

Vicriviroc Long-term Safety and Efficacy: 96-Week Results from the VICTOR-E1 Study

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AUTHOR CONCLUSIONS

VCV was generally well tolerated in this highly treatment-experienced population, with no apparent VCV-related toxicities.

Mild upper respiratory infections were the most commonly observed event of interest, consistent with findings in the double-blind phase (VICTOR-E1 study).

Sustained antiviral effect, including full virologic suppression, and durable CD4+ cell count increases were observed.

Resistance to VCV was infrequent and developed slowly, generally in subjects after prolonged therapy with suboptimal OBT, ie, fewer than 2 active drugs.

ABSTRACT

Background: This extension of VICTOR-E1 evaluated the continued safety and efficacy of vicriviroc (VCV) in treatment-experienced subjects.

Methods: After completing 48 weeks of blinded treatment with VCV 30 mg, VCV 20 mg, or placebo in a protease inhibitor/ritonavir (PI/r)-containing regimen, subjects were offered open-label VCV (30 mg in a PI/r-containing regimen) for 48 more weeks. Adverse events (AEs) were assessed every 3 months. HIV RNA and CD4 counts were monitored.

Results: 85 of the 86 subjects who completed VICTOR-E1 enrolled in the extension. Mean duration of open-label therapy was 13 months (total 26 months). The only AEs in 35% of subjects were sinusitis, cough, and insomnia. One subject was discontinued upon simultaneous diagnosis of Hodgkin's lymphoma and Kaposi's sarcoma, which were not treatment-related. Another patient discontinued due to pregnancy. There were no treatment-emergent deaths,

seizures, or hepatotoxic events.

Mean Change in HIV-RNA and CD4 Cell Count (SD)

	Baseline* (n=116)	Week 48† (n=85)	Week 96 (n=71)	Change from Week 48
Log ₁₀ HIV RNA, copies/mL	4.55 (0.85)	2.51 (1.23)	2.07 (0.86)	-0.32 (0.88)
CD4 Count, cells/mm ³	210 (167)	366 (192)	422 (216)	+50 (137)

*Baseline of VICTOR-E1.

†Baseline of open-label extension.

Conclusions: VCV showed promising safety and tolerability with no clear VCV-related toxicity. Sustained antiviral effect and maintenance of improved CD4 counts were observed.

INTRODUCTION

Vicriviroc (VCV) is a next-generation extracellular inhibitor of HIV infection designed to block entry of infectious virions into uninfected CD4+ cells via antagonism of the CCR5 co-receptor (CCR5 antagonist).¹

VCV plasma half-life of >24 hours allows for once-daily dosing² and may be taken with or without food.³

VCV has demonstrated 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 ritonavir-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 ritonavir-containing, PI-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.

METHODS

This ongoing, open-label extension of VICTOR-E1 trial was designed to provide continued therapy with VCV and to collect safety data. Evidence for sustained viral suppression and CD4+ cell count improvement was monitored.⁵

After completing 48 weeks of blinded treatment in VICTOR-E1, subjects were

offered open-label VCV 30 mg QD plus PI/r-containing OBT.

- Subjects who discontinued before Week 48 of the double-blind phase for reasons other than AEs were offered re-screening.
- OBT could be re-optimized at the discretion of site investigator.

Subjects returned every 3 ± 1 months for evaluation, including:

- Physical examination, vital signs, and clinical laboratory testing
- HIV-1 RNA level and CD4+ cell count measurements
- Treatment-emergent adverse events (AEs)
 - Seizure, malignancy, premalignancy, hepatocellular AEs, dyslipidemia, cardiovascular AEs, herpes simplex virus infection, and upper respiratory tract infection were designated as AEs of interest.

Tropism testing (using the first-generation Trofile™ assay) and VCV susceptibility testing (using the PhenoSense Entry® assay) were performed in all subjects at baseline (Week 48 of double-blind phase) except those whose HIV RNA was <500 copies/mL.

- Thereafter, tropism testing was performed every 6 months and at final visit.
- VCV susceptibility testing was to be performed at final visit.
- VCV resistance was assessed using maximal percent inhibition plateau value of <85% as cutoff for resistance.

Overall sensitivity scores (OSS), by combining genotypic and phenotypic resistance scores, for the OBT were calculated for subjects who experienced virologic failure during the open-label phase.

