This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 SYNOPSIS

Title of Study:	Vicriviroc (SCH 417690) in Combination Treatment with Optimized ART Regimen in Experienced Subjects (VICTOR-E1) (Protocol No. P03672) – Final Analysis of Week 48 Data	
Investigators:	Multicenter, multinational	
Study Centers:	36 sites in USA, Canada, Europe, Latin America, and South Africa.	
Publications:	None	
Studied Period:	28 JUN 2006 to 19 OCT 2007	**Clinical Phase:** 2

Objectives

Primary: To evaluate the antiviral efficacy of two dose levels of vicriviroc (30 mg and 20 mg once daily [QD]) compared to placebo, each in combination with a newly optimized antiretroviral regimen containing a ritonavir-boosted protease inhibitor (PI/r) in CCR5-tropic human immunodeficiency virus (HIV)-infected individuals failing a standard three-drug antiretroviral regimen.

Secondary: The key secondary objective was to assess the durability of the antiviral response of vicriviroc.

Other secondary objectives related to efficacy were:

- To compare the dose-response relationship between 2 dose levels of vicriviroc.
- To evaluate the pharmacokinetic–pharmacodynamic (PK–PD) relationship of vicriviroc through the use of PK–PD population analyses.
- To evaluate the time to occurrence of acquired immunodeficiency syndrome (AIDS)-defining clinical events.
- To evaluate the incidence of AIDS-defining clinical events.

Other secondary objectives related to safety included assessments of:

- Frequency of detectable resistance to vicriviroc or other components of OBT.
- Frequency of detectable CXCR4-tropic virus.
- Frequency of detectable CXCR4-tropic virus with concomitant decline in CD4 count by ≥50% below baseline.
- Frequencies of adverse events (AEs) and clinically significant abnormalities in electrocardiograms (ECGs), laboratory findings, or central nervous system (CNS) findings.

Methodology: This was a randomized, placebo-controlled, multi-site, parallel-group, double-blind study of vicriviroc (VCV) in adults infected with CCR5-tropic HIV who were failing a standard three-drug antiviral regimen. Screening occurred during a 6-week period before randomization. Eligible subjects were randomized in a 1:1:1 ratio to 48 weeks of treatment with VCV 30 mg QD, VCV 20 mg QD, or placebo, each in addition to an open-label newly-optimized background regimen (OBT). OBT was selected by investigators based on viral susceptibility testing performed during screening. Each optimized regimen contained ≥3 drugs, including a ritonavir-boosted protease inhibitor (PI/r). Subjects returned at Weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, and 48 for assessments related to antiviral efficacy, safety, and pharmacokinetics.

Efficacy was evaluated primarily by measurements of HIV RNA, which were scheduled at all visits. Other efficacy assessments included measurements of CD4 cells and recording of AIDS-defining events. The evaluation of safety included physical examinations, vital signs assessments, ECGs, clinical laboratory tests, emergence of complicating medical conditions, and monitoring coreceptor tropism of HIV isolates and susceptibility to vicriviroc and components of OBT. Subjects were observed and questioned for occurrence of possible AEs and AIDS-defining events. Concomitant medications were recorded.

Number of Subjects: The study was designed to enroll 120 subjects. The sample size (40 per arm) was powered at 90% to detect a difference of ≥0.7 $\log_{10}$ HIV RNA copies/mL between groups, assuming a pooled standard deviation of 0.9 $\log_{10}$ HIV RNA copies/mL.

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Diagnosis and Criteria for Inclusion: Subjects eligible for the study were: adults (≥18 years of age) with documented R5-tropic HIV infection; prior antiretroviral therapy (ART) for ≥3 months with ≥3 classes of marketed agents (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], or fusion inhibitors) at any time prior to Screening; HIV RNA ≥1000 copies/mL on a stable ART regimen for ≥6 weeks prior to Screening and ≥8 weeks prior to randomization; ≥1 genotypically documented resistance mutation to a reverse transcriptase (RT) inhibitor and ≥1 primary resistance mutation to a PI; no history of previous malignancy (excepting Kaposi's sarcoma that resolved fully on highly active antiretroviral therapy [HAART] without systemic anti-cancer therapy, or basal cell carcinoma completely resected); no history of recurrent seizures, or central nervous system (CNS) condition or drug use judged to predispose to seizure; no active untreated AIDS-defining opportunistic infection; and acceptable hematologic, renal and hepatic laboratory parameters.

