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Version 2

Phase 2a Study of the CCR5 Monoclonal Antibody PRO 140 Administered Intravenously to HIV-infected Adults

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ABSTRACT

The anti-CCR5 antibody PRO 140 has shown potent and prolonged antiretroviral activity in subjects infected with CCR5-tropic (R5) HIV-1. Prior studies have examined single intravenous doses ranging to 5 mg/kg or up to three subcutaneous doses ranging to 324 mg. Here we report results of a randomized, double-blind, placebo-controlled trial that examined the antiviral activity, tolerability and pharmacokinetics of single 5 mg/kg and 10 mg/kg intravenous infusions of PRO 140 in 31 treated subjects. Eligibility criteria included HIV-1 RNA >5,000 copies/mL, $CD4^+$ cells >300/μL, no antiretroviral therapy for ≥12 weeks, and only R5 HIV-1 detectable in the original Trofile assay. Following post-study testing with an enhanced-sensitivity Trofile assay, one 10 mg/kg subject was reclassified as having dual/mixed-tropic virus at screening and was censored from efficacy analyses. The mean maximum reduction from baseline HIV-1 RNA was 1.8 $\log_{10}$ for both 5 mg/kg and 10 mg/kg doses (P<0.0001 relative to placebo). Viral loads nadired at Day 12 post-treatment and remained significantly (P<0.01) reduced through Day 29 for both PRO 140 dose groups. Treatment was generally well tolerated with no dose-limiting toxicity observed. Peak serum concentrations and overall exposures increased proportionally with dose. In summary, single 5 mg/kg and 10 mg/kg doses of PRO 140 exhibited potent, long-lived antiviral activity and were generally well tolerated. The findings further delineate the safety and antiviral properties of this novel, long-acting antiretroviral agent.

INTRODUCTION

The chemokine receptor CCR5 plays a physiological role in the activation and migration of T cells and other leukocytes. CCR5 also binds the HIV-1 envelope glycoprotein gp120 and serves as a co-receptor for HIV-1 entry into $CD4^+$ cells (11). Certain strains of HIV-1 can use the chemokine receptor CXCR4, either exclusively (X4 viruses) or in addition to CCR5 (R5X4 or dual-tropic viruses). Viruses that use CCR5 exclusively (R5 viruses) are the only strains detected in most individuals during the initial to middle stages of disease. CXCR4-using virus can be detected in an increasing percentage of individuals as disease progresses (1,2,14,24). A small-molecule CCR5 antagonist (maraviroc; Pfizer/ViiV Healthcare) has been approved by the U.S. Food and Drug Administration (FDA) for use in patients with only R5 virus detectable (5) and serves to validate CCR5 as a target for new HIV-1 therapies.

PRO 140 is a humanized monoclonal antibody that binds CCR5 and potently inhibits R5 but not CXCR4-using viruses in laboratory studies (15,22). PRO 140 or its murine counterpart shows synergy and limited cross-resistance with small-molecule CCR5 antagonists in vitro (9,13,15). Both intravenous and subcutaneous (SC) forms of PRO 140 have been previously evaluated in short-term monotherapy studies in HIV-1 subjects with only R5 virus detectable. Both dosage forms of PRO 140 were generally well tolerated relative to placebo and demonstrated potent, prolonged, and dose-dependent antiretroviral activity (6,7).

In a prior study, intravenous PRO 140 was evaluated as single doses of 0.5 mg/kg, 2 mg/kg or 5 mg/kg. Antiviral effects increased in a dose-dependent manner, with a 1.83 $\log_{10}$ mean reduction in HIV-1 RNA observed at 5 mg/kg. Based on these findings, the present study was conducted to evaluate single 5 mg/kg and 10 mg/kg intravenous doses for antiviral effects, tolerability and pharmacokinetics (PK) in HIV-infected individuals with R5 virus.

