicriviroc in treatment-experienced, human immunodeficiency virus (HIV)-infected subjects experiencing virologic failure while receiving a ritonavir-containing antiretroviral regimen of ≥ 3 drugs with an HIV-1 RNA level of at least 5000 copies/mL (Amplicor HIV-1 ultrasensitive assay; Roche Molecular Systems) and R5 virus as determined by a validated tropism assay (Trofile [original assay]; Monogram Biosciences). Initially, subjects were required to have CD4⁺ cell counts greater than 50 cells/mm³ and to be hepatitis B surface antigen and hepatitis C antibody negative at screening; these restrictions were removed in a protocol amendment. Vicriviroc at 5, 10, or 15 mg or placebo was added to the failing regimen for 14 days, after which the antiretroviral

regimen was optimized on the basis of resistance testing. The frequency of protease inhibitor use in the optimized background regimen by vicriviroc dose treatment arm is shown in Table 1. The primary end point was the change in plasma HIV-1 RNA levels at day 14; secondary end points included safety/tolerability and HIV-1 RNA changes at weeks 24 and 48. The study was approved by the institutional review boards at each of the participating institutions. Written, informed consent was obtained from study participants. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this research.

Pharmacokinetic Data Assembly

In study A5211, two PK samples, separated by at least two hours, were obtained from enrolled HIV positive subjects at their week 2 and week 8 clinical visits. PK sampling times were recorded but were not fixed relative to the last dose of vicriviroc. Vicriviroc dosing interval was assumed to be 24 hours during the 48-week study period. A validated bioanalytical method (range 0.5–1000 ng/ml) was used to determine vicriviroc plasma concentrations using LC-MS/MS. Due to the sparse sampling nature in this study, data from five other Phase I studies with intensive PK sampling scheme were combined and used for a population PK analysis to estimate the pharmacokinetic parameters for subjects enrolled in study A5211. In brief, these five Phase I studies were drug-drug interaction studies in assessing the impact of other anti-HIV drugs on vicriviroc pharmacokinetics (Table 2).

Since all subjects in A5211 were taking ritonavir, subjects in these five Phase I studies were included only if they received vicriviroc concomitant with ritonavir. Moreover, only vicriviroc concentrations at steady state were included for this data analysis.

Pharmacodynamic Data Assembly

Subjects in study A5211 who met the following criteria were included for pharmacodynamic analysis: (1) viral load data available at weeks 2, 16, 24 and 48; (2) PK data (drug concentration data) available; (3) virus tropism recorded as R5 (only) at study entry and (4) no discontinuation of randomized drug (vicriviroc or placebo as appropriate) before HIV-1 RNA tests at weeks 2, 16, 24 or 48.

Population Pharmacokinetic Model

Population pharmacokinetic analysis was carried out using the NONMEM V software (Globomax, Ellicott City, MD). The selection of the PK base model was based on AIC (Akaike Information Criterion) values and diagnostic plots. A two-compartment model with first-order absorption and elimination was chosen as the pharmacokinetic model. An exponential error model was used to characterize the interindividual variability, and a combination of additive and proportional error models were used to characterize the intraindividual variability.

Based on post hoc Bayesian estimates of PK parameters, individual vicriviroc exposures of subjects in study A5211 were simulated while subjects were assumed to be taking vicriviroc once a day. The estimated plasma concentration-time profiles for each subject were then used to determine the maximum plasma concentration at steady state (C_{max}), the minimum plasma concentration at steady state (C_{min}), and the area under the plasma concentration - time curve during the dosing interval at steady state (AUC).

Pharmacodynamic Analysis

A recursive partitioning analysis was performed using the HelixTree program (version 5, Golden Helix, Inc. Bozeman, MT) to determine partitioning breakpoints of vicriviroc concentrations on the basis of viral load change from baseline. Statistical significance of the

portioning breakpoints was determined using the Bonferroni-adjusted p-value, derived from the Student's t-test, at the significance level $p \leq 0.01$. Based on the determined breakpoints, the percentage of subjects with at least a one $\log_{10}$ copies/ml HIV RNA decrease from baseline was calculated in the patient subgroups, and compared using Fisher's exact test ($\alpha=0.05$). An inhibitory sigmoid $E_{\max}$ model (WinNonlin, version 4, Pharsight Corp., Cary, NC) was applied to define the correlation between vicriviroc exposure and viral load decrease from baseline.