Test Product, Dose, Mode of Administration, Batch No(s): Vicriviroc maleate 30 mg (3x10 mg tablets) or vicriviroc maleate 20 mg (2x10 mg tablets) administered orally (PO) QD (batch nos. [redacted] provided in 30-tablet bottles).

Duration of Treatment: Subjects were treated for 48 weeks. After Week 48, subjects were offered open-label VCV 30 mg QD. Results of the post-Week 48 extension will be presented in a separate report.

Reference Therapy, Dose, Mode of Administration, Batch No.: Placebo matching 10 mg vicriviroc tablets PO QD (batch no. [redacted] provided in 30-tablet bottles).

Criteria for Evaluation

Primary Endpoint:

- The $\log_{10}$ change from baseline HIV RNA at Week 48.

Key Secondary Endpoints:

- Proportion of subjects with ≥1.0 $\log_{10}$ change from baseline HIV RNA at Week 48.
- Proportion of subjects with HIV RNA <400 copies/mL at Week 48.
- Time to virologic failure, defined as the time from randomization to either:
  - Failure to experience HIV RNA decline of ≥0.5 $\log_{10}$ from Baseline at Week 4, in which case time was set to 0; or
  - Rebound of HIV RNA to within 0.5 $\log_{10}$ of baseline value at any time after maximum suppression.

Other Secondary Endpoints — Efficacy:

- Log_{10} change from baseline HIV RNA at Weeks 12 and 24.
- Change from baseline CD4 count at Weeks 12, 24, and 48.
- Proportion of subjects with <400 copies/mL HIV RNA at Weeks 12 and 24.
- Proportion of subjects with <50 copies/mL HIV RNA at Weeks 12, 24, and 48.
- Incidence of AIDS-defining events.
- Time to occurrence of AIDS-defining event.
- Evaluation of the PK–PD relationship of vicriviroc to antiviral activity based on population PK analyses using PK samples obtained at Weeks 4, 12, and 24 correlated with PD parameters at Weeks 12, 24, and 48.

Other Secondary Endpoints — Virologic Safety:

- Frequency of detectable vicriviroc resistance.
- Frequency of detectable CXCR4-tropic virus.
- Frequency of detectable CXCR4-tropic virus with concomitant decline in CD4 count by ≥50% below baseline.

Clinical Safety: Description and tabulation of AEs and clinically significant abnormalities in ECGs, laboratory findings, or CNS findings.

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Statistical Methods

Efficacy: The Week 48 final efficacy analysis was carried out when all subjects had completed 48 weeks of treatment or discontinued. The analysis included all randomized subjects who received at least one dose of study medication. The primary efficacy variable was analyzed using an analysis of variance (ANOVA) model that adjusted for treatment and stratification factors (baseline HIV RNA > or ≤100,000, and use or non-use of enfuvirtide [T20; Fuzeon®]). Descriptive statistical summaries were provided for the primary endpoint by randomization strata. The primary endpoint was also analyzed in subpopulations based on relevant baseline demographics and clinical characteristics. Results of genotype/phenotype tests performed at Screening were used to determine each subject's overall sensitivity score (OSS) to his or her OBT regimen at Baseline. VCV was not included in the tabulation of OSS.

To evaluate the proportions of subjects who achieved HIV RNA <50 or <400 copies/mL, analyses based on the Non-Completer = Failure (NC=F) approach and the Time to Loss of Virologic Response (TLOVR) approach were performed. The results from each analysis were compared between treatments by the stratified Cochran-Mantel-Haenszel test, adjusting for T20 use in OBT and baseline HIV RNA (> or ≤100,000 copies/mL).

The TLOVR algorithm was also implemented to analyze durability of viral response. According to the TLOVR algorithm, a responder must have achieved and sustained the response without interim viral rebound, a drug change (defined as introduction of a new class of antiretroviral [ARV]), study discontinuation for any reason, or death. Subjects who never achieved the defined virologic response were assigned time to virologic failure of 0. Two definitions of virologic response were used in the analyses: the protocol-defined 0.5 $\log_{10}$ reduction in HIV RNA from Baseline at Week 4 and onward, and sustained suppression of HIV RNA below assay detection level (50 copies/mL and 400 copies/mL). Differences between treatments in distribution of TLOVR duration time endpoints were graphically presented in Kaplan-Meier plots and assessed by the log-rank test.

In order to protect against inflation of Type I error, the Hochberg approach for multiple comparisons was used in analyzing the primary and key secondary efficacy endpoints.

The change in CD4 cell count at Week 48 was evaluated in an ANOVA model controlling for treatment, baseline HIV RNA, and use of T20 in OBT. Missing CD4 counts were handled according to the NC=F approach.

