MAJOR ARTICLE

Phase 2 Study of the Safety and Efficacy of Vicriviroc, a CCR5 Inhibitor, in HIV-1–Infected, Treatment-Experienced Patients: AIDS Clinical Trials Group 5211

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(See the editorial commentary by Clotet, on pages 178–80.)

Background. Vicriviroc, an investigational CCR5 inhibitor, demonstrated short-term antiretroviral activity in a phase 1 study.

Methods. The present study was a double-blind, randomized phase 2 study of vicriviroc in treatment-experienced, human immunodeficiency virus (HIV)–infected subjects experiencing virologic failure while receiving a ritonavir-containing regimen with an HIV-1 RNA level ⩾5000 copies/mL and CCR5-using virus. Vicriviroc at 5, 10, or 15 mg or placebo was added to the failing regimen for 14 days, after which the antiretroviral regimen was optimized. The primary end point was the change in plasma HIV-1 RNA levels at day 14; secondary end points included safety/tolerability and HIV-1 RNA changes at week 24.

Results. One hundred eighteen subjects were randomized with a median HIV-1 RNA level of 36,380 (4.56 $\log_{10}$) copies/mL and a median CD4 cell count of 146 cells/mm^3. At 14 days and 24 weeks, mean changes in HIV-1 RNA level ($\log_{10}$ copies/mL) were greater in the vicriviroc groups (−0.87 and −1.51 [5 mg], −1.15 and −1.86 [10 mg], and −0.92 and −1.68 [15 mg]) than in the placebo group (+0.06 and −0.29) ($P < .01$). Grade 3/4 adverse events were similar across groups. Malignancies occurred in 6 subjects randomized to vicriviroc and in 2 to placebo.

Conclusions. In HIV-1–infected, treatment-experienced patients, vicriviroc demonstrated potent virologic suppression through 24 weeks. The relationship of vicriviroc to malignancy is uncertain. Further development of vicriviroc in treatment-experienced patients is warranted.

Although there are 22 antiretroviral drugs approved for the treatment of HIV-1 infection, additional antiretroviral agents with activity against drug-resistant virus are needed for HIV-1–infected, treatment-experienced patients with virologic failure. Current guidelines recommend that treatment-experienced patients experiencing treatment failure change to a regimen containing ⩾2 fully active antiretroviral agents to achieve maximal virologic suppression [1, 2]. Antiretroviral agents with novel mechanisms of action may provide virologic activity in this setting.

Viral entry is the first step in the HIV-1 replication cycle and consists of 3 substeps: viral attachment to the CD4 receptor, viral binding to the chemokine coreceptor (CCR5 or CXCR4), and viral-cell membrane fusion [3]. The first HIV-1 entry inhibitor, enfuvirtide, a fusion inhibitor, demonstrated virologic activity in treat-

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ment-experienced patients [4, 5] and was approved in 2003. Investigational HIV-1 entry inhibitors including CD4 attachment inhibitors and chemokine receptor inhibitors are in clinical development.

Vicriviroc (formerly known as SCH 417690 or Schering D) is an investigational agent that specifically binds the CCR5 chemokine coreceptor [6]. A phase 1 study of vicriviroc demonstrated safety and virologic activity of the compound over 14 days of dosing [7]. Vicriviroc is a substrate for the 3A4 isozyme of the hepatic cytochrome P450 enzyme system (CYP3A4); vicriviroc plasma concentrations are increased 2–6-fold by ritonavir, a potent CYP3A4 inhibitor [8], which allows once-daily dosing. In AIDS Clinical Trials Group (ACTG) 5211, we evaluated the safety/tolerability and virologic activity of vicriviroc as part of a ritonavir-containing regimen in HIV-1–infected, treatment-experienced subjects over 24 weeks.

SUBJECTS, MATERIALS, AND METHODS

Study subjects. Eligible subjects were HIV-1–infected adults with plasma virus that used the CCR5 coreceptor exclusively (R5 virus), as determined by a CLIA-certified tropism assay (Trofile; Monogram Biosciences). Subjects had experienced virologic failure while receiving ⩾1 antiretroviral regimen containing ⩾3 drugs before their current regimen. Subjects were experiencing virologic failure while receiving a ritonavir-containing regimen (100–800 mg/day) with a plasma HIV-1 RNA level ⩾5000 copies/mL (Amplicor HIV-1 ultrasensitive assay; Roche Molecular Systems). Initially, subjects were required to have CD4 cell counts ⩾50 cells/mm^3 and to be hepatitis B surface antigen and hepatitis C antibody negative at screening; these restrictions were removed in a protocol amendment. The study was approved by the institutional review boards at each of the participating institutions. Written, informed consent was obtained from study participants. Human experimentation guidelines of the US Department of Health and Human Services were followed in the conduct of this research.