RESULTS

A total of 118 subjects were enrolled in ACTG study 5211—35 under the original protocol and 83 under a protocol amendment, including 30 who were randomized to receive placebo and 88 who were randomized to receive one of the vicriviroc doses. Study subjects were 92% men and 8% women and were 20% black, 12% Hispanic, 66% white, and 2% other race/ethnicity; 4% had a history of injection drug use. A total of 39 (33%) subjects were enfuvirtide experienced. The median HIV-1 RNA level was 36,380 (4.56 $\log_{10}$) copies/mL; the median CD4 count was 146 cells/mm³. At screening, 118 (100%) had documented R5 (only) virus; at study entry (before receiving study treatment), 102 (86%) had R5 (only) virus, 12 (10%) now had dual/mixed virus, and 4 (4%) had no result because of assay amplification issues or specimen processing problems.

Pharmacokinetic Data Analysis

The final PK database consisted of 110 healthy HIV-seronegative subjects and 86 HIV-infected subjects who received vicriviroc with ritonavir, ages 18 to 67 years, including 46 women and 150 men. Their demographic information is summarized in Table 3. The following pharmacokinetic parameters were used to characterize the two-compartment model: absorption rate constant (K_a), clearance (CL), inter-compartmental clearance (Q), central volume of distribution (V_c), and peripheral volume of distribution (V_p). Figure 1 plots the observed vicriviroc concentrations in these 196 individuals versus the predicted concentrations from the population pharmacokinetic modeling. The predicted and observed vicriviroc concentrations were highly correlated ($r^2=0.91$), indicating that the two-compartment model fitted the data appropriately. For the studied population, vicriviroc absorption rate constant was estimated to be 0.3 hr^{-1} , clearance was 3.5 L/h, the inter-compartmental clearance was 29.5 L/h, the central volume of distribution was 41.3 L and the peripheral volume of distribution was 662 L. The relative standard error of these parameters ranged from 3.7% to 41.6%.

A summary of the $C_{\max}$, $C_{\min}$ and AUC from the NONMEM population pharmacokinetics analysis is presented in Table 4 for the three vicriviroc doses for the 86 subjects in the A5211 study. Vicriviroc pharmacokinetic parameters in HIV-infected subjects were similar to those in healthy subjects.

Pharmacodynamic Analysis at Week 2

Following the data inclusion criteria, a total of 99 subjects in ACTG study A5211 were used for the pharmacodynamic analysis at week 2, including 26 subjects in the placebo arm and 73 subjects in the vicriviroc treated arms. The mean viral load change from baseline was an increase of 0.045 $\log$ copies/ml in the placebo group, but a decrease of 1.13 $\log$ in the combined vicriviroc arms at week 2 ($p<0.05$; Table 5). An inhibitory sigmoid $E_{\max}$ model appropriately described the relationship between $\log$ viral load change at week 2 and vicriviroc PK individual parameters (AUC, $C_{\max}$ and $C_{\min}$) at steady state. Figure 2 illustrates the correlation of viral load change at week 2 and vicriviroc $C_{\min}$ at steady state. As calculated, when vicriviroc trough concentrations at steady-state reached 56 ng/mL, 90% of the maximum efficacy of viral load decrease at week 2 was achieved (EC_{90}).

The breakpoints identified by recursive partitioning for the log viral load changes from baseline at week 2 are summarized in Table 6. Significant breakpoints of vicriviroc C_{min} , C_{max} and AUC occurred between vicriviroc-treated subjects and placebo. Significant breakpoints of vicriviroc C_{min} , C_{max} and AUC, separating high from low likelihood of response at week 2, were 53.7 ng/ml, 72.4 ng/mL and 1460 hr*ng/mL, respectively. About 70% of subjects achieved a greater than one log viral load decrease when vicriviroc trough concentrations were higher than 53.7 ng/mL, or the AUC was higher than 1460 hr*ng/ml (Table 6). We assessed the influence of patient characteristics on viral load changes and found no significant impact of race, gender, age, or body weight on vicriviroc efficacy (not shown).