Safety: The Week 48 final safety analysis was carried out when all subjects had completed 48 weeks of treatment or discontinued. The analysis included all randomized subjects who received at least one dose of study drug. The proportion of subjects with detectable CXCR4 virus was summarized by treatment group. The proportion of subjects with detectable CXCR4 virus and a concomitant decline in CD4 count of ≥50% below baseline was also computed. The incidence of AEs and development of viral resistance to VCV and other components of the OBT were tabulated. Laboratory data were listed and values outside the normal ranges were flagged. Additionally, if any significant toxicities related to VCV were observed, the possible relationship to VCV pharmacokinetic parameters was evaluated.

Interim Analyses: There were two planned interim analyses when all subjects had completed 12 and 24 weeks of treatment. A nominal significance level of 0.0001 was used for each interim analysis.

Data Safety Monitoring Board (DSMB): An independent, external DSMB was constituted to review data on a periodic basis.

SUMMARY-CONCLUSIONS:

RESULTS: One-hundred-fourteen (Intent-to-Treat [ITT] population) of the 116 randomized subjects received at least one dose of study medication. Two subjects in the placebo group discontinued from the study prior to dosing. Sixty-eight (86%) of the 79 subjects randomized to VCV completed 48 weeks of blinded treatment, compared with only 18 (49%) of 37 subjects in the placebo group. The mean duration of treatment was 44, 45, and 33 weeks in the VCV 30 mg, VCV 20 mg, and placebo groups, respectively. Treatment failure was the most common reason for discontinuation in all treatment arms and was more frequent in the placebo group. Adjusting exposure for the number of subjects who received a full 365 days of treatment yielded 33.20, 34.67, and 22.39 subject-years of study drug exposure in the VCV 30 mg, VCV 20 mg, and placebo groups, respectively.

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Efficacy: The mean $\log_{10}$ change from baseline HIV RNA at Week 48 was significantly greater with both VCV 30 mg and VCV 20 mg compared to placebo (-1.77 and -1.75 vs. -0.79 $\log_{10}$ copies/mL, respectively; p=0.0017 and p=0.0026, VCV 30 mg and VCV 20 mg vs. placebo). Superior antiviral efficacy with either VCV 30 mg or VCV 20 mg QD was also observed at Week 12 (-2.11 and -1.96 vs. -1.10 $\log_{10}$ copies/mL; p=0.0002 and p=0.0020, respectively) and Week 24 (-2.06 and -2.05 vs. -0.95 $\log_{10}$ copies/mL; p=0.0003 and p=0.0004, respectively), and was sustained at 48 weeks, supporting the durability of the early antiviral effect. The antiviral effect of the 30 mg dose was greater than the 20 mg dose among subjects with a baseline viral load >100,000 copies/mL. In subjects who started treatment with low (≤200 cells/mm^3) or very low (<50 cells/mm^3) CD4 counts, the 30 mg dose level of VCV provided the greatest viral reduction. Both doses of VCV were superior in achieving and maintaining full virologic suppression (<50 copies/mL, ITT-TLOVR) compared with placebo (59% of VCV 30 mg and 50% of VCV 20 mg subjects, vs. 26% of placebo subjects; p=0.0028 and p=0.0265, VCV 30 mg and VCV 20 mg vs. placebo, respectively). The distribution of time to loss of virologic response was toward significantly greater times in either VCV group compared with placebo (p=0.0029 and p=0.0180, VCV 30 mg and VCV 20 mg vs. placebo, respectively). At Week 48, subjects in the VCV 30 mg and VCV 20 mg groups had a mean increase in CD4 count of +102 and +136 cells/mm^3, respectively, compared to +63 cells/mm^3 in the placebo group; the difference between VCV 20 mg and placebo was statistically significant (p=0.0387; 95% CI: 3.64, 134.52). Time to early discontinuation was shorter in the placebo group as compared with either VCV group (p=0.0014 and p=0.0005 for VCV 30 mg and VCV 20 mg vs. placebo, respectively).

Analysis of samples collected for VCV population PK at Weeks 4, 12, and 24 suggested a trend toward greater virologic response in subjects with VCV trough levels >100 ng/mL, with 58% of subjects above this level achieving virologic suppression of HIV RNA at <50 copies/mL, compared with 30% of those with lower Cmin values. Among subjects receiving VCV 30 mg QD, median Cmin was 43% higher compared to recipients of the VCV 20 mg QD dose level. Ninety-two percent of subjects in the VCV 30 mg arm achieved a Cmin >100 ng/mL versus 83% of subjects in the 20 mg arm.