MATERIALS AND METHODS

Study design. A randomized, double-blind, placebo-controlled, parallel-group study was conducted in HIV-infected adults. Subjects (approximately 30 planned) were randomized 1:1:1 to receive a single intravenous infusion of placebo, 5 mg/kg PRO 140 or 10 mg/kg PRO 140. The protocol was approved by the institutional review board at each site. All subjects provided written informed consent. Eligibility criteria included age ≥18 years, plasma HIV-1 RNA ≥5,000 copies/mL, $CD4^+$ lymphocytes ≥300/μL with no documented count ≤250/μL, no antiretroviral therapy for ≥12 weeks, no history of acquired immunodeficiency syndrome-defining illness and only R5 HIV-1 detectable in the original Trofile assay (Monogram Biosciences, Inc.) (23). PRO 140 was provided at a concentration of 10 mg/mL in a sterile phosphate-buffered solution. Placebo was a matched, sterile, buffer solution without PRO 140. Study drug was administered over 30 minutes. Subjects were followed for 58 days post-treatment.

Virological evaluations. The Amplicor HIV-1 Monitor Test (version 1.5; Roche Diagnostics) was used to measure plasma levels of HIV-1 RNA at screening, baseline (pre-dose on Day 1) and Days 3, 5, 8, 10, 12, 15, 22, 29, 43, and 59. Samples <400 copies/mL were re-analyzed with the ultrasensitive specimen processing procedure. Co-receptor tropism was determined at screening for all subjects and after viral rebound for PRO 140-treated subjects using the original Trofile assay (23) given that the enhanced assay was not yet available. Tropism data were reported as R5 if only CCR5 use was observed, X4 if only CXCR4 use was observed, or dual/mixed if use of both CCR5 and CXCR4 was observed in the assay. When it became available post-study, a version of Trofile with enhanced sensitivity in detecting CXCR4-using virus (17) was used in post-study analyses. Blood samples for viral susceptibility analyses were collected on Days 1 (pre-dose), 15, 29 and 59. Viral susceptibility to PRO 140 was determined for all subjects on Day 1 and after viral rebound for PRO 140-treated subjects using the Phenosense Entry assay (Monogram Biosciences, Inc.) (6). Susceptibility data were reported as Fold Change values, defined as (EC_{50} for test isolate/EC_{50} for reference isolate), where EC_{50} is the concentration required for 50% inhibition.

Safety assessments. Vital signs, concomitant medications, and adverse events were recorded during screening and on Days 1, 2, 3, 5, 8, 10, 12, 15, 22, 29, 43 and 59. Physical examinations and laboratory safety tests (serum chemistries, hematology and urinalysis) were performed during screening and on Days 1, 8, 15, 29 and 59. Twelve-lead electrocardiograms were obtained during screening and on Days 1, 5, 15 and 59.

Bioanalytical methods. Serum concentrations of PRO 140 were determined by ELISA as previously described (6). The assay range was 80 to 5,000 ng/mL. The percent coefficients of variation were 13% and 19% at the low and high concentrations, respectively. Antibodies to PRO 140 were measured by ELISA as described elsewhere (6). Sera with detectable levels of anti-PRO 140 antibodies were tested for neutralizing activity according to a published method (7). Serum for PK analysis was obtained at 0h (pre-dose), 0.5h, 1h, 3h, 6h, 24h, 32h, 48h, 56h and 96h post-treatment during the first week and then on Days 8, 10, 12, 15, and 22. Serum for detecting anti-PRO 140 antibodies was obtained on Days 1 (pre-dose), 8, 15, 29 and 59. $CD4^+$ lymphocytes and CCR5 receptor occupancy were measured as described (7) on samples collected on Days 1 (pre-dose), 3, 8, 12, 15, 22, 29, 43 and 59.

