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Protocol Cover Page

Protocol Title: An Extension Protocol for Subjects who Successfully Completed PRO140_CD02 or PRO140_CD02_Open Label Study

Protocol Number: PRO 140_CD 02 Extension

Version: 5.0

Document Date: 02-Apr-2021

NCT Number: NCT02990858

An Extension Protocol for Subjects who Successfully Completed PRO140_CD02 or PRO140_CD02_Open Label Study

Protocol Number:	**PRO 140_CD 02 Extension**
Version:	**5.0**
Date:	**02 Apr 2021**

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PROTOCOL APPROVAL PAGE

Protocol Number:	**PRO 140_CD 02 Extension**
Version:	**5.0**
Date:	**02 Apr 2021**

PROTOCOL APPROVAL FOR USE

I have read the protocol and the appendices and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

Prepared by:

[redacted]

Date

Reviewed by:

[redacted]

Date

[redacted]

Date

[redacted]

Date

Approved by:

[redacted]

Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**PRO 140_CD 02 Extension**
Version:	**5.0**
Date:	**02 Apr 2021**

INVESTIGATOR'S SIGNATURE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations and Investigational Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Address _____

Site Number _____

SPONSOR INFORMATION

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CONTRACT RESEARCH ORGANIZATION INFORMATION

[redacted]

PROTOCOL SYNOPSIS

Name of Sponsor: CytoDyn, Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)	
Protocol Number: PRO 140 _CD02 Extension	**Therapeutic Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection
Title of Study: An Extension Protocol for Subjects who Successfully Completed PRO140_CD02 or PRO140_CD02_Open Label Study	
Study Center(s): Up to 30 centers in the United States	
Planned Number of Subjects: Up to 50 subjects	**Study Development Phase:** Phase-2b/3
Study Population: Study population includes treatment-experienced HIV-infected patients with CCR5-tropic virus who successfully complete 24 weeks of treatment with PRO140 in addition to Optimized Background Therapy within the PRO140_CD02 or CD02_OpenLabel protocol and requires continued access to PRO 140 in order to continue deriving clinical benefit and maintain HIV-1 viral suppression, in the opinion of the treating physician.	
Objective: The primary objective is to provide PRO 140 on a continued basis to subjects who complete participation in PRO140_CD02 or CD02_OpenLabel and would require continued access to PRO 140 to form a viable regimen, in the opinion of the treating physician.	
Safety Measures: • Mean change in viral load (HIV-1 RNA levels) at the conclusion of treatment period • Mean change in CD4 cell count at the conclusion of treatment period • Emergence of Dual/Mixed (D/M)- and CXCR4-tropic virus in patients who had exclusive CCR5-tropic virus at study entry. • Tolerability of repeated subcutaneous administration of PRO 140 as assessed by investigator-evaluation of injection site reactions • Frequency of treatment-related adverse events resulting in study drug discontinuation • Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale	

Name of Sponsor: CytoDyn, Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)	
Protocol Number: PRO 140 _CD02 Extension	**Therapeutic Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection

- Frequency of treatment–emergent serious adverse events

Trial Design:

This is an extension study, to provide continued access to PRO 140 to subjects who complete participation in PRO140_CD02 or CD02_OpenLabel and continue to receive clinical benefit and would require PRO 140 to form a viable regimen, in the opinion of the treating physician. The patient population for this trial is treatment-experienced HIV-infected patients with CCR5-tropic virus who demonstrate evidence of HIV-1 suppression after successfully completed 24 weeks of treatment in the PRO140_CD02 or CD02_OpenLabel study.

The study is divided into three phases: Screening, Treatment and Follow-up

Screening Phase (up to 21 days):

This phase is designed to determine whether subjects are eligible to proceed to the Treatment Phase of the study. This phase consists of a series of assessments designed to determine eligibility. A written informed consent from the subject will be obtained by the Investigator or suitably qualified individual before the performance of any protocol-specific procedure.

All subjects will continue taking PRO 140 along with OBT during the Screening Phase.

NOTE: Subject consent and screening assessments should be completed prior to EOT visit in the PRO140_CD02 or CD02_OpenLabel study.

Treatment Extension Phase:

The Treatment Extension Phase begins with an evaluation of most recent laboratory results (viral load & CD4 count) obtained in PRO140_CD02 or CD02_OpenLabel study. All subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without further evaluation. Subjects who meet all eligibility criteria will receive first treatment injection at Treatment Extension (TE) Visit 1 (*which corresponds to EOT from PRO140_CD02 or CD02_OpenLabel study*).

