Vicriviroc in Combination Therapy With an Optimized Antiretroviral Regimen for Treatment-Experienced Subjects: The VICTOR-E1 Trial

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Abstract

Background: Vicriviroc (VCV) is a next-generation small molecule CCR5 antagonist, administered orally QD, now in worldwide Phase 3 development for treatment of HIV. This Phase 2 study determined the optimal dose for Phase 3 in combination with an optimized background antiretroviral regimen (OBT) containing a ritonavir (RTV)–boosted protease inhibitor (PI), based on efficacy, safety and durability of antiretroviral effect.

Methods: This was a multinational, randomized, double-blind, placebo (PBO)-controlled trial comparing VCV 20 or 30 mg QD plus optimized background therapy (OBT) to placebo (PBO) plus OBT for 48 weeks. Eligible subjects were CCR5-tropic HIV-1-infected adults who had received 3 prior classes of antiretroviral therapy (ART) and had ≥1000 copies/mL plasma HIV RNA despite a current 3-drug ART regimen. Subjects with HBV or HCV coinfection were allowed; prior seizure disorder or malignancy was excluded. OBT could include any available ART except efavirenz, including those on EAPs.

Results: 116 subjects were randomized 1:1:1 to VCV 20 mg, 30 mg or PBO QD, administered with a new OBT. Mean age was 45 years: 77% were male; 68% white, 17% black, 72% Latino. Mean plasma HIV RNA was 4.5 $\log_{10}$ copies/mL and CD4 count was 210 cells/μL. 51% had an AIDS-defining event prior to study; 6 (5%) were HCV coinfected. OBT included 2 active drugs in 43% of subjects; 27 (23%) received darunavir. Two never received study drug, 21 (18%) discontinued prematurely due to virologic failure (14 on PBO), and 2 discontinued due to adverse events, neither attributable to study drug. At 24 weeks (N=91), mean decline in HIV RNA was -2.04, -2.04 and -0.96 $\log_{10}$ in the 3 groups, respectively (p<0.001, active vs. PBO). Percent with HIV RNA <400 copies were 75%, 72% and 34% (p<0.01) and <50 copies were 58%, 64% and 26% (p<0.01) in the 3 groups, respectively. Mean CD4 counts rose 100, 94 and 56 cells/μL in the 3 groups, respectively (p=0.15). No toxicities or signals of safety issues were observed.

Conclusions: VCV at 20 and 30 mg once daily demonstrated superior antiviral efficacy over optimized ART alone. Virologic benefit was achieved even when OBT contained >2-3 active drugs; there was no geographic difference in efficacy. The most stringent criteria of efficacy favored VCV 30 mg QD. No clinically significant differences in the safety profile between VCV and PBO groups emerged in this study, including hepatotoxicity, opportunistic infections, malignancies or other conditions. Efficacy and safety supported 30 mg once daily for Phase 3 studies. Forty-eight week results will be available.

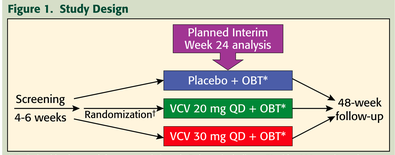
Introduction

- 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 concentrations are increased 2-6 fold by CYP3A inhibitors, including ritonavir.[2]
- VCV plasma half-life of >24 hours allows for once-daily dosing.[3]
- VCV may be taken with or without food.[4]
- VCV has demonstrated potent and durable antiretroviral activity in CCR5-tropic ART-experienced patients.[5]

Methods

- VICTOR-E1 is a multicenter, multinational, randomized, Phase 2b study comparing VCV 20 and 30 mg QD plus optimized background therapy (OBT) to placebo plus OBT.

Figure 1. Study Design



* Optimized background therapy consisting of ≥3 drugs, including a PI with ≥100 mg ritonavir.
† Tropism results from screening required prior to randomization.

- Primary endpoint: $\log_{10}$ plasma HIV RNA change from baseline at Week 48
- Key secondary endpoints
  - Proportion of subjects with ≥1.0 $\log_{10}$ change from baseline in HIV RNA at 48 weeks
  - Proportion of subjects with HIV RNA <400 copies/mL and <50 copies/mL at 48 weeks
  - Time to confirmed virologic failure, defined as either failure to experience HIV RNA decline of ≥0.5 $\log_{10}$ by Week 4 (time to failure = 0) or rebound of HIV RNA to within 0.5 $\log_{10}$ of baseline at any time after maximum suppression
  - Interim analyses after 12 and 24 weeks of treatment
- After 48 weeks, subjects were to continue on VCV 30 mg QD plus OBT