PK and pharmacodynamic analyses. PK metrics were estimated after non-compartmental analysis using WinNonlin software (version 5.2; Pharsight). PK metrics included the maximum observed serum concentration (C_{max}), area under the concentration-time curve extrapolated to infinity (AUC_∞), clearance, mean residence time (MRT), volume of distribution following a single dose (V_d), and terminal serum half-life ($T_{1/2}$). $T_{1/2}$ was estimated by linear regression of the log-transformed concentration data as a function of time during the terminal phase of the decay curve. PK metrics were calculated for individual subjects and then summarized by dose cohort. Antiviral and PK data were fit to an E_{max} equation using WinNonlin:

$$E = E_{max} \times AUC/(AUC + AUC_{50}),$$

where E is the $\log_{10}$ change in HIV-1 RNA level, Emax is the maximum predicted change in HIV-1 RNA, AUC is the area under the concentration-time curve, and AUC_{50} is the AUC required to achieve

50% of E_{max}. AUC_{∞} values and nadir $\log_{10}$ HIV-1 RNA changes for individual subjects were used in the model. Modeling was performed using data from subjects treated in the present study and in a prior study of single intravenous doses of PRO 140 (6).

Statistical methods. All subjects who received study drug were included in the safety evaluations. The primary efficacy variable was the maximum change in viral load at any time following treatment. Efficacy analyses were performed on $\log_{10}$ transformed HIV-1 RNA data, and changes were calculated relative to baseline (Day 1, pre-dose). Treatment and placebo groups were compared using an analysis of variance model and using pairwise t-tests as described previously (6). Fisher's exact tests were used to compare treatment groups with placebo for the percentage of subjects with a $\geq$1 $\log_{10}$ or a $\geq$2 $\log_{10}$ reduction in HIV-1 RNA from baseline at any time post-treatment. Results are reported for 2-sided tests.

RESULTS

Subject characteristics and disposition. A total of 115 subjects were screened, of which 35 were randomized and 31 were treated with study drug. All 31 treated subjects completed the study. Table 1 summarizes demographic and other characteristics of the treated subjects, which comprised 29 males and 10 non-white individuals. At screening, treated subjects had a median age of 42.7 years, $CD4^+$ cell count of 382 cells/μL and plasma HIV-1 RNA of 33,100 copies/mL. These characteristics were similar for the different treatment groups. Twelve subjects reported at least one historical antiretroviral therapy. Genotypic resistance to existing antiretroviral drugs was limited to single-class resistance in six subjects and two-class resistance in one subject. Viruses from all subjects were genotyped as subtype B.

Antiviral effects. Both dose levels (5 mg/kg and 10 mg/kg) of PRO 140 demonstrated potent, rapid and prolonged antiviral effects that were highly statistically significant relative to placebo (Table 2). All PRO 140-treated subjects experienced a $\geq$1 $\log_{10}$ reduction in HIV-1 RNA except for one 10 mg/kg treated subject, who experienced a minimal (<0.5 $\log_{10}$) decrease in viral load. This subject had dual/mixed virus detected in the original Trofile assay at Day 15. A post-study analysis using the enhanced-sensitivity Trofile assay determined that this subject had dual/mixed virus at screening. This subject, therefore, was censored from the efficacy analyses described in this report.

The mean maximum reduction from baseline viral load was 1.83 $\log_{10}$ for each of the PRO 140 dose groups. The reductions are statistically significant (P<0.0001) relative to the 0.32 $\log_{10}$ mean reduction observed for placebo. The corresponding median reductions are 0.23, 1.84 and 2.09 $\log_{10}$ for the placebo, 5 mg/kg and 10 mg/kg dose groups, respectively. The mean and median maximum reductions for the 10 mg/kg group are 1.67 $\log_{10}$ and 1.82 $\log_{10}$ if data for the censored subject are included (P<0.0001 relative to placebo). Individual viral nadirs were observed on Day 10 (5 subjects) or Day 12 (5 subjects) for subjects treated with 5 mg/kg PRO 140 and on Day 12 (5 subjects), Day 15 (3 subjects) or Day 22 (1 subject) for subjects in the 10 mg/kg group.

Similar mean $\log_{10}$ decreases in viral load were observed for the 5 mg/kg and 10 mg/kg dose groups through Day 12, when the nadir reduction was observed in each group (Fig 1). Thereafter, mean viral loads rebounded somewhat more slowly for the 10 mg/kg dose group; however, the differences between the 5 mg/kg and 10 mg/kg dose groups were not statistically significant at any time point (P>0.1).