RESULTS

Subject Disposition and Baseline Characteristics

85 subjects were enrolled in the open-label treatment phase from the 48-week double-blind treatment arms (Tables 1 and 2):

- 32 from VCV 30 mg QD arm
- 35 from VCV 20 mg QD arm
- 18 from placebo arm

More than half of subjects began open-label treatment with an HIV-1 RNA level <50 copies/mL and two thirds <400 copies/mL (Table 2).

Table 1. Subject Disposition in the Double-Blind 48-Week Trial and Open-Label Extension Treatment

Subject Status	Number (%) of Subjects		
	VCV 30 mg	VCV 20 mg	Placebo
Double-Blind Study			
Randomized	39 (100)	40 (100)	37 (100)
Completed treatment	33 (85)	35 (88)	18 (49)
Discontinued due to treatment failure	5 (13)	3 (8)	14 (38)
Other Discontinuations	1 (2)	2 (5)	5 (13)
Enrolled into 48-week open-label extension	32	35	18
Open-Label Extension Study			
Received at least 1 dose of open-label VCV 30 mg		85 (100)	
Discontinued treatment		15 (18)	
Treatment failure ^a		7 (8)	
Lost to follow-up		2 (2)	
Subject withdrew consent		2 (2)	
Noncompliance with protocol		2 (2)	
Adverse event		1 (1)	
AIDS-defining event		1 (1)	
Ongoing		70 (82)	

^a Defined as a lack of clinical benefit as judged by the investigator.

Table 2. Baseline Characteristics at Initiation of Open-Label Extension Study

Characteristic	VCV 30 mg (n=85)
Mean age, yr (SD)	45.6 (7.8)
Range	28–65
Sex, no. (%)	
Male	65 (76)
Female	20 (24)
Race, no. (%)	
White	59 (69)
Black or African-American	13 (15)
Asian	1 (1)
Multiracial	12 (14)
Region, no (%)	
North America + Europe	26 (31)
Latin America or South Africa	59 (69)
Mean CD4+ cell count, cells/mm³ (SD)	366 (192)
Range	17–995
CD4+ cell count, no. (%)	
≤200 cells/mm ³	16 (19)
>200 cells/mm ³	69 (81)
Mean HIV-1 RNA level, log₁₀ copies/mL (SD)	2.51 (1.23)
HIV-1 RNA level, no. (%)	
<50 copies/mL	48 (56)
50–399 copies/mL	10 (12)
≥400 copies/mL	27 (32)

Note: Baseline of open-label extension defined as Week 48 visit of double-blind phase.

VCV Exposure

All subjects received 31 dose of open-label VCV 30 mg.

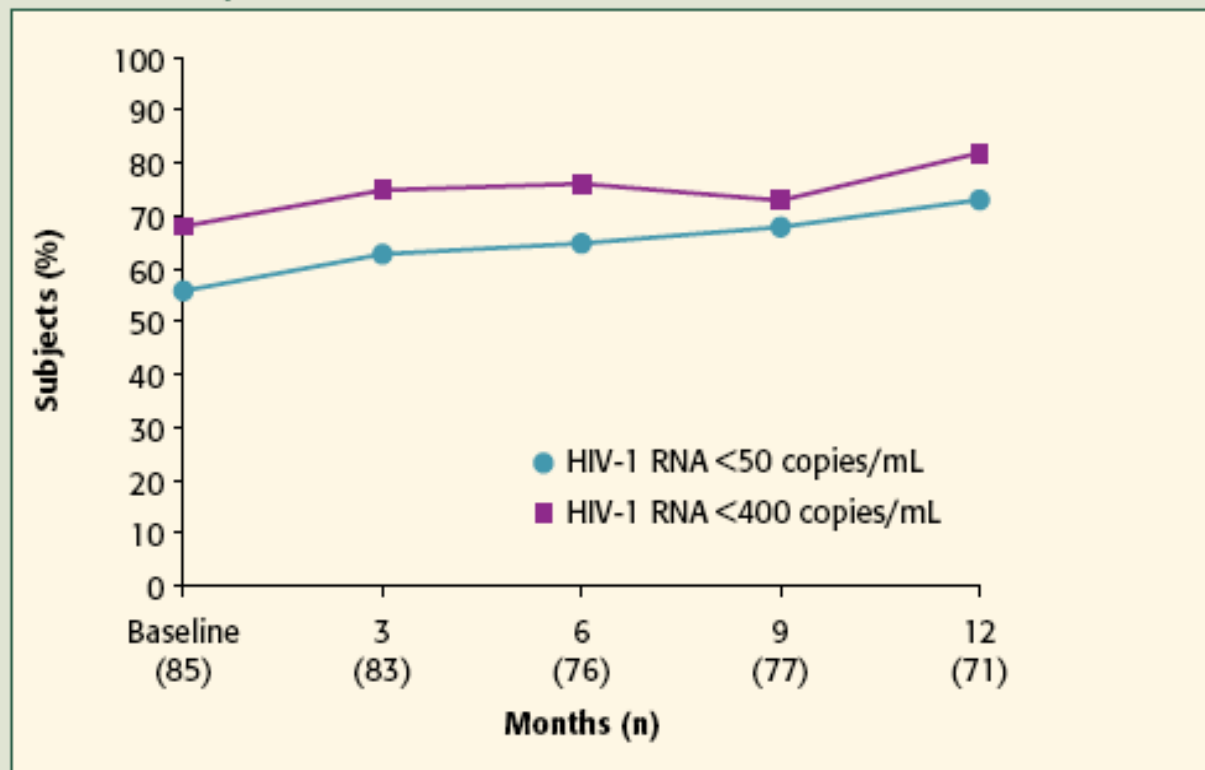
- Mean duration of open-label VCV treatment was 13 months.
- Total exposure was 88 person-years.

