H-230

Assessment of Pharmacokinetic and Safety Interactions Between Vicriviroc and CYP3A4 Substrates, Inhibitors, and Inducers

C. Kasserra[1], E. O'Mara[1], M. Caceras[1], and E. Lisbon[2]

[1]Schering-Plough Research Institute, Kenilworth, NJ; [2]Quintiles, Inc., Overland Park, KS

Abstract

Background: **The objective of this study was to investigate vicriviroc (VCV) as a CYP3A4 substrate or inhibitor/inducer. Drugs evaluated included midazolam (MDZ), a CYP3A4 substrate; ketoconazole (keto), a CYP3A4 inhibitor; the antituberculosis drugs rifabutin and rifampin, and the anticonvulsant carbamazepine (CBZ). Rifabutin, rifampin, and CBZ are all CYP3A4 inducers and potential concomitant medications with VCV.**

Methods: **This open-label, drug-interaction study was conducted at a single center in 74 healthy adults. Each part of the study was a fixed-sequence one-way crossover design with VCV at a dose of 30 mg, with or without ritonavir (RTV).**

Results: **MDZ exposure was not affected by VCV administered alone, but was markedly increased when VCV was administered with RTV, a potent CYP3A4 inhibitor. Exposure of VCV was substantially increased (503% based on AUC) when administered concomitantly just with ketoconazole, while ketoconazole only modestly increased VCV concentrations (136% based on AUC) in the presence of RTV, compared to VCV alone. Rifabutin did not alter VCV exposure when dosed with 200 mg QD RTV. Rifampin, a potent CYP3A4 inducer, markedly decreased VCV exposure when dosed with 100 mg BID RTV; the relative oral bioavailability of VCV + RTV with rifampin compared to VCV + RTV alone was 11.6% based on AUC. Carbamazepine did not alter VCV exposure when dosed with 100 mg BID RTV.**

Conclusion: **VCV is not itself a CYP3A4 inhibitor/inducer, but is a CYP3A4 substrate. However, in the presence of RTV, addition of another CYP3A4 inhibitor or modestly potent CYP3A4 inducer will not require VCV dose adjustment. If CBZ or rifabutin are coadministered with VCV in a RTV-boosted PI-containing regimen, no VCV dose adjustment is required, but the RTV dose should be increased, to 100 mg BID or 200 mg QD. Coadministration of rifampin with VCV is not recommended. Vicriviroc with or without RTV was safe and well tolerated alone or coadministered with the drugs used in this study.**

Introduction

- Vicriviroc (VCV), a CCR5 antagonist, is a novel extracellular inhibitor of HIV infection designed to block HIV entry into uninfected CD4+ cells via antagonism of the CCR5 coreceptor.[1]
- VCV is a CYP3A substrate, and its plasma concentrations are increased 2-6 fold by CYP3A inhibitors, such as ritonavir (RTV).[2]
- VCV plasma half-life of >24 hours allows for once-daily dosing.[3]
- VCV has shown potent and durable antiretroviral activity in CCR5-tropic antiretroviral-experienced patients.[4]
- In a randomized, placebo-controlled Phase 2b study (VICTOR-E1), vicriviroc 30 or 20 mg once daily plus RTV-boosted protease inhibitor (PI/r)-containing optimized background therapy (OBT) given to treatment-experienced HIV-infected patients with CCR5-tropic only virus demonstrated sustained superior virologic and immunologic efficacy compared with OBT alone.[5]
- Vicriviroc 30 mg QD as part of a PI/r-based regimen is now in Phase 3 clinical trials evaluating HIV-monoinfected and HIV/HCV-coinfected treatment-experienced patients; all patients have completed at least 48 weeks of treatment.
- The objective of this study was to investigate vicriviroc (VCV) as a CYP3A4 substrate or inhibitor/inducer for labeling/registration purposes and to provide dosing guidance.

Methods

- This was a 5-part, open-label, single-center, drug interaction study in healthy volunteers.
- Each of the 5 parts was a fixed-sequence, one-way, crossover evaluation of the pharmacokinetic (PK) and safety effects of VCV, with and without RTV, when coadministered with drugs that are well-characterized CYP3A4 substrates (midazolam), inhibitors (ketoconazole), or inducers (rifabutin, rifampin, carbamazepine).