As noted above, all PRO 140-treated subjects experienced a ≥1 $\log_{10}$ decrease in HIV-1 RNA post-treatment with the exception of the individual who was reclassified as having dual/mixed virus prior to treatment. No placebo subject experienced a ≥1 $\log_{10}$ decline in viral load during the study (Table 2). Two 5 mg/kg subjects and five 10 mg/kg subjects (P<0.01 relative to placebo) experienced ≥2 $\log_{10}$ decreases in viral load. Five subjects treated with 5 mg/kg PRO 140 (P=0.012 relative to placebo) and two treated with 10 mg/kg had viral loads reduced to <400 copies/mL, but no placebo subject did. One subject in the 10 mg/kg group had a viral load of 50 copies/mL on Days 10 and 12.

Co-receptor tropism and viral susceptibility to PRO 140 *in vitro*. Tropism was assessed at screening and at the time of viral rebound in PRO 140-treated subjects. As noted above, one subject in the 10 mg/kg group was observed to have dual/mixed virus at Day 15. This subject was later reclassified as having dual/mixed virus at screening based on data generated post-study using the enhanced-sensitivity Trofile assay. All other PRO 140-treated subjects maintained R5 co-receptor tropism following treatment.

Viral susceptibility to PRO 140 was measured in the PhenoSense Entry assay prior to treatment in all subjects and at the time of viral rebound in PRO 140-treated subjects. In the R5 Phenosense Entry assay, which examined CCR5-mediated viral entry into U87-CD4-CCR5 cells, PRO 140 inhibited all study viruses tested. Prior to treatment, the mean Fold Change was 1.7 (range 0.77 to 3.1), Based on the ratio of the Fold Change value at the time of viral rebound to the value prior to treatment, no appreciable change in R5 virus susceptibility was observed in PRO 140-treated subjects (median ratio = 0.83, range 0.49 to 1.71). Three-fold or lower differences in Fold Change are considered to be within the normal range of interassay variation (3,8). The maximum percent

inhibition was ≥98% in all cases prior to treatment and was ≥99% in all cases following treatment. CXCR4-mediated entry of dual/mixed viruses into U87-CD4-CXCR4 cells was not inhibited by PRO 140, as expected.

Safety. No serious adverse events or dose-limiting toxicities were reported. All eleven placebo subjects and 26 of 31 subjects overall reported at least one adverse event (AE). AEs reported in more than two subjects were headache in one 5 mg/kg subject and two 10 mg/kg subjects, nasal congestion in two placebo subjects and one 10 mg/kg subject, and puritus in three placebo subjects. No obvious dose-related trend in the incidence of AEs was observed. There was no clinically relevant change in any electrocardiogram parameter, including QTc intervals, associated with administration of PRO 140 or placebo. There were no notable findings in clinical laboratory hematology or chemistry assessments or in vital-sign measurements.

Pharmacokinetics and pharmacodynamics. Mean serum concentrations of PRO 140 over time are illustrated by dose group in Fig. 2A, and PK metrics are listed in Table 3. C_{max} was reached within 2h for both PRO 140 dose groups. The mean C_{max} values were 109±31 μg/mL and 211±57 μg/mL for the 5 and 10 mg/kg dose groups, respectively. The area under the PRO 140 concentration-time curve from time zero (dosing) to infinity (AUC_{∞}) also increased in approximate proportion with dose, from 224±60 μg × day/mL at the 5 mg/kg dose to 423±150 μg × day/mL at 10 mg/kg. The corresponding mean terminal half-lives were 3.13±1.30 days and 3.33±0.70 days. Clearance (1.97±0.61 and 2.36±1.85 L/day), mean residence time (2.76±0.84 and 3.15±0.39 days) and volume of distribution (9.17±5.52 and 10.8±6.5 L) were similar for the 5 and 10 mg/kg dose groups, respectively.

The relationship between viral load reductions and PRO 140 exposure was modeled using a hyperbolic E_{max} equation. Combined data from the present study and a prior study of single-dose IV PRO 140 (6) were used in the analysis (Fig. 2B). The best-fit parameters for the combined data (E_{max} = -2.06±0.12 $\log_{10}$ and AUC_{50} = 34.1±9.7 mg × day/L) are similar to those reported previously for data from the prior study only (E_{max} = -2.14±0.22 $\log_{10}$ and AUC_{50} = 43.6±15.6 mg × day/L) (6).

