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:	Safety and Efficacy of SCH 417690 in HIV-Infected Treatment-Naive Subjects (Protocol No. P03802)	
Investigators:	Multiple investigators.	
Study Centers:	Multicenter: 22 international sites.	
Publication(s):	None.	
Studied Period:	08 JUL 2004 to 01 DEC 2005	**Clinical Phase:** 2

Objectives:

Primary: The primary objective of this study was to evaluate the virologic efficacy of three dosing regimens of vicriviroc (SCH 417690) in human immunodeficiency virus (HIV)-infected treatment-naive patients, and to determine a dose or doses to be carried forward in the Phase-3 program.

Secondary: The secondary objective of this study was to assess the long-term safety and tolerability of vicriviroc.

Methodology: This was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study designed primarily to evaluate the virologic efficacy of three dosing regimens of vicriviroc in approximately 80 HIV-infected treatment-naive patients. After a 6-week screening phase, eligible patients were randomized to 14 days of double-blind monotherapy with vicriviroc 25 mg QD, 50 mg QD, or 75 mg QD, or placebo QD. The primary efficacy endpoint during this phase of the study was the mean change from Baseline in $\log_{10}$ HIV-1 RNA at Day 14. During the 46 weeks that immediately followed, patients who had received vicriviroc during the monotherapy phase continued to receive their originally randomized double-blind treatment (ie, one of three doses of vicriviroc, with the dose level remaining double-blind) plus Combivir® (lamivudine + zidovudine), while patients who had received placebo during the monotherapy phase received open-label efavirenz plus Combivir. Patients were seen by study personnel at least weekly for the first 4 weeks of treatment, at 4-week intervals to Week 24, and thereafter at 8-week intervals to Week 48. Patients whose HIV-1 RNA level at Week 4 (confirmed on retesting within 4 weeks) decreased <1.0 $\log_{10}$ copies/mL compared with the baseline value were considered to have an inadequate virologic response and were withdrawn from the study to be managed according to standard HIV treatment guidelines.

During the combination-therapy phase, patients who developed intolerance to efavirenz could be switched to nevirapine, if appropriate. Patients who developed intolerance to the zidovudine component of Combivir could be switched to lamivudine + stavudine, if appropriate.

Physical examinations, vital signs assessments, electrocardiograms (ECGs), and clinical laboratory evaluations, including $CD4^+/CD8^+$ cell counts, were conducted at Screening and at scheduled times during the study. Drug susceptibility testing and evaluation of changes in coreceptor tropism of HIV isolates were also evaluated throughout the study to confirm eligibility of patients to continue in the trial. Patients were continuously observed and questioned throughout the study for possible occurrence of adverse events (AEs).

Number of Patients: Approximately 80 subjects were planned to be enrolled at 22 centers; 92 subjects were enrolled; 91 subjects completed the monotherapy phase of the study and were eligible to enter the combination therapy phase. With this sample size, assuming a standard deviation of 0.7, the study was anticipated to have approximately 90% power (α=0.05, two-sided) to detect a difference of 1.0 $\log_{10}$ change in HIV-1 RNA from Baseline at Day 14 between the highest dosage of vicriviroc (75 mg QD) and placebo.

Diagnosis and Criteria for Inclusion: To be eligible for this study, patients had to be ≥18 years of age, and have a documented HIV-1 infection (with only R5 phenotype at Screening, no detectable X4). Patients also had to be treatment-naive (ie, cumulative lifetime anti-retroviral therapy exposure of ≤2 weeks and none in the 2 months preceding randomization). Patients with a history of any type of seizures (excluding typical childhood febrile seizures) or head trauma with loss of consciousness, or those with CNS conditions or taking medications known to increase risk of seizure were excluded from participation in the study.