Primary and Secondary Objectives

Part 1

- *Primary:* to determine the effects of vicriviroc (VCV) alone and of VCV in a ritonavir (RTV)-containing regimen on the PK of midazolam (MDZ).
- *Secondary:* to evaluate the safety and tolerability of VCV alone and of VCV in RTV-containing regimen when administered with MDZ.

Part 2

- *Primary:* to determine the effect of ketoconazole on the PK of VCV alone and of VCV in a RTV-containing regimen.
- *Secondary:* to evaluate the safety and tolerability of VCV alone and of VCV in a RTV-containing regimen when coadministered with ketoconazole.

Parts 3–5

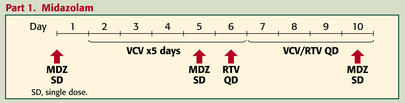
- *Primary:* to determine the effect of rifabutin, rifampin, and carbamazepine (CBZ) on the PK of VCV in a RTV-containing regimen.
- *Secondary:* to the evaluate safety and tolerability of VCV in a RTV-containing regimen when coadministered with rifabutin, rifampin, or carbamazepine (CBZ).

Methods (cont'd)

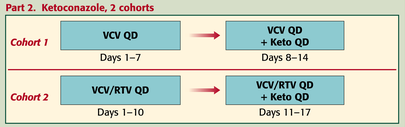
Study Design

- Healthy adult volunteers were confined at the study center ≥12 hours before dosing until completion of the study procedures.
  - VCV, RTV, and all comparator drugs were given orally.
  - VCV doses were 30 mg; RTV doses were 100 mg QD in Cohorts 1 and 2, 200 mg QD in Cohort 3, and 100 mg BID in Cohorts 4 and 5.
  - Comparator drug doses: midazolam, 4 mg; ketoconazole, 400 mg; rifabutin, 150 mg; rifampin, 600 mg; carbamazepine, 100 mg.

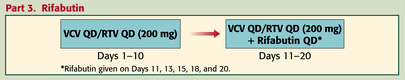
Part 1. Midazolam



Part 2. Ketoconazole, 2 cohorts



Part 3. Rifabutin



*Rifabutin given on Days 11, 13, 15, 18, and 20.

Part 4. Rifampin

Part 5. Carbamazepine

- Safety evaluations included vital signs, electrocardiograms (ECGs), clinical laboratory tests, and adverse events (AEs).
- A previous study showed intrasubject variability for oral MDZ as approximately 20%. Part 1 of the current study was designed to detect approximately 21% difference in MDZ exposure when MDZ was coadministered with VCV vs MDZ alone, with 80% power and 90% confidence interval (CI).
- A previous study showed estimated intrasubject variability for the area under the concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) of VCV to be less than 20%. The current study was designed to detect approximately 23% difference in VCV exposure when VCV was administered alone or with either ketoconazole, rifabutin, rifampin, or CBZ, with 80% power and 90% CI.

Statistical Methods

Pharmacokinetics

- For each study part, the log-transformed AUC and C_{max} for VCV and concomitant drugs were analyzed using one-way analysis of variance (ANOVA) model, extracting the effects due to treatment and subject.
  - Part 1 primary comparisons: MDZ alone vs with VCV; MDZ alone vs with VCV/RTV.
  - Part 2 primary comparisons: VCV alone vs with ketoconazole; VCV/RTV alone vs with ketoconazole.
  - Part 3 primary comparison: VCV/RTV alone vs with rifabutin.
  - Part 4 primary comparison: VCV/RTV alone vs with rifampin.
  - Part 5 primary comparison: VCV/RTV alone vs with CBZ.

Safety

- All treatment-emergent and treatment-related AEs were tabulated by body system/organ class.
- Data from laboratory safety tests, vital signs assessments, and ECGs were listed and reviewed, and clinically significant findings were recorded as AEs.

Results

Demographic and Baseline Characteristics

- 74 adult subjects were treated and 63 (85%) completed the study (**Table 1**).