Virologic Efficacy

HIV-1 RNA levels were sustained during open-label treatment, with a mean log₁₀ change from baseline of -0.32.

Increases in the proportion of subjects achieving undetectable viral loads were observed (Figure 1).

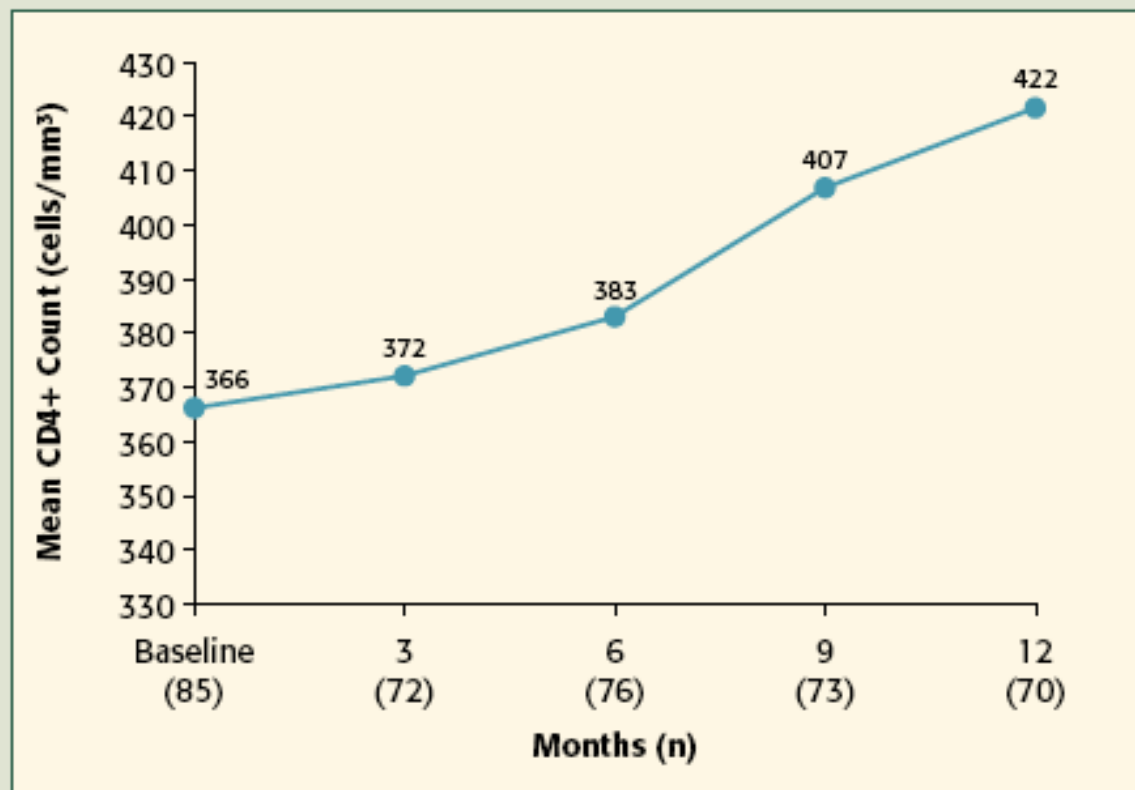
Figure 1. Percentage of Subjects with Virologic Suppression During the Open-Label Extension Study



Immunologic Efficacy

Further improvements in CD4+ cell counts were observed with prolonged VCV treatment, with a mean increase of 50 cells/mm³ from baseline by Month 12 (Figure 2).