Study design. This study was a double-blind, randomized, 48-week study of vicriviroc in treatment-experienced patients conducted by 33 sites of the ACTG. At study entry, eligible subjects were randomly assigned to 1 of 3 doses of vicriviroc (5, 10, or 15 mg once daily; Schering-Plough Research Institute) or a matching placebo added to their ritonavir-containing antiretroviral regimen. Randomization used a stratified dynamic permuted blocks approach with approximate treatment balance within each clinical unit. Subjects were stratified at randomization by current or prior use of enfuvirtide, the primary provider's plan to use enfuvirtide in the optimized antiretroviral regimen, and a screening CD4 cell count of either <50 or ⩾50 cells/mm^3.

After 14 days, subjects continued their randomized, double-blind study treatment and started an antiretroviral regimen that contained ritonavir (100–800 mg/day). The regimen was selected by the site provider on the basis of treatment history and the results of genotypic (TRUGENE; Bayer Healthcare) and phenotypic (PhenoSense; Monogram Biosciences) drug resistance testing done during screening. Study visits occurred at entry; days 4, 7, 14; weeks 3 and 4; and then every 4 weeks through week 24 and every 8 weeks through week 48. At study visits, a clinical assessment, safety laboratory tests, HIV-1 RNA level, and CD4 cell count were obtained. Coreceptor tropism assays were performed at screening; entry; day 14; weeks 8, 24, and 48; and the confirmatory virologic failure visit, if applicable.

The baseline HIV-1 RNA level was determined as the geometric mean of the preentry and entry (prestudy therapy) levels. Virologic failure was defined as a confirmed HIV-1 RNA level of <1 $\log_{10}$ copies/mL below the baseline level at/after 16 weeks. If virologic failure occurred, the subject could request unblinding, reoptimize the ritonavir-containing antiretroviral regimen (based on treatment history and repeated drug resistance testing conducted at the confirmatory virologic failure visit), and employ the following strategy: placebo recipients added vicriviroc 10 mg daily; vicriviroc 5 mg recipients increased vicriviroc to 10 mg; and vicriviroc 10 and 15 mg recipients continued vicriviroc at the same doses.

Subjects who experienced toxicity from the background antiretroviral regimen could modify the regimen as indicated clinically. Subjects who required efavirenz or nevirapine or who developed a confirmed electrocardiographic QTc interval >500 ms or that increased >60 ms from baseline were required to discontinue study drug. Subjects who had a confirmed change in coreceptor usage (i.e., from R5 to X4 or dual/mixed virus) initially were required to discontinue study drug; however, a protocol amendment allowed subjects to continue study treatment if they had not experienced virologic failure or a decrease in CD4 cell count to below baseline. All subjects were encouraged to complete study follow-up whether or not they continued taking study treatment. The planned duration of the study was 48 weeks.

Study monitoring. An independent Study Monitoring Committee (SMC) periodically reviewed the study. At their third review on 6 October 2005, the SMC recommended that the vicriviroc 5-mg dose be discontinued because of the suggestion of a higher rate of virologic failure than with that seen with the 10- and 15-mg dosing groups, more changes in HIV-1 coreceptor usage, and information from a Schering-Plough–sponsored study of vicriviroc in treatment-naive individuals in which the 25-mg dosing group (a dose that achieved plasma drug concentrations similar to the 5-mg dose given with ritonavir) was discontinued because of an increased rate of virologic rebound [9].

At that time, the study had enrolled 118 of a planned 120 patients. Consequently, the study was closed to enrollment, and

Table 1. Baseline characteristics of the study subjects.