Safety: Most subjects (95% VCV 30 mg, 98% VCV 20 mg, 94% placebo) experienced at least one treatment-emergent AE. Most treatment-emergent AEs were mild or moderate (Grade 1/2) in severity, and occurred with similar frequency across treatment groups (74% VCV 30 mg, 78% VCV 20 mg, 74% placebo). The cumulative exposure-adjusted rate of treatment-emergent AEs (incidence/100 person-years) was highest among subjects in the placebo group. Diarrhea was the most common treatment-emergent AE. Other gastrointestinal complaints, such as dyspepsia, nausea, and vomiting, were reported across treatment groups. Events with a higher exposure-adjusted rate in the VCV groups compared with placebo included hypercholesterolemia and hypertriglyceridemia, superficial fungal infections (tinea pedis and onychomycosis), and influenza. The reason for these findings is not readily apparent from this small study.

The rate of treatment-related AEs reported by investigators was highest in the placebo arm. The proportion of subjects with Grade 3 or 4 AEs was similar across treatment groups (21% VCV 30 mg; 20% VCV 20 mg; 20% placebo), and most were considered by investigators to be unlikely related to study medication. Serious adverse events were reported with a similar frequency across treatment arms (10% VCV 30 mg, 13% VCV 20 mg, 14% placebo). All SAEs were considered unlikely related to study medication. Four deaths were reported (VCV 20 mg n=2; placebo n=2). Two deaths occurred while subjects were on study and two were reported after subjects had discontinued. No death was attributed to study drug. There were four discontinuations due to adverse events; these were associated with the four deaths.

Seizures, malignancies, upper respiratory tract infections, herpes simplex virus (HSV) infections, hepatocellular disorders, hyperlipidemias, and ischemic cardiovascular events were monitored carefully as events of interest. There were no seizures in the VCV groups. [redacted] No malignancies were reported during the 48-week treatment period of this study. One subject developed carcinoma in situ within HPV-related genital warts (not meeting the oncologic criteria for “malignancy”) after 12 weeks of blinded VCV 20 mg. The event was considered unlikely related to study medication, and resolved with topical treatment. The event recurred 8 months later during the open-label extended treatment phase, and was ongoing at the time of the writing of this clinical study report. An additional subject who had received blinded VCV 30 mg while on study developed Hodgkin’s lymphoma and Kaposi’s sarcoma contemporaneously during the open-label extension phase of the protocol. The events were reported after approximately 64 weeks of VCV therapy. The subject was discontinued after diagnosis and began chemotherapy. The number of subjects who experienced hepatocellular disorders was similar across treatment groups (VCV 30 mg, n=2; VCV 20 mg, n=3; placebo, n=2) despite much longer treatment exposures in both VCV arms. These events included jaundice, hepatosplenomegaly, and hyperbilirubinemia. HSV infections were reported as AEs in all three treatment arms, but the rate was highest in the placebo arm. No treatment-emergent ischemic cardiovascular events were

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reported. Upper respiratory tract infections were common and comparable across treatment arms. Hyperlipidemia events included hypertriglyceridemia, hypercholesterolemia, and dyslipidemia. The rate of lipid disorders was highest in the VCV 30 mg and 20 mg arms. This finding was explored carefully in the evaluation of laboratory data on study.

Elevated serum cholesterol levels were observed more frequently in both VCV arms compared to placebo. Most of these elevations were Grade1/2 increases from normal baseline values. No other trends in laboratory values, specifically, the reported adverse events related to elevated triglycerides, were confirmed by evaluation of laboratory data. No clinically relevant changes in blood pressure, pulse, or body temperature evaluations were noted.

Six of 112 subjects (5%) with CCR5-tropic HIV at Screening had CXCR4 virus detected at Baseline prior to dosing. Nineteen additional subjects (VCV 30 mg, n=9; VCV 20 mg, n=7; placebo, n=3) had detectable CXCR4 virus after dosing, with most occurring on or before Week 8. Seventeen of the 25 subjects (68%) with detectable CXCR4 virus eventually met a protocol-defined criterion for virologic failure, with 9 subjects discontinuing from the study. Of these 17 subjects, 4 subjects experienced a decrease in CD4 count of ≥50% from baseline. Three of these 4 subjects had detectable CXCR4 virus at Baseline (before receiving any study drug). One subject with detectable CXCR4 and a ≥50% decrease in CD4 count discontinued from the study at Week 12. The distribution of time from first dose to emergence of detectable CXCR4 virus showed that detection of CXCR4 virus tended to occur earlier in the VCV 30 mg arm than in the placebo arm (p=0.04).