Pharmacodynamic Analysis at Weeks 16, 24 and 48

Following the data inclusion criteria, a total of 92 subjects in ACTG study A5211 were used for the pharmacodynamic analysis at week 16, including 26 subjects in the placebo arm and 66 subjects in the vicriviroc-treated arms (Table 5). A total of 84 subjects were used for the pharmacodynamic analysis at week 24, including 25 subjects in the placebo arm and 59 subjects in vicriviroc-treated arm (Table 5). The mean HIV RNA change from baseline was -0.49 log copies/ml and -0.75 log in the placebo arm, vs. -1.98 log copies/ml and -2.05 log copies ml in vicriviroc arms, at week 16 and 24 respectively ($p < 0.05$ at both times). No apparent PK-PD relationship could be defined between the log viral load change and vicriviroc exposures (C_{min} , C_{max} and AUC) at weeks 16 or 24, respectively. Significant breakpoints could be determined between placebo and vicriviroc arms (not shown). However, no statistically significant breakpoints of vicriviroc exposures likely to predict a response were identified within the vicriviroc-treated arms. There was no apparent impact of subjects' race, gender, age, or body weight on viral load change at week 16 or 24 (not shown).

According to the study protocol, vicriviroc dose would be increased for subjects receiving low doses of vicriviroc if protocol-defined virologic failure (less than a one log₁₀ copies/mL decrease from baseline at/after week 16) was confirmed during the study; in addition, subjects in the placebo arm with confirmed virologic failure could add VCV to their regimen. Under these circumstances, only 52 subjects met the data inclusion criteria for week 48, including 5 subjects in the placebo arm and 47 subjects in vicriviroc treatment arm. Given this small sample size, further PK-PD data analysis was not conducted.

Discussion

In our study, a two-compartment model described vicriviroc pharmacokinetics in treatment-experienced HIV infected subjects also taking ritonavir-containing protease inhibitor regimens, when combined with data from healthy HIV-seronegative subjects using population pharmacokinetic modeling. At week 2, higher vicriviroc concentrations were associated with a greater decrease in viral load. However, after subjects received optimized ART regimens, no PK-PD correlation could be defined at weeks 16 and 24. The virologic response to vicriviroc reported here is comparable to that observed by other investigators. Schurman et al. (12) observed mean HIV RNA reductions of 1.08, 1.56 and 1.62 log copies/ml at doses of 10 mg, 25 mg and 50 mg BID (without ritonavir), respectively, in treatment-naïve individuals on vicriviroc monotherapy at day 14. Their observed values of mean C_{max} at steady-state were 63 ng/ml, 142 ng/ml and 276 ng/ml, respectively, compared to our results of 33 ng/ml, 69 ng/ml, 95 ng/ml at vicriviroc doses of 5 mg, 10 mg and 15 mg QD (with ritonavir), respectively. Landovitz et al. (15) reported mean HIV RNA reductions of 0.93, 1.18 and 1.34 log₁₀ using vicriviroc doses of 25 mg, 50 mg and 75 mg once daily respectively in naïve subjects on vicriviroc monotherapy (without ritonavir) at day 14.