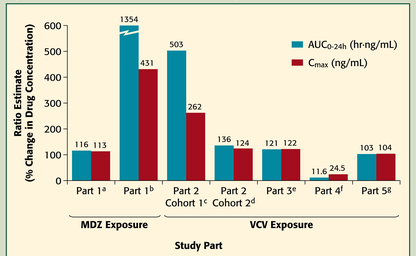
Table 1. Subject Demographic Characteristics, All Study Parts

	Number of Subjects (%)						
		Part 2					
Characteristic	Part 1	Cohort 1	Cohort 2	Part 3	Part 4	Part 5	Total
Total	14 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	74 (100)
Sex							
Male	11 (79)	8 (67)	10 (83)	7 (58)	11 (92)	8 (67)	55 (74)
Female	3 (21)	4 (33)	2 (17)	5 (42)	1 (8)	4 (33)	19 (26)
Age (range)	37.2 (20-63)	36.7 (20-48)	32.6 (21-52)	29.4 (19-59)	31.5 (20-60)	35.2 (20-53)	33.9 (19-63)
Race							
White	6 (43)	9 (75)	8 (67)	5 (42)	10 (83)	6 (50)	44 (59)
Non-white	8 (57)	3 (25)	4 (33)	7 (58)	2 (17)	6 (50)	30 (41)
Completed study	14 (100)	11 (92)	10 (83)	6 (50)	11 (92)	11 (92)	63 (85)

Clinical Pharmacology

- MDZ (Part 1) and VCV exposure (Parts 2–5) are shown in the **Figure** below.
- Exposure is shown as the ratio of MDZ coadministered with VCV or VCV/RTV compared to MDZ alone (Part 1), or the ratio of VCV with or without RTV when coadministered with the reference drug compared to VCV alone or with RTV, as appropriate (Parts 2–5).
- A ratio estimate of 100% indicates no change in exposure.

Figure. Midazolam (MDZ) and Vicriviroc (VCV) Exposure



[a] Effect of VCV alone on midazolam concentration.
[b] Effect of VCV/RTV on midazolam concentration.
[c] Effect of ketoconazole on VCV concentration (without coadministered RTV).
[d] Effect of ketoconazole on VCV concentration (in the presence of RTV).
[e] Effect of rifabutin on VCV concentration (in the presence of RTV).
[f] Effect of rifampin on VCV concentration (in the presence of RTV).
[g] Effect of carbamazepine on VCV concentration (in the presence of RTV).

Note: The AUC and C_{max} data shown in **Tables 2–6** are model-based (least squares) geometric means with confidence intervals (90% CI), using analysis of variance (ANOVA) extracting the effects due to treatment and subject.

Part 1 Pharmacokinetic Results (Table 2)

- MDZ exposure (AUC and C_{max}) was not affected when coadministered with VCV alone.
- MDZ exposure was markedly increased when VCV was coadministered with RTV, a potent CYP3A4 inhibitor.

Table 2. Statistical Assessment of Relative Bioavailability of Midazolam (MDZ) Alone Versus Vicriviroc (VCV) Alone and VCV with Ritonavir (RTV)

PK Parameter	Least-Squares Mean (90% CI) MDZ	VCV + MDZ	VCV/RTV + MDZ	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=14)	43.4 (38.1-49.4)	50.4 (44.2-57.4)	588 (516-669)	19.7%	VCV + MDZ vs MDZ	116	102-132
					VCV/RTV + MDZ vs MDZ	1354	1192-1537
C_{max} (ng/mL) (n=14)	13.4 (11.9-15.1)	15.2 (13.5-17.1)	57.7 (51.2-65.1)	14.7%	VCV + MDZ vs MDZ	113	103-125
					VCV/RTV + MDZ vs MDZ	431	392-473

Part 2 Pharmacokinetic Results (Tables 3a and 3b)

Cohort 1

- VCV exposure was substantially increased when coadministered with ketoconazole alone.