One subject in the VCV 30 mg group and 4 subjects in the VCV 20 mg group developed resistance to VCV. All 5 subjects had an OSS score of one or fewer active drugs in their OBT. Resistance developed slowly in most subjects. These results suggest that despite the absence of an optimally active OBT, resistance to VCV occurred slowly and infrequently, and was less common in the higher dose group.

CONCLUSIONS:

- The antiviral activity of both vicriviroc 30 mg and 20 mg was superior to placebo when added to an OBT containing a PI/r. The difference was noted as early as 12 weeks and was durable throughout the 48-week study period. Efficacy results were confirmed by multiple stringent sensitivity analyses.

- The antiviral activity of vicriviroc was apparent regardless of the composition of the OBT and generally resulted in approximately an additional 1.0 $\log_{10}$ decrease in HIV RNA over OBT alone. The magnitude of benefit was greatest among subjects receiving vicriviroc with two or more active drugs in the OBT, and the incremental benefit of adding vicriviroc was apparent even among subjects who had 3 or more active drugs in their OBT.

- Vicriviroc was superior to OBT alone in achieving full virologic suppression (<50 copies/mL). This response was apparent as early as Week 12 (46% of VCV 30 mg and 43% of VCV 20 mg subjects vs. 23% of placebo subjects) and was sustained through Week 48 (56% and 53% vs. 14%, respectively). The 30 mg dose was numerically better than the 20 mg dose in this respect. Additionally, time to protocol-defined virologic failure was longer in the vicriviroc groups compared to placebo.

- Vicriviroc plus OBT offered more improvement in raising CD4 counts compared with OBT alone. This response to vicriviroc was noted as early as Week 12 (+110 cells/mm^3, VCV 30 mg and +96 cells/mm^3, VCV 20 mg vs. +51 cells/mm^3, placebo) and was sustained through Week 48 (+102 and +136 vs. +63 cells/mm^3, respectively).

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- Efficacy results (antiviral activity/suppression) in subpopulations based on demographics and baseline disease characteristics, in particular, subjects with advanced HIV disease (high viral load, low CD4 count, low OSS) favor the use of vicriviroc 30 mg over vicriviroc 20 mg.

- Data in this small study suggested a trend toward greater virologic response in subjects with VCV trough levels >100 ng/mL, with 58% of subjects above this level achieving virologic suppression of HIV RNA at <50 copies/mL compared with 30% of those with lower Cmin.

- Vicriviroc was well tolerated and safe in this highly treatment-experienced population with advanced HIV disease.

- The cumulative exposure-adjusted rate of AEs was highest in the placebo arm. The most commonly reported AE was diarrhea. Higher rates for hypertriglyceridemia, hypercholesterolemia, influenza, and superficial fungal infections, specifically tinea pedis and onychomycosis, were reported among VCV recipients. The reasons for these differences are not apparent from this small study, but warrant further observation. Analysis of safety labs revealed a finding of hypercholesterolemia more frequently in both VCV arms; most elevations were mild to moderate (Grade 1/2). The reported adverse event of elevated triglycerides was not confirmed by evaluation of laboratory data.

- The cumulative exposure-adjusted rate of any reported infections/infestations was lower in VCV recipients compared with subjects in the placebo group. No adverse events of seizure or malignancy or increased rates of hepatotoxicity were reported in VCV recipients during the 48-week blinded study period. There were no ischemic myocardial events reported.

- The detection of CXCR4 at Baseline (prior to dosing with study drug) is likely due to variability of the Trofile™ assay used. Earlier detection of CXCR4 in subjects receiving vicriviroc may be related to more potent suppression of CCR5 virus. In most subjects, the detection of CXCR4 did not herald an immunologic decline that required discontinuation from the study.

- VCV resistance occurs infrequently, and usually after prolonged therapy in the context of an inadequate (ie, <2 active drugs) background regimen. VCV resistance was associated with the detection of CXCR4 virus in more than half of subjects, was most common in the VCV 20-mg arm, and was infrequently associated with emerging resistance to agents in the OBT.

- The 30-mg dose of vicriviroc was found to confer an advantage over the 20-mg dose on the basis of better efficacy in subpopulations (viral load >100,000 copies/mL and CD4 count <50 cells/mm^3), a better PK-PD profile, and less resistance to VCV at the time of virologic failure.

- The efficacy and safety of vicriviroc 30 mg QD demonstrated in this Phase 2 trial supported proceeding to Phase 3 confirmatory trials.

Date of the Report: 12 SEP 2008