Data generated from pharmacokinetic-pharmacodynamic (PK-PD) studies can reveal important aspects of a drug's behavior, including absorption and elimination kinetics, and

identify a range of doses where drug concentrations produce therapeutic and toxic effects. Further, these data can be used to optimize dosing in phase III studies where the clinical efficacy of the drug will be most rigorously evaluated. For example, exposure-effect relationships have been explored for abacavir, using population pharmacokinetic data (16) and for elvitegravir in a randomized, double-blind placebo-controlled trial (17). Using step-wise additive logistic modeling, McFadyen *et al.* (18) identified an average maraviroc concentration of 75 ng/ml as having an 80% probability of producing HIV RNA <50 copies/ml in the MERIT study of treatment-naïve HIV-infected patients. Rosario *et al.* (19) developed a comprehensive PK-PD disease model which sought to combine drug effects on viral elimination dynamics from cellular compartments, pharmacokinetics and virologic response to the CCR5 inhibitor maraviroc. This model was designed to incorporate data from various *in vivo* and *in vitro* sources including maraviroc pharmacokinetics in healthy volunteers and maraviroc viral inhibitory constants *in vitro*. This PK-PD disease model was used to estimate a mean decay rate of actively infected cells expressed as the rate of exponential HIV RNA decline, determined to be $-0.58 \pm 0.12 \text{ day}^{-1}$ at a dose of 300 mg maraviroc BID.

An important finding of our analysis was the observation that viral load reduction was associated with higher vicriviroc plasma concentrations after two weeks of vicriviroc therapy, while remaining on an otherwise failing regimen. Landovitz *et al.* (15) found that the reduction in viral load by day 14 correlated with the vicriviroc $C_{\min}$, but that subjects who subsequently failed therapy had a lower mean $C_{\min}$ (43.2 vs. 66.2 ng/ml) and AUC (1896.9 vs. 2788.3 ng.h/ml). Consistent with these findings, we observed maximum virologic suppression in subjects achieving a steady-state plasma concentration of 56 ng/ml. The vicriviroc 5 mg arm had a substantial number of subjects who were switched from this dose to higher doses due to suboptimal virologic responses and a trend towards emergence of D/M tropism during the study (14).

The most likely explanation for the lack of PK-PD correlation at weeks 16 and 24 is the effect of the optimized background regimen started at week 2. The mean change in viral load from baseline to week two in the pooled vicriviroc groups was $-1.13 \log_{10}$ copies/ml, while the mean change from baseline to weeks 16 and 24 was -1.98 and $-2.05 \log_{10}$ copies/ml, respectively. The additional decrease in HIV RNA comparing weeks 2 with weeks 16 and 24 did not correlate with the assigned dose of vicriviroc. For example, subjects in the 10 mg vicriviroc arm had a greater additional decline in $\log_{10}$ HIV RNA copies/ml than subjects in the highest (15 mg) dose arm at week 16 (10 mg, $-1.01 \log$ vs. 15 mg, $-0.47 \log$), and similarly at week 24 (not shown). Moreover, the majority of subjects had sustained plasma concentrations of vicriviroc above 56 ng/ml at weeks 16 and 24, and this concentration was shown by recursive partitioning analysis to be associated with increased likelihood of viral suppression. This concentration is very close to the *in vitro* IC_{90} of vicriviroc against wild-type virus, and this finding is consistent with the observation in studies of other antiretroviral agents that optimal pharmacologic response occurs at trough plasma drug concentrations at or above the IC_{90} (17). Valdez *et al.* (20) developed a weighted susceptibility score to rank the efficacy of optimized background regimens in treatment experienced patients from the MOTIVATE study who were randomized to maraviroc with OBT or OBT alone. The number of active drugs in the OBT regimen combined with maraviroc was the strongest predictor of virologic suppression at week 48. Collectively, these observations support the importance of the optimized background regimen in the virologic responses seen at weeks 16 and 24. For achieving durable virologic suppression, maintaining plasma concentrations comfortably above of the IC_{90} may be warranted, particularly in treatment experienced patients. Analysis of larger numbers of treatment-experienced subjects has suggested favorable long-term outcomes in subjects achieving trough concentrations of greater than 100 ng/ml (21).