Characteristic	Treatment group				
	Placebo (n = 28)	5 mg (n = 30)	10 mg (n = 30)	15 mg (n = 30)	Total (n = 118)
Sex					
Male	26 (93)	28 (93)	28 (93)	26 (87)	108 (92)
Female	2 (7)	2 (7)	2 (7)	4 (13)	10 (8)
Age					
Median, years	47.5	46.5	47.5	44.5	46.0
⩽30 years	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
31–40 years	5 (18)	4 (13)	5 (17)	7 (23)	21 (18)
41–50 years	14 (50)	15 (50)	12 (40)	14 (47)	55 (46)
51–60 years	9 (32)	8 (27)	12 (40)	6 (20)	35 (30)
>60 years	0 (0)	3 (10)	1 (3)	2 (7)	6 (5)
Race, ethnicity					
White, non-Hispanic	21 (75)	20 (67)	22 (73)	15 (50)	78 (66)
Black, non-Hispanic	5 (17)	6 (20)	6 (20)	7 (23)	24 (20)
Hispanic, regardless of race	1 (4)	4 (13)	2 (7)	7 (23)	14 (12)
Asian/Pacific Islander	0 (0)	0 (0)	0 (0)	1 (4)	1 (1)
Other/unknown	1 (4)	0 (0)	0 (0)	0 (0)	1 (1)
IV drug use					
Never	27 (96)	29 (97)	29 (97)	28 (93)	113 (96)
Previously	1 (4)	1 (3)	1 (3)	2 (7)	5 (4)
Prior enfuvirtide use	10 (36)	10 (33)	10 (33)	9 (30)	39 (33)
Planned enfuvirtide use at day 14	13 (47)	12 (40)	13 (42)	14 (47)	52 (44)
HIV-1 RNA level, median, copies/mL	25,229	44,819	56,488	34,238	36,380
CD4 cell count, median, cells/mm^3	161	155	118	128	146

NOTE. Data are no. (%) of subjects, unless otherwise indicated. IV, intravenous.

all patients randomized to 5 mg of vicriviroc were unblinded and could increase the study drug dose to 15 mg. At their fifth review on 15 February 2006, the SMC noted the occurrence of 5 malignancies in study subjects taking vicriviroc and recommended that patients be informed of this information, be unblinded to treatment assignment, and continue to be followed; consequently, the study became open label on 6 March 2006.

Statistics. The primary study objective was to evaluate over 14 days the virologic activity of 3 dose levels of vicriviroc in treatment-experienced subjects failing their current antiretroviral regimen. The sample size of 120 subjects (30/arm) was designed to provide >85% power to detect a difference in the mean change in HIV-1 RNA level of at least 0.7 $\log_{10}$ copies/mL between each vicriviroc dose and placebo at day 14, allowing for a loss-to-follow-up rate of no more than 10% and using a 2-sided hypothesis test with a significance level of .05. The study was not explicitly designed to compare the 3 doses of vicriviroc.

All analyses were based on data from the blinded period of follow-up, plus data at week 24 for 4 subjects who had not reached week 24 when the study became open label. The primary study end point was the change in HIV-1 RNA level from baseline to day 14. If the HIV-1 RNA result was not available at day 14, the result from the closest visit before optimization of the background regimen was used. In the analysis of HIV-1 RNA change from baseline to week 24, the last measurements obtained on randomized treatment were carried forward for subjects who changed study treatment because of virologic failure or loss to follow-up before week 24. Seven subjects randomized to receive the 5-mg dose of vicriviroc had not reached week 24 when the dose group was discontinued and increased to 15 mg, and they were not included in the analyses of week 24 outcomes; however, all follow-up data until that time were included.

Two statistical methods were used for the analysis of HIV-1 RNA changes: (1) linear regression models for censored data in which the baseline HIV-1 RNA level and stratification factors were adjusted and levels below the assay quantification limit were censored at 50 copies/mL; and (2) a Wilcoxon exact rank sum test in which stratification factors were considered and HIV-1 RNA levels below the assay quantification limit were set to 50 copies/mL. Because results from both methods were similar, we report here the results obtained using the first method only. Mean changes in HIV-1 RNA levels were calculated replacing levels below the limit of detection (<50 copies/mL) with 50 copies/mL. CD4 cell count changes were analyzed similarly, without censoring.