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Test Product, Dose, Mode of Administration, Batch Nos.: The test product tablet, referred to as vicriviroc (SCH 417690), is composed of vicriviroc maleate salt plus excipients. During the 14-day, double-blind, monotherapy phase: vicriviroc was administered orally QD as a 25 mg dose (1 x 25 mg vicriviroc tablet, and 2 x 25 mg placebo tablets), a 50 mg dose (2 x 25 mg vicriviroc tablets, and 1 x 25 mg placebo tablet), or a 75 mg dose (3 x 25 mg vicriviroc tablets).

During the 46-week combination-therapy phase, vicriviroc was continued at the same dose as in the monotherapy phase (as above), along with Combivir® (lamivudine + zidovudine). Combivir was given at the standard recommended dosage.

Batch numbers for the 25 mg vicriviroc tablets were [redacted] and [redacted] the batch number for the matching placebo tablet was [redacted] Combivir was to be prescribed at the study sites.

Duration of Treatment: Patients received study drugs once daily for up to 48 weeks: monotherapy for 14 days (see Methodology above), and combination therapy for up to 46 weeks (see Methodology above).

Reference Therapy, Dose, Mode of Administration, Batch Nos.:

- During the 2-week, double-blind, monotherapy phase: Vicriviroc placebo was administered orally QD (3 x 25 mg vicriviroc placebo tablets [Batch No. [redacted]
- During the 46-week combination-therapy phase: The control group received open-label efavirenz and Combivir® (lamivudine + zidovudine) as prescribed and administered orally by the study sites at standard recommended dosages.

Criteria for Evaluation

Efficacy Evaluation: Blood samples for analysis of HIV-1 RNA were collected at all study visits. The primary efficacy parameter was the mean change from Baseline in $\log_{10}$ HIV-1 RNA at Day 14. Blood samples were also collected at scheduled time points throughout the study for quantification of $CD4^+$ lymphocytes.

Safety Evaluation: Clinical assessment and review of laboratory data were used to monitor safety and tolerability of study drugs. Safety assessments included, but were not limited to, monitoring of AEs with particular interest in serious AEs (SAEs), new infections and AIDS-defining conditions including bacterial pneumonia; physical examinations; clinical laboratory tests including $CD4^+/CD8^+$ cell counts; measurement of vital signs; ECGs; drug susceptibility testing; and evaluation of changes in coreceptor tropism of HIV isolates.

Pharmacogenetic Evaluation: CCR5 messenger RNA (mRNA) expression was examined to explore mechanisms of previously described increases in receptor density associated with vicriviroc treatment..

Statistical Methods

Efficacy: The primary analysis (ie, mean change in $\log_{10}$ HIV-1 RNA from Baseline at Day 14) was performed using an analysis of variance (ANOVA) model that extracted effects due to treatment. Based on this ANOVA model, a step-down method, starting with the highest dose (vicriviroc 75 mg QD), was used in the treatment comparisons between the active groups and the placebo group in order to account for multiple comparisons.

The secondary variables, the proportion of patients with at least a 1.0 $\log_{10}$ decrease in HIV-1 RNA from Baseline at Day 14 and the proportion of patients with <50 and <400 copies/mL of HIV-1 RNA at Day 14 were analyzed using a logistic regression model that extracted effects due to treatment. The mean change from Baseline in CD4+ cell count at Day 14 was analyzed using an ANOVA model that extracted effects due to treatment.

In addition, descriptive statistics for the primary and secondary efficacy variables were provided for long-term data at Weeks 24 and 48.

Safety: The number of patients reporting any AEs, the occurrences of specific AEs, and discontinuations due to AEs were tabulated. Laboratory data were listed, and values outside the normal range were flagged. Data from vital signs assessments, ECGs, and physical examinations were reviewed for each patient, and clinically significant findings were recorded as AEs.

SUMMARY - CONCLUSIONS:

RESULTS: A total of 92 subjects were randomized; 1 subject randomized to 50 mg vicriviroc did not complete the 14-day monotherapy phase and was lost to follow-up. Ninety-one subjects completed the monotherapy phase and were eligible to enter the combination therapy phase; 88 subjects continued in the combination therapy phase. One subject was discontinued because of an AE, 1 subject chose not to continue in the study, 18 subjects were discontinued because of treatment failure, 54 subjects discontinued at the time of study termination, and 14 subjects had completed the combination therapy phase by the time the trial was stopped.