Table 3a. Statistical Assessment of Relative Bioavailability of Vicriviroc (VCV) Alone Versus VCV with Ketoconazole (KCZ): Cohort 1

PK Parameter	Least-Squares Mean (90% CI) VCV	VCV + KCZ	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=11)	798 (686-927)	4016 (3455-4667)	15.4%	VCV + KCZ vs VCV	503	447-567
C_{max} (ng/mL) (n=11)	113 (101-127)	296 (263-332)	18.8%	VCV + KCZ vs VCV	262	227-303

Data from 1 subject excluded due to missing data.

Cohort 2

- Ketoconazole only modestly increased VCV concentrations when coadministered with VCV/RTV, compared with its effect when given with VCV alone.

Table 3b. Statistical Assessment of Relative Bioavailability of Vicriviroc (VCV) and Ritonavir (RTV) Alone Versus VCV and RTV with Ketoconazole (KCZ): Cohort 2

PK Parameter	Least-Squares Mean (90% CI) VCV/RTV	VCV/RTV + KCZ	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=10*)	5987 (5422-6611)	8147 (7377-8996)	5.83%	VCV/RTV + KCZ vs VCV/RTV	136	130-143
C_{max} (ng/mL) (n=10*)	368 (337-402)	456 (418-498)	6.10%	VCV/RTV + KCZ vs VCV/RTV	124	118-130

*Data from 2 subjects excluded due to missing data.

Part 3 Pharmacokinetic Results (Table 4)

- Rifabutin did not alter VCV exposure to a clinically relevant degree when dosed with RTV 200 mg QD.

Table 4. Statistical Assessment of Relative Bioavailability of Vicriviroc (VCV) and Ritonavir (RTV) Alone Versus VCV and RTV with Rifabutin

PK Parameter	Least-Squares Mean (90% CI) VCV/RTV	VCV/RTV + Rifabutin	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=6)	5642 (5080-6267)	6807 (6128-7560)	10.8%	VCV/RTV + RIFAB vs VCV/RTV	121	106-137
C_{max} (ng/mL) (n=6)	347 (298-404)	423 (363-492)	6.64%	VCV/RTV + RIFAB vs VCV/RTV	122	113-131

Data from 6 subjects excluded due to missing data.

Part 4 Pharmacokinetic Results (Table 5)

- Rifampin, a potent CYP3A4 inducer, markedly decreased VCV exposure in the presence of RTV 100 mg BID.

Table 5. Statistical Assessment of Relative Bioavailability of Vicriviroc (VCV) and Ritonavir (RTV) Alone Versus VCV and RTV with Rifampin

PK Parameter	Least-Squares Mean (90% CI) VCV/RTV	VCV/RTV + Rifampin	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=11)	1923 (1524-2427)	224 (177-283)	36.3%	VCV/RTV + RIFAM vs VCV/RTV	11.6	8.8-15.4
C_{max} (ng/mL) (n=11)	136 (112-164)	33.2 (27.5-40.2)	25.3%	VCV/RTV + RIFAM vs VCV/RTV	24.5	20.1-29.7

Data from 1 subject excluded due to missing data.

Part 5 Pharmacokinetic Results (Table 6)

- CBZ did not alter VCV exposure when in the presence of RTV 100 mg BID.

Table 6. Statistical Assessment of Relative Bioavailability of Vicriviroc (VCV) and Ritonavir (RTV) Alone Versus VCV and RTV with Carbamazepine (CBZ)

PK Parameter	Least-Squares Mean (90% CI) VCV/RTV	VCV/RTV + CBZ	Intra-Coefficient of Variation	Treatment Comparison	Ratio Estimate (%)	90% CI
$AUC_{0\text{-}24h}$ (hr·ng/mL) (n=11)	6077 (5215-7082)	6236 (5351-7268)	8.8%	VCV/RTV + CBZ vs VCV/RTV	103	95.9-110
C_{max} (ng/mL) (n=11)	369 (324-421)	384 (337-438)	12.5%	VCV/RTV + CBZ vs VCV/RTV	104	94.4-115

Data from 1 subject excluded due to missing data.