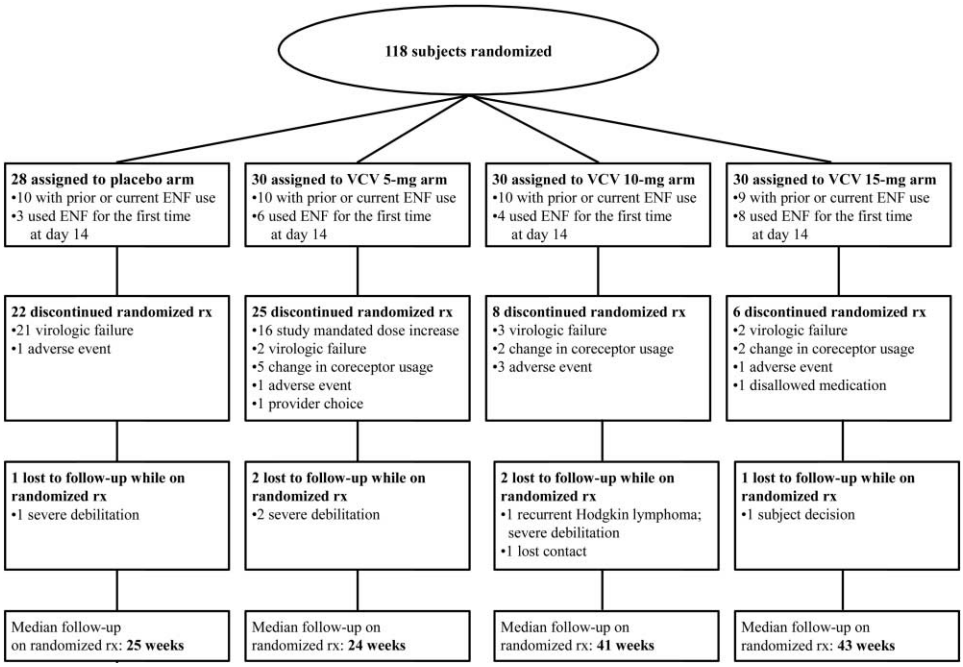

Figure 1. Disposition of the study subjects. ENF, enfuvirtide; rx, treatment; VCV, vicriviroc.

Adverse events were assessed by the site investigators and graded according to the toxicity scale of the Division of AIDS, National Institutes of Health [10]. The log-rank test was used in comparing the time to first occurrence of grade 3 or greater toxicities between groups. Data used in the safety analysis were from blinded follow-up on randomized study treatment except for the assessment of malignancy, which was based on all available data through January 2007.

RESULTS

A total of 118 subjects were enrolled—35 under the original protocol and 83 under a protocol amendment. Baseline characteristics are shown in table 1. Study subjects were 92% men and 8% women and were 20% black, 12% Hispanic, 66% white, and 2% other race/ethnicity; 4% had a history of injection drug use. A total of 39 (33%) subjects were enfuvirtide experienced. The median HIV-1 RNA level was 36,380 (4.56 $\log_{10}$) copies/mL; the median CD4 count was 146 cells/mm^3. At screening, 118 (100%) had R5 virus; at study entry (before receiving study treatment), 102 (86%) had R5 virus, 12 (10%) had dual/mixed virus, and 4 (4%) had no result because of assay amplification issues or specimen-processing problems.

Disposition. All subjects received randomized study treatment. At day 14, 26 continued enfuvirtide as part of their background regimen, and 21 started enfuvirtide for the first time. At the time of study unblinding, 61 subjects (22 receiving placebo, 25 receiving 5 mg, 8 receiving 10 mg, and 6 receiving 15 mg) had discontinued randomized study treatment early for various reasons (figure 1). The median duration of originally randomized study treatment was 25 (placebo), 24 (5 mg), 41 (10 mg), and 43 (15 mg) weeks.

Virologic responses. At day 14, the mean change in HIV-1 RNA level ($\log_{10}$ copies/mL) was +0.06 (placebo), −0.87 (5 mg), −1.15 (10 mg), and −0.92 (15 mg) ($P < .01$, for pairwise comparisons of each vicriviroc dose with placebo) and was not different between vicriviroc doses. At week 24, the 10- and 15-mg vicriviroc doses were associated with the greatest mean decreases in HIV-1 RNA level (figure 2) and had the greatest proportions of subjects with HIV-1 RNA levels suppressed to <400 or <50 copies/mL (table 2). Protocol-defined virologic failure occurred in 23 (placebo), 12 (5 mg), 8 (10 mg), and 9 (15 mg) subjects. Time to virologic failure was significantly longer for each vicriviroc dose than for placebo ($P = .02$, for 5 mg, and $P < .0001$, for 10 mg and 15 mg) (figure 3). The estimated median time to virologic failure was 16 weeks (placebo), 32 weeks (5 mg), and >48 weeks (10 and 15 mg). Compared with the 5-mg group, subjects in the 10- and 15-mg dosing groups experienced marginally lower rates of virologic failure ($P = .055$ and $P = .068$, respectively).