The Treatment Extension Phase consists of weekly treatment injections of PRO140 700mg* SC in addition to OBT. Optimized background therapy (OBT) is a standard-of-care regimen comprised of 3 or more antiretroviral agents selected by the Investigator based on treatment history and genotypic and/or phenotypic assessments. Subjects will continue the same OBT regimen initiated within the PRO140_CD02 or CD02_OpenLabel study.

Note: Subjects enrolled prior to Protocol v4.0 may still be receiving the original 350mg dose and have the option of increasing their dose to 700mg.

Name of Sponsor:
CytoDyn, Inc.

Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)

Protocol Number:	**Therapeutic Indication:**
PRO 140 _CD02 Extension	Human Immunodeficiency Virus Type-1 (HIV-1) Infection

As shown in Table 0-1, all subjects will receive PRO 140 SC injection and Optimized Background Therapy.

Table 0-1: Open-label treatment extension phase [PRO 140 + OBT]

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 X 2 mL/inj.) per week	SC injection

The injectable study treatment (PRO 140) will be administered:

- by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or
- self-administered by subjects

Study participants will be monitored every 4 weeks for viral load and CD4 count. Should subjects experience virologic failure, they will be allowed to continue PRO 140 with existing OBT regimen while waiting for new regimen to be constructed by the Investigator.

Virologic failure is defined two consecutive HIV-1 RNA levels ≥ 400 copies/mL.

Subjects who experience virologic failure at any point during the Treatment Extension Phase will undergo the Virologic Failure (VF) Visit assessments and then return in 4 weeks (± allowed window) for the Safety Follow-up Visits.

Safety Follow-up Visit:

Duration of the Follow-up Phase is determined upon whether or not subject has experienced virologic failure during the Treatment Extension Phase.

- Subjects who experience virologic failure within Treatment Extension Phase will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels below level of detection) or up to a maximum of 6 months after cessation of therapy if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.
- Subjects who do not experience virologic failure at the end of Treatment Extension Phase, will be followed up every 2 weeks for total of 4 weeks.

Duration of Study:

- **Screening Phase:**
  - up to 21 days
- **Treatment Extension Phase:**

Name of Sponsor: CytoDyn, Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)	
Protocol Number: PRO 140 _CD02 Extension	**Therapeutic Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection

- weekly (± allowed windows) until subject withdraws consent, experience virologic failure or PRO 140 is approved or CytoDyn decides to discontinue its development

- **Follow-up Phase:**
  - 4 weeks* (± allowed windows)

    **or up to maximum of 6 months after experiencing Virologic Failure (VF) if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.*

Inclusion Criteria: Potential subjects are required to meet all of the following criteria for enrollment into the study.

1. Subjects who have completed 24 weeks of treatment in PRO 140_CD 02 or CD02_OpenLabel study, and Investigator believes subject requires continued access to PRO 140 in order to continue deriving clinical benefit and maintain HIV-1 viral suppression
2. HIV-1 RNA ≤ 50 copies/ml at T23 Visit in PRO140_CD02 or CD02_OpenLabel study
3. Both male and female patients and their partners of childbearing potential must agree to use 2 medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative urine pregnancy test prior to receiving the first dose of study drug.
4. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

Exclusion Criteria: Potential subjects meeting any of the following criteria will be excluded from enrollment.

1. Not currently enrolled in PRO 140_CD 02 or CD02_OpenLabel study
2. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)
3. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
4. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety measures

Statistical Considerations:

Name of Sponsor: CytoDyn, Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)	
Protocol Number: PRO 140 _CD02 Extension	**Therapeutic Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection

Sample Size Determination and Rationale:

Sample size determination is not applicable as only those subjects who are currently enrolled in PRO 140_CD 02 or CD02_OpenLabel study are allowed to participate in this study.

Analysis Populations:

The **Safety** population is defined as the set of subjects who received at least one dose of PRO 140. This population will be used for the analysis of safety parameters.