Entry Criteria

- CCR5-tropic virus only
- Triple-class experienced HIV+ patients
- ≥1 reverse transcriptase resistance mutation
- ≥1 primary protease inhibitor resistance mutation
- HIV RNA ≥1000 copies/mL
- On a stable antiretroviral regimen for ≥6 weeks prior to screening (≥8 weeks prior to randomization)
- Acceptable laboratory parameters
- Hepatitis B or C coinfection allowed with stable disease and acceptable liver enzymes. Liver enzymes within the range of inclusion criteria: AST (SGOT) and ALT (SGPT) ≤3 × ULN; and alkaline phosphatase ≤5 × ULN; total bilirubin ≤2.5 × ULN.

Exclusion Criteria

- Recurrent seizures, or CNS condition that may predispose to seizure
- History of prior malignancy (except resolved Kaposi's sarcoma of the skin or fully resected basal cell carcinoma)
- Active untreated AIDS-defining opportunistic infections

Statistical Considerations

- Planned enrollment of approximately 120 subjects randomized in a 1:1:1 ratio (20 mg vicriviroc: 30 mg vicriviroc: placebo)
  - 90% power to detect a difference of at least 0.7 $\log_{10}$ HIV RNA copies/mL, assuming a pooled standard deviation of 0.9 $\log_{10}$ HIV RNA copies/mL
- Analysis of primary efficacy variable (change from baseline in $\log_{10}$ HIV RNA at Week 48) using an ANOVA model that adjusts for treatment and stratification factors
  - Stratification: baseline HIV RNA ≤100,000 and use of enfuvirtide
- If a continuing subject did not have data at the time point of interest, the change from baseline was set at zero for that time point ("missing = failure")
- Time to virologic failure and time to AIDS-defining events were analyzed using the stratified log-rank test

Results

BASELINE PARAMETERS

Figure 2. Global Distribution of Trial Participants

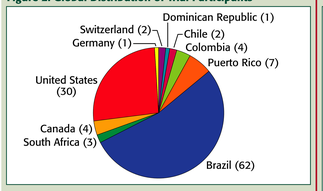


Table 1. Baseline Characteristics

	VCV 30 mg (n=39)	VCV 20 mg (n=40)	Placebo (n=37)
Male, n (%)	33 (85)	31 (78)	26 (70)
White, n (%)	26 (67)	32 (80)	21 (57)
Hispanic/Latino, n (%)	24 (62)	31 (78)	27 (73)
Mean age, years (SD)	44.9 (7.3)	44.0 (8.0)	45.5 (8.8)
Mean CD4 count, cells/mm³ (SD)	202.2 (159.2)	202.1 (144.5)	226.1 (196.6)
CD4 count <200, n (%)	22 (56)	22 (55)	22 (59)
Mean plasma HIV RNA, $\log_{10}$ (SD)	4.5 (0.9)	4.5 (0.9)	4.6 (0.8)
HIV RNA >100,000, n (%)	12 (31)	12 (30)	10 (27)
Prior AIDS-defining event, n (%)	18 (46)	20 (50)	13 (35)

Table 2. Background Regimen

	VCV 30 mg N (%)	VCV 20 mg N (%)	Placebo N (%)
Enfuvirtide (T-20)	9 (23)	11 (28)	8 (22)
First-time enfuvirtide use	9 (23)	10 (25)	5 (14)
Darunavir *(all first-time use)*	12 (31)	9 (23)	6 (16)
Active Drugs in OBT			
0	7 (18)	8 (20)	7 (19)
1	16 (41)	13 (33)	11 (30)
2	6 (15)	13 (33)	11 (30)
3+	7 (18)	6 (15)	6 (16)

- 54 (47%) patients had an active PI in their OBT.
- 59 (51%) patients had ≥1 active NRTI in their OBT.

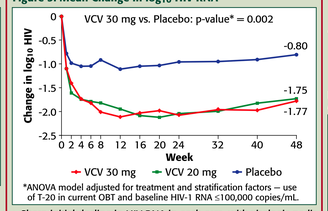
Table 3. Patient Disposition

	VCV 30 mg	VCV 20 mg	Placebo
Randomized	39 (100)	40 (100)	37 (100)
Completed	33 (85)	35 (88)	18 (49)
Discontinued	6 (15)	5 (13)	17 (46)
Adverse event	0 (0)	2* (5)	2* (5)
Treatment failure†	5 (13)	3 (8)	14 (38)
Other	1 (3)	0 (0)	1 (3)
Randomized, but not treated	0 (0)	0 (0)	2 (5)

*Four deaths occurred after the subjects had discontinued due to AEs that were not related to study drug. No deaths occurred while on study.
†As defined by study investigator.