In subgroup analyses, virologic responses at week 24 according to enfuvirtide use were explored. In subjects randomized to vicriviroc, the greatest HIV-1 RNA decrease occurred in subjects who first used enfuvirtide at day 14 as part of their optimized background regimen ($n = 17$; −2.36 $\log_{10}$ copies/mL). This response was greater than that seen in subjects who never used enfuvirtide ($n = 40$; −1.75 $\log_{10}$ copies/mL; $P =$

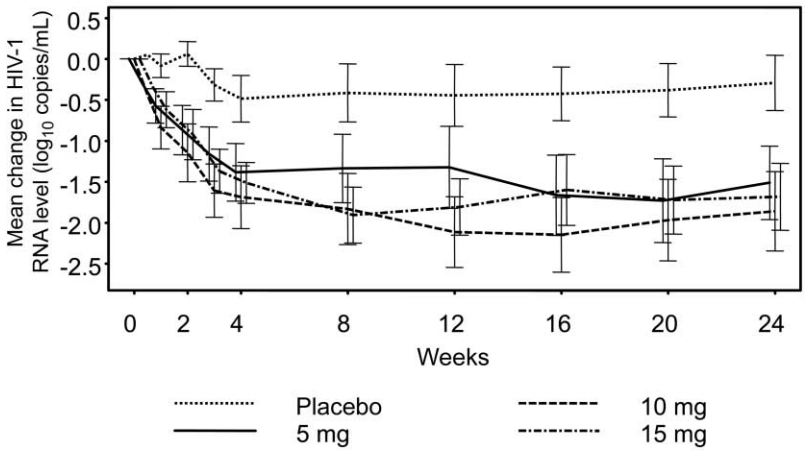

Figure 2. Mean change in HIV-1 RNA level (log_{10} copies/mL) through week 24. Bars represent the 95% confidence intervals.

.06) or in subjects with prior enfuvirtide use ($n = 26$; −1.18 log_{10} copies/mL; $P < .0001$). Similar trends according to enfuvirtide use were observed among placebo recipients (data not shown).

Immunologic responses. The mean change in CD4 cell count (cells/mm^3) from baseline to week 24 was −9 (placebo), +84 (5 mg), +142 (10 mg), and +142 (15 mg) (table 2 and figure 4). Compared with placebo, there was a marginally significant CD4 cell count increase in the 5-mg group ($P = .06$) and a significant increase in the 10-mg ($P = .001$) and 15-mg ($P = .002$) groups. There were no differences between the 3 vicriviroc doses.

Coreceptor changes. At study entry, before receiving study drug, 12 subjects with R5 virus at screening had dual/mixed-tropic virus: 2 (placebo), 2 (5 mg), 3 (10 mg), and 5 (15 mg). In the 2 subjects with dual/mixed virus randomized to placebo, subsequent coreceptor tropism assays showed R5 virus. Among the 10 subjects with dual/mixed virus randomized to vicriviroc, all subsequent tropism assays demonstrated dual/mixed or X4 virus.

At week 24, in subjects randomized to vicriviroc, the mean change in HIV-1 RNA level for the 10 subjects with dual/mixed virus at study entry was −0.77 log_{10} copies/mL, compared with −1.83 log_{10} copies/mL for the 71 subjects with R5 virus at study entry ($P = .001$). None of the 10 subjects with dual/mixed virus at entry achieved HIV-1 RNA levels <400 or <50 copies/mL at week 24, compared with 39 (55%) and 26 (37%), respectively, of subjects with R5 virus. The mean change in CD4 cell count (cells/mm^3) was +61 for those 10 subjects with dual/mixed virus at entry, compared with +140 for the 71 subjects with R5 virus at study entry ($P = .38$).