The lack of correlation between pharmacokinetic parameters and virologic response has been observed in a number of HIV treatment scenarios. For example, Mould et al. (22) observed that virologic response to enfuvirtide was independent of enfuvirtide plasma concentrations, likely because dosing 90 mg BID produced drug concentrations in the plateau portion of the dose response curve. The lack of correlation between plasma vicriviroc concentration and virologic response at weeks 16 and 24 might suggest that all vicriviroc doses produced concentrations in the plateau range of the dose response curve in the presence of an OBT regimen; however, the inferiority of the 5 mg dose makes this explanation unlikely. There is also the possibility that the maximum effect of vicriviroc was not yet achieved by the two weeks when the optimal background regimen was initiated, but the inferiority of the 5 mg dosing arm makes this explanation unlikely.

As with maraviroc, the response to vicriviroc is optimal in subjects having only R5 virus detected before initiating treatment (23). While all subjects in our study had R5-only virus at entry, the first generation tropism assay used in this study is slightly less sensitive in detecting dual/mixed and X4 viruses than the currently available enhanced tropism assay (24). For example, in a re-analysis of the MERIT study, 15% of the subjects with virus classified as R5 (only) prior to receiving maraviroc were re-classified as having dual/mixed tropism virus by the enhanced tropism assay (25). When these subjects were removed from the analysis, maraviroc demonstrated an effect superior to that observed in the previous analysis of efficacy. Because the predominant quasispecies were R5-only viruses, patients may have an initial virologic response, but subsequently experience virologic failure as the dual/mixed or X4 quasi-species emerge. In our study, a subsequent analysis revealed that 15 out of the 73 subjects designated initially as having R5 virus and randomized to vicriviroc were found to have dual-mixed virus by the enhanced tropism assay (26). These subjects likely experienced a virologic response initially which gradually diminished and may have contributed to the lack of PK-PD correlation at weeks 16 and 24.

Mutations in the env gene that alter HIV-1 gp120 can confer resistance to maraviroc and vicriviroc (27). Ogert et al. (28) have identified key determinants for vicriviroc resistance in the C2-V5 domain of gp-120. Acquisition of these mutations during the vicriviroc “monotherapy” phase might have altered the association between pharmacokinetics and pharmacodynamics at later points in the study. Initially, vicriviroc resistant virus was only identified in one subject in this study (a subject with clade C HIV, reference 29), but three other cases of resistance were subsequently detected. Since the target of vicriviroc is a host receptor, the ability of chemokine receptor antagonists to modulate the expression of these receptors should be considered as a factor that may affect drug exposure–response relationships, although long-term down-regulation of receptor expression has not been reported.

Structurally diverse small-molecule CCR5 antagonists all appear to bind to the same site within the transmembrane domain of CCR5 (30). In clinical studies with vicriviroc as short-course monotherapy (14 days), suppression of viral load persisted 2–3 days beyond the end of treatment (12), an effect observed with other CCR5 antagonists (31). In some studies, viral load continued to decrease after discontinuation of the drug, suggesting prolonged CCR5 receptor occupancy. While the unique effects of these drugs at the receptor could confound the interpretation of PK-PD relationships at 16 and 24 weeks, this is unlikely the case here since such a relationship was observed at week 2.

Consideration of potential pharmacokinetic interactions with other antiretrovirals is important in assessing vicriviroc pharmacokinetics and pharmacodynamics. Metabolic pathways for vicriviroc include N-oxidation, O-demethylation, N,N-dealkylation, N-dealkylation and oxidation to a carboxylic acid. Cytochrome P450 3A4 catalyzed production of all these metabolites whereas CYP3A5 and CYP2C9 produced restricted sets of these metabolites