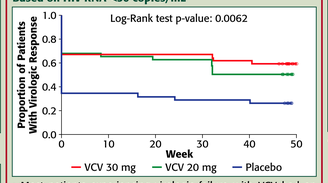
VIROLOGIC EFFICACY

Figure 3. Mean Change in $\log_{10}$ HIV RNA



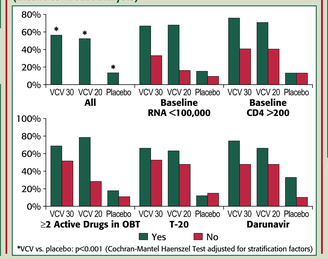
- Sharp initial decline in HIV RNA in each arm, with virologic nadir by Week 4 for PBO arm, Week 12 for the VCV-containing arms.
- Loss in mean virologic suppression after Week 24 in the VCV and PBO arms (+0.29 $\log_{10}$ for VCV 30 mg, +0.31 $\log_{10}$ for VCV 20 mg, and +0.16 $\log_{10}$ for PBO) suggests that the decline in virologic suppression is primarily due to a gradual failure of the OBT.

Figure 4. Time to Loss of Virologic Response (TLOVR) Based on HIV RNA <50 copies/mL



- Most patients experiencing virologic failure with VCV had an initial response.
  - The number failing to exhibit a 0.5 $\log_{10}$ reduction in HIV RNA at Week 4 was 1 (3%), 2 (5%) and 3 (9%) in the VCV 30 mg, VCV 20 mg and placebo arms, respectively.
  - Rebounds tended to occur in patients who exhibited HIV RNA <400 copies/mL by Week 12 but did had no further virologic suppression.

Figure 5. Week 48 HIV RNA <50 copies/mL by Subgroup (Intent-to-Treat Analysis)



- For the entire population and in each subgroup, the VCV-containing arms demonstrated a superior virologic response compared with placebo.
  - Vicriviroc showed a trend to superiority even when the OBT contained 3 active drugs.
- The 30 mg VCV arm showed a trend to superiority compared with the 20 mg VCV arm in more advanced HIV-infected population.
  - Patients with HIV RNA ≥100,000 copies/mL.
  - Patients with 0-1 active drugs in their OBT.

Figure 6. C_{min} Threshold: Correlation with Virologic Efficacy
Relationship Between Vicriviroc C_{min} and HIV RNA Virologic Suppression

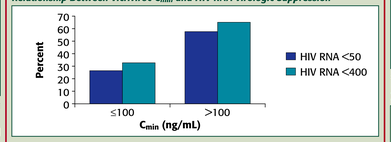
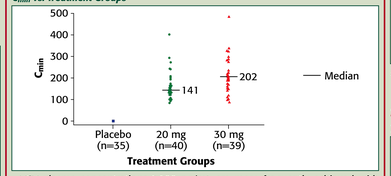
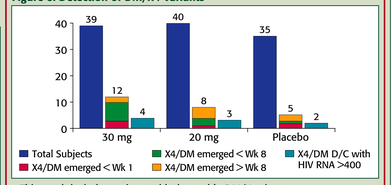


Figure 7. C_{min} Threshold: Correlation with Virologic Efficacy
C_{min} vs. Treatment Groups



- VCV plasma concentrations >100 ng/mL are more frequently achieved with the 30 mg dose.
  - The vicriviroc 30 mg median C_{min} was 202 ng/mL, compared with 141 mg/mL for the 20 mg dose.
- These consistent minimum concentrations >100 ng/mL are closely associated with virologic suppression, particularly by the most stringent <50 copies/mL criteria.
  - C_{min} highly correlates with total vicriviroc exposure (area under the curve).
- The pharmacokinetic-pharmacodynamic results may underlie the superior performance of the vicriviroc 30 mg dose in this trial's more advanced HIV-infected population.

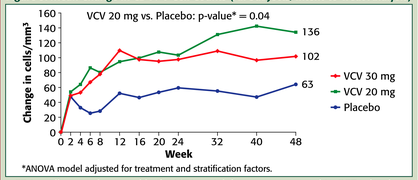
Figure 8. Detection of DM/X4 Variants



- This graph includes patients with detectable DM/X4 virus.
  - The occurrence of DM/X4 variants at <8 weeks was 30 mg 10/12 (83%), 20 mg 4/8 (50%), PBO 3/5 (60%).
  - Early detection of changes in coreceptor use are most likely due to the existence of undetectable minor CXCR4-using HIV strains (exclusively X4 or dual/mixed tropic) in patients' prescreening viral population.[6]
- Detection of DM/X4 variants was not linked to virologic failure.