Of the 106 subjects who did not have dual/mixed or X4 virus

Table 2. Virologic and immunologic responses.

Response	Treatment group			
	Placebo ($n = 28$)	5 mg ($n = 30$)[a]	10 mg ($n = 30$)	15 mg ($n = 30$)
HIV-1 RNA level				
Day 14 change from baseline, mean, log_{10} copies/mL	+0.06	−0.87[b]	−1.15[b]	−0.92[b]
Week 24 change from baseline, mean, log_{10} copies/mL	−0.29	−1.51[b]	−1.86[b]	−1.68[b]
⩾1 log_{10} copies/mL decrease below baseline at week 24	5 (18)	14 (61)[b]	22 (73)[b]	21 (70)[b]
<400 copies/mL at week 24	3 (11)	10 (43)[c]	16 (53)[b]	14 (47)[b]
<50 copies/mL at week 24	2 (7)	6 (26)	12 (40)[b]	8 (27)[c]
CD4 cell count				
Week 24 change from baseline, mean, cells/mm^3	−9	+84	+142[b]	+142[b]

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Analyses are based on the intent-to-treat approach; the last observation was carried forward after virologic failure or study discontinuation.

[a] $n = 30$ for the day 14 results; $n = 23$ for the week 24 results. Seven subjects in the 5−mg group who increased their dose to 15 mg before week 24 were not included in the analysis (see Subjects, Materials, and Methods).

[b] $P < .01$, for pairwise comparisons between the vicriviroc dosing group and the placebo group.

[c] $P < .05$, for pairwise comparisons between the vicriviroc dosing group and the placebo group.

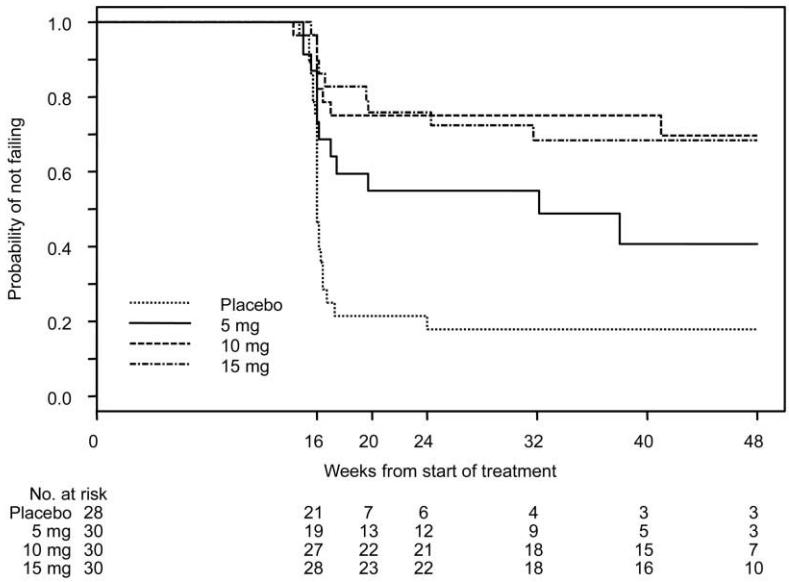

Figure 3. Time to virologic failure through week 48

at study entry, 9 experienced confirmed (i.e., 2 successive) coreceptor changes on the study: 0 (placebo), 5 (5 mg), 3 (10 mg), and 1 (15 mg) subjects. By week 2, there were more tropism changes in the vicriviroc 5-mg group compared with the placebo group (6 changes—5 confirmed and 1 unconfirmed—in the 5-mg group vs. 0 in the placebo group).

Toxicity. On initial randomized study treatment, the maximum toxicity was grade 3 in 10 (placebo), 12 (5 mg), 12 (10 mg), and 15 (15 mg) subjects and grade 4 in 3 (placebo), 2 (5 mg), 5 (10 mg), and 2 (15 mg) subjects. There were no significant differences in grade 3 or 4 adverse events among the treatment groups ($P \geqslant .57$, for all pairwise comparisons). No subject experienced a prolongation of QT interval to >500 ms or >60 ms above baseline. Seizures did not occur in any subject.