Antibodies to PRO 140 were detected in two subjects in each of the PRO 140 dose groups. Antibodies were first detected on Day 15 (n=1), Day 29 (n=2) or Day 59 (n=1). In all cases, the anti-PRO 140 antibodies were of low titer (1:32 or less) and did not neutralize binding of PRO 140 to $CCR5^+$ cells in vitro. The anti-PRO 140 antibodies did not have any apparent effect on PK or viral load reductions.

Lymphocyte and receptor occupancy analyses. Changes in $CD4^+$ lymphocyte counts following treatment with PRO 140 were not statistically significant. For the combined PRO 140 dose groups, the median (range) change in $CD4^+$ lymphocyte counts was +1 (-225 to +407), +111 (-204 to +286), +57 (-198 to +386) and +18 (-362 to +370) cells/μL at Days 8, 12, 15 and 22, respectively. The corresponding values for the placebo group were +24 (-250 to +279), +38.5 (-399 to +145), +45 (-117 to +339) and +82 (-173 to +291) cells/μL at these time points.

Receptor occupancy was assessed by flow cytometry using fluorescently labeled PRO 140. Occupancy of CCR5 by study drug results in a reduction of the number of lymphocytes with detectable levels of free CCR5. High levels of receptor occupancy (>85% reduction in the number of cells detected) were observed from Day 3 through Day 29 for both PRO 140 dose groups (Fig. 3). The results were statistically significant ($P<0.01$ relative to placebo) throughout this time period. Significant receptor occupancy (81%, $P<0.01$) was also observed at Day 43 for the 10 mg/kg group. At Day 59, receptor occupancy levels were not statistically significant for either PRO 140 dose group relative to placebo ($P>0.05$). Lymphocytes were analyzed in parallel with a non-competing fluorescently labeled CCR5 antibody as previously described (6), and this analysis demonstrated that $CCR5^+$ lymphocytes were not depleted from the circulation following treatment (data not shown).

DISCUSSION

In this study, PRO 140 demonstrated potent, rapid and prolonged antiretroviral activity when administered as single 5 mg/kg or 10 mg/kg intravenous infusions to individuals with CCR5-tropic HIV-1. The mean maximum decrease in viral load was 1.8 $\log_{10}$ at each dose level, and this value compares favorably to the reductions observed in prior studies of PRO 140 (6,7) and of small-molecule CCR5 antagonists (4,10,16,19). Overall, single doses of 5 mg/kg or 10 mg/kg were generally well tolerated when administered as short-term monotherapy. Notably, we observed that 10 mg/kg, the highest dose tested to date, did not demonstrate any dose-dependent pattern of adverse events relative to placebo or to the 5 mg/kg dose. The present study adds to our understanding of the pharmacologic, pharmacokinetic and safety profiles of this agent.

There was a striking consistency in antiviral effects observed in the present study and a prior study of intravenous PRO 140 (6). Remarkably, the mean maximum reduction in HIV-1 RNA was 1.8 $\log_{10}$ for doses of 5 mg/kg or higher in each study. The consistency of outcomes underscores the robustness of the single-dose activity observed for intravenous PRO 140. The median reduction in viral load was slightly higher in the 10 mg/kg group, and more 10 mg/kg subjects achieved a $\geq$2 $\log_{10}$ reduction in HIV-1 RNA. In addition, there was a trend toward more prolonged antiviral effects at 10 mg/kg. Overall, the findings indicate that doubling the dose from 5 mg/kg to 10 mg/kg resulted in modestly greater single-dose antiviral effects.