(32). When dosed at 10 mg QD, vicriviroc exposure is increased to a similar extent by ritonavir at any dose equal to or greater than 100 mg (33). Co-administration of vicriviroc (15 mg QD) with ritonavir-boosted protease inhibitors produced no significant changes in any vicriviroc pharmacokinetic parameters compared to vicriviroc dosed with 100 mg of ritonavir QD or BID (34). Efavirenz can induce vicriviroc metabolism resulting in significant reductions in vicriviroc AUC and $C_{\max}$ when dosed at 10 mg; however, the addition of ritonavir 100 mg attenuates this interaction (33). The findings from our study can be informative in the selection of doses and the design of phase III studies with vicriviroc in treatment-experienced subjects also taking ritonavir. Matthias *et al.*, (35) demonstrated that doses of 100 mg of ritonavir can produce maximal “boosting” of plasma concentrations of different CYP3A substrates, including the HIV integrase inhibitor elvitegravir. A dose of 10 mg vicriviroc with 100 mg of ritonavir produced an average $C_{\min}$ (91 ng/ml) which is higher than the steady-state plasma concentration we found to be associated with 90% maximal viral suppression (56 ng/ml). The virologic response we observed at this dose of vicriviroc is comparable to the response observed in studies of treatment-naïve subjects using unboosted vicriviroc at higher doses (12,15). On the other hand, a dose of 15 mg vicriviroc with ritonavir 100 mg QD produced a higher $C_{\min}$, $C_{\max}$ and AUC than the 10 mg dose, but no improvement in virologic response at week 2. Long-term virologic suppression was confirmed in treatment-experienced patients receiving 20 mg (QD) or 30 mg (QD) vicriviroc with ritonavir-boosted PI-containing regimen in a phase 2b study (36). The PK-PD findings from our analysis, combined with the data identifying the dose producing the most durable suppression in treatment-experienced patients, led to the selection of the 30 mg dose for phase III studies.

We have shown a relationship between the pharmacokinetics of vicriviroc in treatment-experienced subjects and the magnitude of short-term virologic benefit. Our results highlight the importance of optimizing the other antiretrovirals in a combination regimen to achieve durable suppression with vicriviroc. Utilization of enhanced tropism assays as well as genotypic and phenotypic resistance testing to select an optimized background regimen are important adjuncts to maximizing benefit from this class of drugs.

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Figure 1. Individual Predicted versus Observed Vicriviroc Plasma Concentrations Following the Final NONMEM Run with Data from A5211 and five Phase I studies (n=196).

Figure 2.

The inhibitory sigmoid Emax model of the log viral load change from baseline and vicriviroc C_{min} in HIV infected subjects at week 2.

Table 1
Protease inhibitor components of Optimized Background Therapy (OBT) started at week 2

This table displays the distribution of HIV protease inhibitors that were added to the regimen at 14 days for each of the vicriviroc treatment arms. It also includes the mean ritonavir dose for each of the three vicriviroc dose arms. No subjects received non-nucleoside reverse transcriptase inhibitors or darunavir. Other antiretrovirals used by subjects were unlikely to affect vicriviroc plasma concentrations. Some patients were optimized to regimens that included dual-boosted (3-drug) protease inhibitor combinations (explaining why the row totals do not add up to 100%).

Vicriviroc treatment arm	Amprenavir/ Fosamprenavir (%)	Lopinavir (%)	Atazanavir (%)	Saquinavir (%)	Tipranavir (%)	Mean ritonavir dose
5 mg	12/29 (41)	10/29 (34)	7/29 (24)	4/29 (14)	1/29 (3)	197 mg/day
10 mg	10/29 (34)	12/29 (41)	4/29(14)	5/29 (17)	0	168 mg/day
15 mg	14/30 (47)	9/30 (30)	4/30 (13)	6/30 (20)	0	183 mg/day

Table 2

Dosing Regimens and PK Sampling Scheme in Healthy Volunteers from Phase I Studies

Study Number	Vicriviroc Maleate	Ritonavir	Concomitant Drugs	Number of Subjects
P03495	10 mg BID	100 – 800 mg/day		35
P03508	10 mg QD	100 mg/day	Efavirenz	9
P03723	10 mg QD	100 mg/day	Lopinavir	16
P04140	15 mg QD	400 mg/day	Tipranavir	12
P04416	15 mg QD	100 or 200 mg/day	Atazanavir, Fosamprenavir, Indinavir, Nelfinavir, Saquinavir	38