Safety

- In all 5 study parts, VCV was safe and well tolerated, and there were no remarkable or unexpected safety concerns or trends in clinical laboratory tests associated with VCV across the studied drug combinations.
- 58 subjects reported one or more adverse event.
  - All AEs were mild to moderate in severity.
  - Overall, more AEs reported when the comparator drug was administered.
  - Certain expected AEs and trends were observed in subjects administered specific drug combinations. The number of AEs increased when rifabutin was added in Part 3, with the most common AEs not reported during the VCV plus RTV period being neutropenia, chromaturia, and pyrexia. These AEs have previously been reported during rifabutin or rifabutin plus RTV administration[6] and therefore were not unexpected. The most common AEs judged to be treatment-related when rifampin was added in Part 4 were ALT/AST increases, nausea, vomiting, chromaturia, and dizziness. Of these AEs, chromaturia was reported only during rifampin alone, and the other AEs were reported only during VCV + RTV + rifampin dosing. These AEs are commonly reported with rifampin, and rifampin/RTV administration, and were expected.[7]
- A total of 6 subjects discontinued due to AEs.
  - Grade 1 elevations in liver transaminases in 1 subject while receiving VCV/RTV plus ketoconazole in Part 2, Cohort 2.
  - Neutropenia in 4 subjects while receiving VCV/RTV plus rifabutin in Part 3.
  - Pyrexia in 1 subject while receiving VCV/RTV plus rifabutin in Part 3.

Conclusions

Overall

- **No dose adjustment of VCV is generally needed in patients receiving a PI/r-containing regimen and other coadministered agents. Exceptions to this are very potent CYP3A4 inducers, such as rifampin.**

Clinical Pharmacology

Part 1
- **VCV administered alone did not affect midazolam exposure in a clinically relevant manner.**
- **VCV administered with RTV markedly increased midazolam exposure.**

Part 2
- **VCV concentrations were substantially increased by concomitant administration of ketoconazole (a potent inhibitor of CYP3A4).**
- **VCV concentrations in the presence of RTV were modestly increased by concomitant administration of ketoconazole.**
- **Coadministration of additional CYP3A4 inhibitor(s) with VCV in a PI/r-containing regimen will not require any dose adjustment of VCV.**

Part 3
- **VCV exposure, when dosed concomitantly with 200 mg QD RTV, was not altered by additional administration of rifabutin (a potent inducer of CYP3A4).**
- **If rifabutin is coadministered with VCV in a PI/r-containing regimen, it is recommended that the dose of RTV be adjusted to at least 200 mg QD.**

Part 4
- **VCV exposure, when dosed concomitantly with 100 mg BID RTV, was substantially decreased by additional administration of rifampin (a potent inducer of CYP3A4).**
- **Coadministration of rifampin with VCV in a PI/r-containing regimen is not recommended.**

Part 5
- **VCV exposure, when dosed concomitantly with 100 mg BID RTV, was not altered by additional administration of carbamazepine.**
- **If carbamazepine is coadministered with VCV in a PI/r-containing regimen, then it is recommended that the dose of RTV be increased to 100 mg BID.**

Safety

- **Vicriviroc with or without RTV coadministration was generally safe and well tolerated either alone or coadministered with the drugs evaluated in this study. While vicriviroc was safe and well tolerated when coadministered with RTV, the number of AEs increased when either rifabutin or rifampin was added to the regimen.**

References

1. Strizki JM, Tremblay C, Xu S, et al. *Antimicrob Agents Chemother.* 2005;49:4911-4919.
2. Sansone A, Keung A, Tetteh E, et al. 13th CROI; February 5-8, 2006; Denver, CO. Abstract 582.
3. Seiberling M, Kraan M, Keung A, et al. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec City, Que., Canada, April 28-30, 2005. Abstract 6.4.
4. Gulick RM, Su Z, Flexner C, et al. *J Infect Dis.* 2007;196:304-312.
5. Zingman B, Suleiman J, DeJesus E, et al. 15th CROI; February 3-6, 2008; Boston, MA. Abstract 39LB.
6. Ford SL, Chen Y-C, Lou Y, et al. *Antimicrob Agents Chemother.* 2008;52:534-538.
7. Burger DM, Agarwala S, Child M, et al. *Antimicrob Agents Chemother.* 2006;50:3336-3342.

Presented at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, CA, September 12-15, 2009