The original Trofile assay was used to determine co-receptor tropism for enrollment into the study. The original assay was validated to have 100% sensitivity in detecting CXCR4-using viruses when present at 10% or more of a virus population (23). The original Trofile assay has since been replaced with an enhanced-sensitivity assay that was validated to have 100% sensitivity in detecting 0.3% CXCR4-using viruses in a virus population (17). The enhanced-sensitivity assay is the method currently used in clinical practice. One subject enrolled into the 10 mg/kg group based on R5 tropism in the original Trofile assay was found to have dual/mixed virus two weeks post-treatment. This subject was later reclassified using the enhanced-sensitivity assay as having dual/mixed virus at

screening, and was censored from the efficacy analysis. Similar approaches have been adopted in efficacy analyses of other studies of CCR5 co-receptor antagonists (18,21), consistent with the view that the enhanced-sensitivity Trofile assay provides an improved method of identifying candidates for therapy with CCR5 co-receptor antagonists. Similar censoring of subjects treated in the MERIT study of maraviroc (18) was performed for efficacy analyses that supported FDA approval of this agent's use in antiretroviral treatment-naïve patients.

Compared with 5 mg/kg, the 10 mg/kg dose of PRO 140 resulted in proportionally higher peak (C_{max}) and overall (AUC_{∞}) exposures to PRO 140. The higher drug exposures attained at 10 mg/kg were not associated with any obvious toxicity or pattern of toxicity. The maximum tolerated dose of IV PRO 140 has not been determined. The 10 mg/kg IV dose resulted in peak serum concentrations that are 15-fold higher on average than those observed following SC dosing (7), suggesting a sizeable margin of safety for SC PRO 140.

All pre-treatment viruses were susceptible to inhibition by PRO 140 *in vitro*. The concentrations required for 50% inhibition varied by <5-fold across the panel of 31 viruses, and all viruses were efficiently inhibited (98-100%) at higher concentrations. With the exception of the one 10 mg/kg subject who was reclassified as having dual/mixed virus at screening, there was no change in co-receptor tropism or emergence of PRO 140-resistant virus during the course of this study. The results support the view that PRO 140 broadly inhibits R5 HIV-1 with a high barrier to resistance.

High levels of receptor occupancy were observed following treatment with either 5 mg/kg or 10 mg/kg PRO 140. Statistically significant levels of receptor occupancy preceded significant reductions in viral load by at least two days. This result is concordant with the dynamics of inhibiting HIV-1 entry and with the half-life of virus-producing T cells (12). Receptor occupancy values also appeared to rebound later than viral loads. This apparent discordance could reflect issues related to assay sensitivity and sampling. Given the modest numbers of $CCR5^{+}$ lymphocytes at baseline (~20 cells/μL on average), the assay had limited ability to determine mean receptor occupancy levels above 90%. Therefore, the times of maximum receptor occupancy and of initial rebound in receptor

occupancy levels could not be determined precisely. In addition, receptor occupancy is measured on cells in the periphery, whereas HIV replication occurs primarily within tissues (20). PRO 140 concentrations and levels of receptor occupancy may differ at local sites of HIV-1 replication. As with viral load reductions, the duration of receptor occupancy was modestly greater at 10 mg/kg relative to 5 mg/kg, consistent with the higher serum concentrations of drug achieved at the higher dose.

To date, eighty-four HIV-infected individuals have been treated with IV or SC forms of PRO 140 in three short-term monotherapy studies (6,7). In each study, 1.5-2.0 $\log_{10}$ mean reductions in HIV-1 RNA were observed at the higher dose levels. The viral load reductions were long-lived and highly statistically significant. No dose-limiting toxicity or pattern of toxicity was identified in these studies. In addition, no emergence of R5 viral resistance was observed even though >1 $\log_{10}$ reductions in viral load were observed for up to 6 weeks in some subjects.

In the present study, the duration of antiviral activity increased somewhat as the IV dose was increased from 5 mg/kg to 10 mg/kg. However, neither IV dose would appear to support highly infrequent (*e.g.*, monthly) administration, and E_{max} analysis indicated that further increases in IV dose would result in incremental increases in antiviral effects. In a study of SC PRO 140, significant antiviral effects were observed when the drug was administered weekly or every other week, and virologic suppression was maintained between successive doses (7). While both IV and SC dosage forms have demonstrated favorable antiviral and tolerability profiles, SC PRO 140 was selected for further development based on its potential to be self-administered by patients. Self-administration may offer greater convenience for many patients. Nevertheless, the SC dosage form is undergoing clinical study, and IV administration may be preferred in certain treatment settings.