Figure 2. Mean CD4+ Cell Count During the Open-Label Extension Study



Adverse Events

- 58 subjects reported one or more adverse event (AE) (Table 3).
- Most (93%) AEs were mild or moderate in severity.

Table 3. Adverse Events by Category

	Number (%)
Subjects reporting any AE	58 (68)
Mild or moderate AE	54 (93)
AEs occurring in $\geq 5\%$ of subjects	
Sinusitis	5 (6)
Cough	4 (5)
Insomnia	4 (5)
AEs judged to be treatment-related	11 (13)
Subjects reporting serious AEs (SAEs)^a	4 (5)
Study discontinuations due to AE^b	2
Grade 4 AEs	0
Treatment-emergent AE-related deaths, seizures, hepatotoxic events	0

^a SAEs included: lymphadenopathy, retroperitoneal lymphadenopathy, urinary tract infection, osteonecrosis, pain in extremity, hysterectomy, bilateral salpingo-oophorectomy, and spinal fusion.

^b One female subject discontinued due to pregnancy followed more than 1 week later by spontaneous abortion; 1 male subject discontinued due to diagnosis with 2 AIDS-defining events (Hodgkin's disease and Kaposi's sarcoma); none of these AEs were judged likely related to study medication.

Adverse Events of Interest

Nineteen (22%) of subjects experienced an AE of interest on study (Table 4).

Table 4. Adverse Events of Interest, Adjusted for Person-Years of Exposure

Category of AE of Interest	VCV 30 mg (N=85) Total Exposure = 87.69 Person-Years	
	Number of Subjects (%)	Rate ^a
Subjects reporting any AE of interest	19 (22)	21.67
Seizure	0	0
Malignancy	3 (4)	3.42
Premalignancy	1 (1)	1.14
Hepatocellular	0	0
Cardiovascular	2 (2)	2.28
Dyslipidemia	6 (7)	6.84
Herpes simplex virus infection	1 (1)	1.14
Upper respiratory tract infection	11 (13)	12.54

^a In units of incidence per 100 person-years, calculated as rate = (incidence × 100)/(total exposure in person-years).
Note: More than 1 AE was reported by some subjects.

Laboratory Abnormalities

No Grade 3 or 4 changes from baseline occurred for any laboratory parameter measured, including liver function tests.

2 cases of new-onset diabetes mellitus occurred—considered possibly related to study drug.

- Mean change in fasting glucose level was not clinically significant over the entire study population.
- The OBTs of the two subjects experiencing new-onset diabetes both contained the PIs SQV and LPV/RTV—antiretrovirals associated with the development of insulin resistance.
- Glucose abnormalities have been reported in patients with extensive antiretroviral exposure.

Mild elevations in serum lipids were observed in a small number of subjects.

- Many antiretrovirals are associated with lipid changes.

Viral Tropism

Of those subjects in whom viral tropism testing was possible (ie, having HIV-1 RNA >500 copies/mL)

- Immunologic decline requiring study discontinuation was not observed in 11 of

the 14

subjects with detectable DM/X4 virus.

- Only 1 subject with documented R5-tropic virus at entry into the open-label extension was later found to have DM/X4 virus; the subject was discontinued for treatment failure.

Interpretation of HIV tropism in this study is complex because the majority of subjects had achieved virologic suppression prior to entry into open-label treatment.

Antiretroviral Resistance

Treatment failure occurred in 11 (13%) subjects.

- 7 of the 11 were protocol-defined virologic failures.
- 4 of the 11 were investigator-determined treatment failures.
- 8 of the 11 had one or fewer active drugs in their OBT.
- Treatment failure was the most common reason for discontinuation from the open-label extension (11%).

2 of the subjects with treatment failure already had documented resistance to VCV during the double-blind phase.

- Both subjects had OSS = 0 at entry to open-label phase, and neither subject achieved virologic suppression during either the blinded or open-label phases.

2 other subjects developed changes in VCV susceptibility during open-label phase consistent with resistance.

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