Table 3

Summary of Demographic Characteristics of the Subjects for PK Analysis

	Healthy HIV-seronegative Volunteers (n=110)	HIV-infected Subjects (n=86)	Overall (n=196)
<i>Categorical Covariate, Number of Subjects (Percentage)</i>			
Gender			
Male	72 (65%)	78 (91%)	150 (77%)
Female	38 (35%)	8 (9%)	46 (23%)
Race			
Black	10 (9%)	18 (21%)	28 (14%)
White	87 (79%)	66 (77%)	151 (78%)
Other	13(12%)	2 (2%)	15 (8%)
Ethnicity			
Hispanic	61 (55%)	13 (15%)	74 (38%)
Non-Hispanic	49 (45%)	73 (85%)	122 (62%)
<i>Continuous Covariate, Median (Range)</i>			
Age (year)	37 (18–55)	46.5 (29–67)	42 (18–67)
Weight (kg)	71.7 (44.8–104.3)	74.5 (49.5–122.6)	72.8 (44.8–122.6)

Table 4Calculated Mean (CV %) of $C_{\max}$, $C_{\min}$ and AUC for subjects in study A5211

Dose (# of Subjects)	5 mg (n=28)	10 mg (n=29)	15 mg (n=29)
$C_{\min}$ (ng/ml)	42 (CV 52%) (Range 16 – 101)	91 (CV 76%) (Range 32 – 416)	121 (CV 43%) (Range 19 – 204)
$C_{\max}$ (ng/ml)	63 (CV 36%) (Range 35 – 122)	131 (CV 54%) (Range 66 – 459)	181 (CV 30%) (Range 64 – 266)
AUC (hr*ng/mL)	1172 (CV 46%) (Range 524 – 2582)	2502 (CV 67%) (Range 1041 – 10286)	3390 (CV 38%) (Range 731 – 5472)

Table 5Change in Log₁₀ Viral Load from Baseline at Weeks 2, 16, 24 and 48 in ACTG Study A5211

Week	Parameter	Placebo	Vicriviroc 5 mg	Vicriviroc 10 mg	Vicriviroc 15 mg	Vicriviroc Overall
2	Number of Subjects	26	24	27	22	73
	Δ Log ₁₀ VL *	+0.045 (0.422)	-0.89 (0.83)	-1.30 (0.78)	-1.18 (0.87)	-1.13 (0.84)
16	Number of Subjects	26	17	25	24	66
	Δ Log ₁₀ VL *	-0.49 (0.88)	-1.95 (1.06)	-2.31 (1.19)	-1.65 (1.13)	-1.98 (1.16)
24	Number of Subjects	25	14	25	20	59
	Δ Log ₁₀ VL *	-0.75 (1.11)	-2.06 (0.94)	-2.21 (1.15)	-1.85 (1.16)	-2.05 (1.10)
48	Number of Subjects	5	5	21	21	47
	Δ Log ₁₀ VL *	-1.05 (0.83)	-2.00 (0.57)	-2.39 (1.11)	-1.81 (1.10)	-2.10 (1.08)

* ΔLog VL - Log₁₀ viral load (copies/mL) change from baseline values. The values are presented as mean (SD)

Table 6

Breakpoints of vicriviroc C_{min} , C_{max} and AUC based on the log viral load change from baseline at week 2 in subjects enrolled in ACTG study A5211

Response Index	Vicriviroc Treated Subjects							
	C_{min}		p	C_{max}		p	AUC	
	$C_{min} \leq 53.7$ (n=27)	$C_{min} > 53.7$ (n=46)		$C_{max} \leq 72.4$ (n=24)	$C_{max} > 72.4$ (n=49)		$AUC \leq 1460$ (n=25)	$AUC > 1460$ (n=48)
$\Delta \text{Log VL}$ (SD)	-0.76 * (0.90)	-1.35 * (0.73)	0.0028	-0.73 * (0.91)	-1.33 * (0.74)	0.0035	-0.70 * (0.90)	- 1.36 * (0.72)
$\Delta \text{Log VL}$ $\downarrow \geq 1 \text{ g}$	12 + (44%)	32 + (70%)	0.048	11 + (46%)	33 + (67%)	0.126	11 + (44%)	33 + (69%)
								0.0012
								0.048

* Student's t-test

+ Fisher's exact test