In summary, single intravenous infusions of 5 mg/kg and 10 mg/kg PRO 140 demonstrated potent, long-lived antiretroviral activity and a favorable tolerability profile in this study. The findings provide new insights into the safety and virological properties of this agent, which represents a novel and long-acting approach to treating R5 HIV-1 infection.

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416 **Table 1. Demographic and baseline characteristics**

Characteristic	Placebo (n=11)	5 mg/kg PRO 140 (n=10)	10 mg/kg PRO 140 (n=10)	All Subjects (n=31)
Age, years	40.2 (22.3 - 56.6)	44.7 (28.0 - 55.9)	45.3 (25.9 - 57.2)	42.7 (22.3 - 57.2)
Sex, male/female (n)	9/2	10/0	10/0	29/2
Race, black/white/other (n)	4/7/0	2/8/0	3/6/1	9/21/1
Weight, kg	82.4 (65.7 - 101.5)	79.1 (62.2 - 126.0)	82.3 (67.5 - 95.0)	81.4 (62.2 - 126.0)
$CD4^+$ cell count, cells/μL	414.5 (316 - 738)	389 (321 - 519)	368 (264 - 595)	382 (264 - 738)
HIV-1 RNA, $\log_{10}$ copies/mL	4.52 (3.76 - 5.12)	4.58 (3.88 - 4.75)	4.63 (3.79 - 5.53)	4.52 (3.76 - 5.53)

FOOTNOTE: Data are median (range) values unless otherwise indicated. Data were collected during screening.

418 **Table 2. Change in HIV-1 RNA**

Effect	Placebo	5 mg/kg PRO 140	10 mg/kg PRO 140
Maximum $\log_{10}$ change in HIV-1 RNA	-0.32±0.24	-1.83±0.23 (*P*<0.0001)	-1.83±0.41 (*P* <0.0001)
Day 12 $\log_{10}$ change in HIV-1 RNA	0.02±0.18	-1.69±0.36 (*P* <0.0001)	-1.73±0.37 (*P* <0.0001)
Number of subjects with a ≥1 $\log_{10}$ decrease in HIV-1 RNA (%)	0/11 (0%)	10/10 (100%) (*P* <0.0001)	9/9 (100%) (*P* <0.0001)
Number of subjects with a ≥2 $\log_{10}$ decrease in HIV-1 RNA (%)	0/11 (0%)	2/10 (20%)	5/9 (56%) (*P* <0.01)

419 **NOTE:** Data are mean ± SD values unless otherwise indicated. The analysis excludes data for one 10

420 mg/kg PRO 140 subject who was reclassified as having dual/mixed virus at screening.

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425 **Table 3. Pharmacokinetic parameters**

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Dose, mg/kg	C_{max}, µg/mL	AUC_{∞}, µg*day/mL	$T_{1/2}$, days	CL, mL/day/kg	MRT, days	V_d, L
5	109±31	224±60	3.13±1.30	1.97±0.61	2.76±0.84	9.17±5.52
10	211±57	423±150	3.33±0.70	2.36±1.85	3.15±0.39	10.8±6.5

427 **NOTE:** Data represent arithmetic means ± standard deviations

Figure 1. Mean log_{10} change in plasma levels of HIV-1 RNA over time by treatment group. *P*<0.0001 for each PRO 140 group relative to placebo at all timepoints from Day 5 through Day 15. *P*<0.001 and *P*<0.01 for each PRO 140 group relative to placebo at Day 22 and Day 29, respectively. The analysis excludes data for one subject in the 10 mg/kg group who was reclassified as having dual/mixed virus at screening. Subjects received a single infusion of study drug on Day 1 as indicated by the arrow. Data reflect mean values and one standard deviation.