IMMUNOLOGIC EFFICACY

Figure 9. Mean Change in CD4+ T-Cell Counts (All Subjects, Intent-to-Treat Analysis)



- CD4+ cell counts increased in the VCV-containing arms compared to OBT+placebo.

Table 4. AIDS-Defining Events

Ruling by Adjudication Committee	VCV 30 mg	VCV 20 mg	Placebo
Confirmed AIDS-Defining Events			• CMV retinitis • Esophageal candidiasis
Non-Confirmed AIDS-Defining Events	• Toxoplasmosis (cerebral) • Colitis • Pneumonia	• CMV (bronchial) • Pneumonia • Mycobacterium infection (TB)	• Toxoplasmosis (cerebral)

- The few AIDS-defining events (ADEs) were spread evenly across treatment arms, with no particular pattern.

SAFETY

Table 5. Summary of Treatment-Emergent Adverse Events

	VCV 30 mg N (%)	VCV 20 mg N (%)	Placebo N (%)
Any TEAEs	37 (95)	39 (98)	33 (94)
Any Serious TEAEs	4 (10)	4 (10)	5 (14)
Any Severe (Grade 3 or 4) TEAEs	8 (21) • 2 creatinine elevation • 1 CPK elevation • 1 QT prolongation	8 (20) • 2 deaths, unrelated to treatment • 1 penile carcinoma in-situ	7 (20) • 2 deaths, unrelated to treatment

TEAE = treatment-emergent adverse events.

Table 6. Adverse Event Rate by Time on Study

All casualties and severities All patients receiving one dose	VCV 30 mg + OBT Rate	VCV 20 mg + OBT Rate	Placebo + OBT Rate
Total exposure in person-years (P-Y)*	33.2	34.67	22.39
SAE's N (P-Y)	4 (12)	5 (14.4)	5 (22.3)
Any Adverse Event	111.4	112.5	147.4
Diarrhea	45.2	31.7	40.2
Respiratory Symptoms	24.1	51.9	22.3
Nausea	15.1	8.7	22.3
Pyrexia	15.1	11.5	17.9
Dizziness	15.1	2.9	17.9
Headache	15.1	8.7	31.2
Tinea Pedis	12.1	0	4.5
Lymphadenopathy	9.0	20.2	8.9
Depression	9.0	11.5	26.8
Musculoskeletal Pain	9.0	8.7	40.2
Asthenia	6.0	2.9	13.4
Fatigue	6.0	14.4	13.4
Upper Abdominal Pain	3.0	14.4	0
Flatulence	3.0	5.8	17.9
Anorexia	0	0	13.4

*Rate >10/100 person-years.

- Overall the incidence of adverse events including serious AE's were similar between vicriviroc and placebo group.
- No SAE's were attributed to study drug
- No deaths occurred on study.

Conclusions

- **Vicriviroc (30 and 20 mg, QD) + OBT demonstrated superior virologic and immunologic efficacy compared with OBT alone in a ART-experienced population.**
- **This efficacy benefit was apparent regardless of number of active drugs in OBT.**
- **The vicriviroc 30 mg dose resulted in greater median C_{min} when compared with the 20 mg dose.**
- **A vicriviroc C_{min} >100 ng/mL had a noticeable association with improvement in virologic efficacy.**
- **Vicriviroc 30 mg showed superior results in advanced HIV-infected patients (baseline HIV RNA >100,000 copies/mL or 0-1 active drug in the OBT).**
  - **This superiority may have been due to the increased VCV exposure observed with the 30 mg dose.**
- **Emergence of detectable dual/mixed or X4-tropic HIV tended to occurring early and was not assoicated with virologic failure.**
  - **Early detection of X4 was likely due to pretreatment existence of undetectable minority strains.**
- **Greater increases in CD4 cell counts were observed with vicriviroc 30 mg and 20 mg.**
- **Vicriviroc's mechanism of action had no noticeable negative impact on immune restoration, as indicated by the lack of occurrence of AIDS-defining events.**
- **There were no clinically relevant safety differences between vicriviroc and the placebo groups.**
- **Vicriviroc (30 mg, QD) as part of a ritonavir-containing, PI-based regimen is now in Phase 3 clinical trials enrolling HIV monoinfected and HIV/HCV coinfected treatment-experienced patients.**

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