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Efficacy: The mean changes from Baseline in $\log_{10}$ HIV-1 RNA at Day 14 were significantly different between vicriviroc and placebo groups. Viral load reduction in recipients of the highest vicriviroc dosage (75 mg QD) was significantly greater than the reduction in the lowest dosage group (25 mg QD). Significantly greater proportions of subjects in each vicriviroc dosage group had achieved >0.5 and >1.0 $\log_{10}$ drops in HIV-1 RNA as compared with the placebo group. CD4+ cell counts were significantly higher in the groups receiving 50 mg or 75 mg vicriviroc QD than in the groups receiving 25 mg vicriviroc maleate QD or placebo.

During long-term combination treatment, virologic breakthrough (≥50 copies/mL HIV-1 RNA, confirmed on retesting) occurred more frequently among the lower-dosage vicriviroc treatment groups than in the control group. Rate of breakthrough in the 75 mg group was not statistically different from that of the control group.

Changes in Day 14 viral load (ie, response to monotherapy) was associated with long-term response; subjects with reductions in HIV-1 RNA >1.5 $\log_{10}$ at 14 days were less likely to experience virologic breakthrough.

Vicriviroc exposure, as assessed by pharmacokinetic values of Cmin, Cmax, and AUC, increased with increasing dose levels. Cmin appeared to correlate with the magnitude of the reduction in $\log_{10}$ viral load at Day 14.

During the study, viral coreceptor phenotype (tropism) changed from pure CCR5 to mixed or pure CXCR4 in 8 subjects; no relationship to treatment was apparent.

Safety: Proportions of subjects reporting treatment-emergent adverse events showed no relationship with treatment or dose. AEs occurring in 10% or more of subjects in all groups combined were nausea (37%), fatigue (25%), headache (20%), diarrhea (16%), dizziness (15%), nasopharyngitis (13%), insomnia (12%), and vomiting (12%).

No death occurred during the study. Serious adverse events, none of which was judged by the investigator to be likely related to vicriviroc, included anaemia, pyrexia, acute sinusitis, condyloma acuminatum, pneumonia, increased C-reactive protein, depression, and suicidal ideation.

Fifteen subjects on active treatment showed elevations from Baseline in liver function tests for AST (4 subjects), ALT (3 subjects), or total bilirubin (9 subjects). No subject showed a Grade 4 elevation in any liver function test, and no subject experienced concomitant elevation of ALT and bilirubin suggestive of hepatocellular injury. Three subjects receiving 50 mg and 2 subjects receiving 25 mg vicriviroc showed Grade 2 or higher elevations in total bilirubin.

CONCLUSIONS:

- At doses of 25, 50, and 75 mg once daily, vicriviroc possesses potent dose-related antiviral activity with greater than 1.0 $\log_{10}$ decrease in HIV-1 RNA at 14 days of treatment, and a corresponding dose-related increase in CD4+ cell count.
- Vicriviroc was found to be safe and well tolerated, with no dose-related or unique toxicity. No drug-related hepatotoxicity, cardiac toxicity or neurologic toxicity was observed. No malignancy of any type was observed.
- During long-term combination treatment, incidence of virologic breakthrough was higher among the subjects receiving lower-dosage vicriviroc with Combivir than among the control subjects receiving efavirenz + Combivir. Incidence of virologic breakthrough in the 75 mg group was not different from that of the control group.
- The study demonstrated the clearly dose-related antiviral activity of vicriviroc. The 25 and 50 mg QD dosages of vicriviroc did not apparently contribute sufficient antiviral activity to the combination regimen to adequately suppress viral replication and prevent emergence of lamivudine resistance. The dose response demonstrated across the range of 25–75 mg QD vicriviroc supports further evaluation of higher dosages of vicriviroc.

Date of the Report: 18 DEC 2006