Figure 2. Pharmacokinetics and E_{max} analysis. (A) Arithmetic mean serum concentrations of PRO 140 over time are shown by treatment group. Error bars depict standard deviations. (B) E_{max} analysis. The maximum $\log_{10}$ changes in HIV-1 RNA are plotted against AUC_{∞} for subjects treated with single intravenous infusions of PRO 140 in the present study and a prior study (6). Data were fit to an E_{max} equation: $E = E_{max} \times (AUC/AUC + AUC_{50})$. The best-fit parameters (± standard errors) are E_{max} = -2.06 ± 0.12 $\log_{10}$ and AUC_{50} = 34.1 ± 9.7 mg × day/L (R = 0.80). Mean data for the different treatment groups in each study are plotted for illustration purposes but were not used for curve fitting.

Figure 3. Receptory occupancy. Receptor occupancy was determined by flow cytometry using fluorescently labeled PRO 140. In this assay, occupancy of CCR5 by study drug is reflected as a reduction in the number of cells that have detectable levels of free CCR5. Mean cell counts are shown over time by treatment group. Error bars depict standard deviations. $P<0.01$ relative to placebo for 5 mg/kg PRO 140 at all timepoints from Day 3 through Day 29 and for 10 mg/kg PRO 140 at all timepoints from Day 3 through Day 43. $P>0.05$ relative to placebo at all other timepoints. $CCR5^+$ cells were not depleted from the circulation (data not shown). Subjects received a single infusion of study drug on Day 1 as indicated by the arrow.

Figure 1.

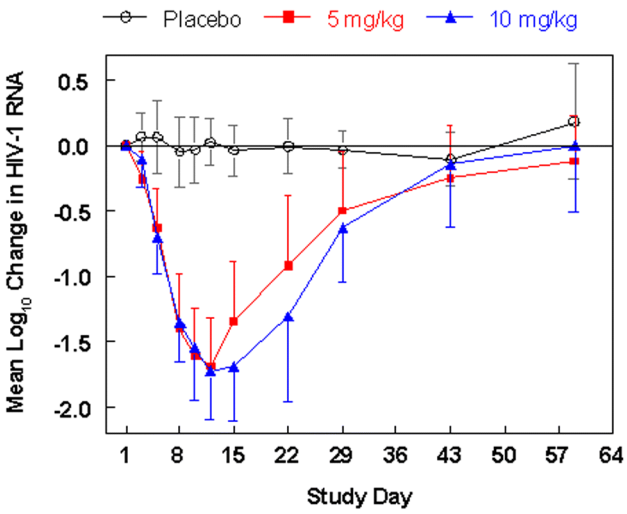

Figure 2.

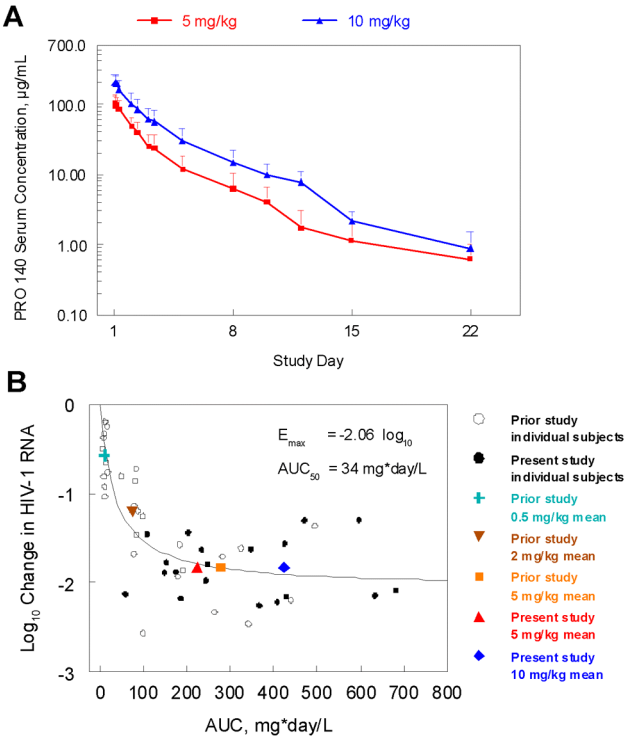

Figure 3.