All safety data measures collected from the study will be presented as a by-subject listing and also summarized according to the variable type as:

- Continuous data summaries will include number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include frequency counts and percentage.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ART	Anti Retroviral Therapy
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Classification
AUC	Area Under Curve
°C	Celsius
CBC	Complete Blood Count
CCR5	C-C chemokine receptor type 5
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
cm	Centimeter
CRF	Case Report Form
C_{max}	Maximal Concentration
CRO	Contract Research Organization
CS	Clinically Significant
DAIDS	Division of AIDS
DNA	Deoxyribonucleic Acid
DO	Doctor of Osteopathic Medicine
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
Emax	Maximum drug effect
et al	et aliae; Latin for "and others"

Abbreviation	Term
EOT	End of Treatment
EOT2	End of Treatment Extension
°F	Fahrenheit
FDA	U.S. Food and Drug Administration
FDP	Fixed Dose Procedure
FU	Follow-Up
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCT	Hematocrit
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	id est; Latin for "that is"
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reactions
ITT	Intent-to-treat
IV	Intravenous
LAR	Legally Acceptable Representative
LDH	Lactate dehydrogenase
LPN	Licensed Practical Nurse
LVN	Licensed Vocational Nurse
mAb	Monoclonal Antibody
MD	Doctor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter

Abbreviation	Term
MOCA	Montreal Cognitive Assessment
MW	Molecular Weight
NCS	Not Clinically Significant
NP	Nurse Practitioner
NVF	Non-Virologic Failure
OBT	Optimized Background Therapy
PA	Physician Assistant
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
Pr	Protease
PT	Prothrombin Time
QC	Quality Control
RBC	Red Blood Cells
RN	Registered Nurse
RNA	Ribonucleic acid
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOP	Standard Operating Procedure
SV	Screening Visit
TE	Treatment Extension
TEAE	Treatment Emergent Adverse Events
ULN	Upper limit of normal
USA	United States of America
VF	Virologic Failure
WBC	White Blood Cells

1 INTRODUCTION

1.1 STATEMENT OF INTENT

The design, conduct and reporting of this trial shall be conducted in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing [redacted] as the Contract Research Organization (CRO).

1.2 THE PROBLEM STATEMENT

Though substantial progress has been made over the past two decades in the development of effective and well tolerated combination antiretroviral regimens, nearly 25% of patients receiving Highly Active Antiretroviral Therapy (HAART) are not virologically suppressed due to various reasons. Recent data suggest that most virologic failure on first-line regimens occurs because of either pre-existing (transmitted) drug resistance or suboptimal adherence. Patient- and regimen-related factors play a crucial role in determining whether an antiretroviral regimen is successful or result in virologic failure [Office of AIDS Research Advisory Council, 2014].

In general, drug resistance can be considered a core issue in patients with limited treatment options. However, there are other known factors apart from drug resistance (such as incomplete adherence, medication intolerance, pharmacokinetic issues, etc.) which also contribute to limiting treatment options in constructing a new regimen for patients who experience treatment failure. New agents and drug classes (e.g., integrase inhibitors, fusion inhibitors and CCR5 antagonists) are necessary to keep up with ongoing viral mutations in an attempt to prevent viral replication and transmission [Tang MW, 2012][Gulick RM, 2008][Moyle G, 2008]. The availability of an effective maintenance regimen would benefit a subset of HIV-1 infected persons who are challenged by transferred resistance, medication adherence and/or chronic nucleoside toxicity.

PRO 140 is a promising new antiretroviral agent that does not have any cross-resistance with drugs from other classes. Although PRO 140 would require subcutaneous (SC) administration, its favorable pharmacokinetics allows for weekly dosing. The purpose of this study is to exhibit antiviral activity of PRO 140 in combination with other antiretroviral agents for treatment of antiretroviral-experienced persons infected with CCR5-tropic HIV-1 virus.

1.3 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

PRO 140 is a humanized IgG4,κ monoclonal antibody (mAb) to the C-C chemokine receptor type 5 (CCR5), under development as a therapy for human immunodeficiency virus (HIV) infection.

PRO 140 binds to the N terminus (Nt) and the extracellular loop 2 (ECL2) domain of the CCR5 cell surface receptor that HIV-1 uses to gain entry to a cell. PRO 140 binding to CCR5 blocks viral entry by interfering with the final phase of viral binding to the cell surface prior to fusion of the viral and cell membranes. PRO 140 has been administered intravenously or subcutaneously to 174 HIV-1 infected individuals in Phase I/II studies of safety, tolerability, pharmacokinetics and pharmacodynamics [Jacobson JM, 2010][Jacobson JM, 2010]. The drug has been well tolerated following administration of single doses of 0.5 to 5 mg/kg or up to three weekly doses of up to 324 mg. Single subcutaneous doses of 324 mg have resulted in drops in plasma HIV-1 RNA levels of approximately 1.0 $\log_{10}$. Repetitive weekly administration of this dose of PRO 140 has been associated with drops in plasma HIV-1 RNA levels of approximately 1.5 $\log_{10}$. Serum concentrations of PRO 140 above the IC_{50} for clinical isolates of HIV-1 are maintained for at least 2 weeks following a single dose of 324 mg. Plasma HIV-1 RNA levels rise to baseline levels as PRO 140 is cleared from the plasma and, presumably, other compartments.