Among vicriviroc-treated subjects, 6 developed malignancies: 2 Hodgkin disease—1 subject receiving vicriviroc at 10 mg for 2 months who had a history of treated Hodgkin disease and 1 subject receiving vicriviroc at 5 mg for 12 months; 2 non-Hodgkin lymphomas—1 subject receiving viciriviroc at 15 mg for 6 months who had a history of treated Hodgkin disease and 1 subject receiving viciriviroc at 5 mg for 6 months; 1 gastric adenocarcinoma in a subject receiving vicriviroc at 15 mg for 3 months; and 1 human papillomavirus (HPV)–related squamous cell carcinoma in a subject receiving vicriviroc at 5 mg for 5 months, 10 mg for 4 months, and 15 mg for 12.5 months (~2 years total). Among placebo recipients, 2 developed malignancies: 1 with a history of squamous cell carcinoma developed multiple cutaneous squamous cell carcinomas at study week 12 and 1 who received 7 months of placebo, then 3 months of vicriviroc at 10 mg, discontinued vicriviroc for virologic failure, and 1 month later developed HPV-related perianal squamous cell carcinoma.

DISCUSSION

In ACTG 5211, treatment-experienced subjects who added vicriviroc to a ritonavir-containing antiretroviral regimen demonstrated substantially greater reductions in plasma HIV-1 RNA levels over 14 days than those who added placebo. After optimization of the ritonavir-containing antiretroviral regimen at day 14, subjects randomized to receive 10- or 15-mg daily doses of vicriviroc demonstrated significantly better virologic and immunologic responses than those receiving placebo over 24 weeks. No differences in virologic or immunologic responses were observed between those receiving the 10- and 15-mg vicriviroc doses. The 5-mg vicriviroc dosing group was discontinued during the study at the recommendation of the independent SMC because of concerns about suboptimal virologic activity both in the present study and in a study of vicriviroc in treatment-naive subjects [9] and because of an increased number of coreceptor tropism changes observed at this dose. These data establish the antiretroviral activity of a vicriviroc-containing regimen in treatment-experienced individuals and are the first to demonstrate prolonged effects of a CCR5 inhibitor–based regimen in HIV-1–infected subjects.

In the present study, the use of the HIV fusion inhibitor enfuvirtide as a new drug in the optimized background antiretroviral regimen was associated with better HIV-1 RNA suppression in both the vicriviroc and placebo groups. However, because enfuvirtide was not randomly assigned in the present study, this comparison needs to be interpreted cautiously. Pre-

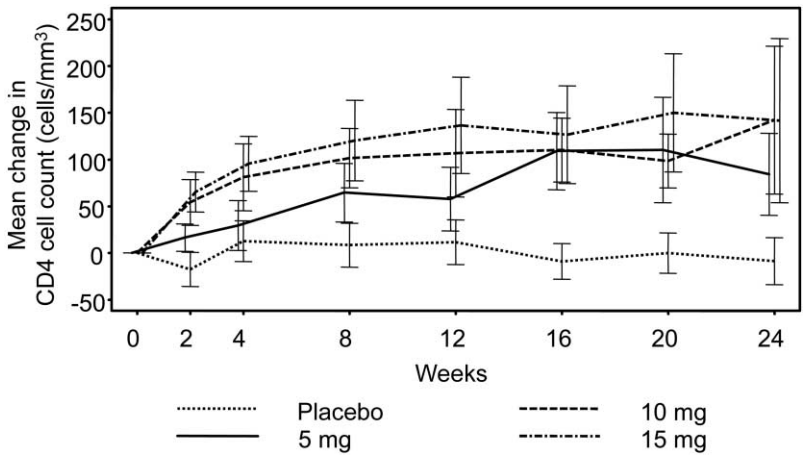

Figure 4. Mean change in CD4 cell count (cells/mm^3) through week 24. Bars represent the 95% confidence intervals.

vious phase 3 studies in heavily treatment-experienced subjects documented that an enfuvirtide-based regimen was associated with a 1.4–1.7 $\log_{10}$ decrease in plasma HIV-1 RNA levels [4, 5]. Synergy between enfuvirtide and vicriviroc (as well as other CCR5 inhibitors) has been demonstrated in vitro [11]. A possible molecular basis for this synergy is prolongation of the time during which the HR-1 domain of gp41 is accessible to enfuvirtide [12]. Future prospective, randomized studies will better address the utility of combinations of enfuvirtide and CCR5 inhibitors in HIV-infected patients, both with and without prior enfuvirtide experience.

Emergence of X4 virus is associated with accelerated CD4 cell count declines and more rapid progression of HIV disease [13]. Thus, there is concern that pharmacologic blockade of the CCR5 receptor could select for X4 virus. In particular, inadvertent administration of CCR5 inhibitors to patients harboring mixed populations of R5 and X4 viruses, with enrichment of the X4 population, could theoretically lead to more rapid immunologic and clinical decline. In this study, 12 (10%) subjects with R5 virus at screening were found to have dual/mixed virus at study entry [14]; however, no reduction in CD4 cell counts occurred in the 10 subjects with dual/mixed virus who received study drug. Stable CD4 cell counts also were maintained in the 13 vicriviroc-treated subjects who experienced a confirmed change in coreceptor usage (i.e., R5 virus to R5/X4 or X4). In the 10 subjects with dual/mixed virus at entry who received vicriviroc, virologic and immunologic responses were diminished, compared with those with R5 virus, although they were still better than for placebo recipients. Preliminary data from a study of another investigational CCR5 inhibitor, maraviroc, in patients with dual/mixed virus also demonstrated suboptimal virologic activity, although CD4 cell counts increased [15].

Approximately 1% of the white population is homozygous for a 32-bp deletion in the CCR5 gene (*ccr5Δ32*/*ccr5Δ32*) [16]. Although initial observations suggested that this deletion had no immunologic consequences, several reports suggest that effects on the immune system do occur. For example, in *ccr5Δ32* heterozygotes, various groups have documented less joint inflammation and morning stiffness with rheumatoid arthritis [17]; decreased risk of Kawasaki disease [18]; less inflammation and fibrosis with hepatitis C virus infection and improved clearance of hepatitis C viremia [19, 20]; and in *ccr5Δ32*/*ccr5Δ32* homozygotes, longer graft survival after renal transplant [21]; and increased morbidity and mortality after West Nile virus infection [22]. These reports suggest that decrease or absence of CCR5 can be clinically significant, although congenital decrease or absence may be different than pharmacologic receptor blockade. In the present study, there was no evidence of vicriviroc-associated immunologic impairment, although this study has both a relatively small sample size and a limited observation time. Moreover, vicriviroc was generally well tolerated, and adverse events were not different between the vicriviroc and placebo groups.

Malignancies occurred in 6 subjects who were randomized to vicriviroc and in 2 who were randomized to placebo (one of whom ultimately received vicriviroc before the malignancy diagnosis). Prior reports found *ccr5Δ32* heterozygotes had a 3-fold *lower* risk of AIDS-related non-Hodgkin lymphoma and no change in the risk of Kaposi sarcoma [23]. The 6 malignancies in the vicriviroc groups were of diverse cell types (2 Hodgkin disease, 2 non-Hodgkin lymphomas, 1 gastric adenocarcinoma, and 1 HPV-related squamous cell carcinoma), and 2 of these occurred in subjects with prior treated Hodgkin disease. The 2 malignancies in the placebo group were both squamous cell carcinomas, one of which was HPV related. Despite effective antiretroviral therapy, malignancies continue to occur commonly in patients with advanced HIV disease [24–26]. Also, it is well established that patients with treated Hodgkin disease are at risk for developing a second malignancy [27].

Consequently, the independent SMC concluded that a causal relationship with vicriviroc could not be determined. A preliminary report also suggested no increased incidence of malignancies in patients taking maraviroc [28, 29]. Nevertheless, given the biologic plausibility that a CCR5 antagonist potentially could adversely impact tumor surveillance, longer term follow-up of patients exposed to CCR5 inhibitors is needed to determine the relationship, if any, to the development of malignancies.

In summary, in HIV-1–infected, treatment-experienced subjects, the CCR5 inhibitor vicriviroc at doses of 10 or 15 mg together with an optimized ritonavir-containing background antiretroviral regimen provided 24-week virologic and immunologic activity and was generally well tolerated. The 5-mg dose of vicriviroc was found to be suboptimal, but no obvious differences between the 10- and 15-mg doses of vicriviroc were noted in terms of safety or efficacy. These results support further clinical development of vicriviroc in HIV-1–infected treatment-experienced patients.

ADDITIONAL MEMBERS OF THE AIDS CLINICAL TRIALS GROUP 5211 TEAM

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