1.4 SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES

1.4.1 Pre-Clinical Studies with PRO 140

In vitro and *in vivo* preclinical studies have been conducted to determine the pharmacokinetic, immunogenicity, and toxicity profiles of PRO 140 following IV and SC administration. Several acute and chronic toxicity studies have been conducted to support the clinical development plan.

Acute toxicity of PRO 140 was evaluated in New Zealand rabbits, following IV administration of 5 or 15 mg/kg. Chronic toxicity was evaluated in cynomolgus monkeys following biweekly administration of IV doses up to 10 mg/kg for six months and biweekly administration of various SC doses up to 50 mg/kg for 24 weeks. The drug was generally well tolerated. Biweekly administration of IV doses up to 10 mg/kg for six months resulted in minimum to mild lymphoid hyperplasia in assorted lymph nodes and spleen, which was considered an expected immune response to a foreign protein. Biweekly administration of SC doses up to 50 mg/kg for 24 weeks resulted in minimum injection-site reactions (minimal, multifocal, mononuclear cell infiltrates in the subcutis), which were considered due to an inflammatory response to the injected antigen. Monkeys tolerated treatment with PRO 140 for 24 weeks without evidence of local or systemic toxicity. PRO 140 caused no mortality, cageside observations, in-life injection-site observations, or gross pathologic findings. Chronic treatment with PRO 140 did not affect body weight, food consumption, hematology, clinical chemistry or coagulation

parameters.

Both IV and SC administration resulted in elimination half-lives of approximately 200 hours, and overall exposure increased with increasing doses. Following SC administration of PRO 140 in monkeys, the maximal concentration (C_{max}) was achieved within 56 hours and bioavailability for PRO 140 after SC dosing was approximately 70%.

1.4.2 Clinical Studies with PRO 140

Current human experience with PRO 140 consists of seven completed clinical trials. These studies are summarized in Table 1-1. In all clinical trials, the majority of adverse events (AEs) were mild or moderate. No dose-limiting toxicities or patterns of drug-related toxicities were observed. Antiviral activity was potent, rapid, prolonged, dose-dependent, and highly significant.

1.4.2.1 PRO 140 1101 Study

For the first-in-human trial, PRO 140 1101, the drug was administered IV at 0.1, 0.5, 2.0, or 5.0 mg/kg and was generally well tolerated, non-immunogenic, and without clinically relevant toxicity. Treatment Emergent Adverse Events (TEAEs) did not increase with rising PRO 140 dose levels. 75% of subjects reported TEAEs, most of which were deemed unrelated to study treatment.

1.4.2.2 PRO 140 1102 Study

In PRO 140 1102 study, the majority of AEs, other than injection-site reactions, were considered mild and possibly related to drug administration. The majority of injection-site reactions were considered mild, self-resolving, and definitely related to drug administration. PRO 140 derived from Chinese Hamster Ovary (CHO) cells and administered SC at 100 mg/mL was generally well tolerated in healthy, normal volunteers. Overall, PRO 140 administered SC using Autoject® 2 appeared better tolerated than manual injection.

1.4.2.3 PRO 140 1103 Study

In PRO 140 1103 study, administration of PRO 140 at 350 mg using Autoject® 2 appeared well tolerated. Manual injections, on the other hand, were associated with a greater number of AEs. There did not appear, however, to be any substantial difference in subject perception of pain or discomfort related to site of drug administration. No anti-PRO 140 antibodies were detected in any subjects in this study. There was a tendency of higher exposure associated with SC administration of PRO 140 at 350 mg in the abdomen and the thigh. A higher number of AEs were associated with injections in the arm. Based on these observations, thigh and abdominal administration of PRO 140 were preferred over arm injection.

1.4.2.4 PRO 140 1302 Study

This initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only CCR5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks. Subjects (n=39) were randomized to receive a single IV injection of placebo or PRO 140 at doses of 0.5, 2, or 5 mg/kg. Subjects were monitored for antiviral effects, safety and PRO 140 pharmacokinetics (PK) for 58 days.

The study enrolled 31 males and 8 females. The median age, $CD4^+$ cell count and HIV-1 RNA at baseline were 40.3 years, 484cells/μL and 26,900 copies/mL, respectively. The baseline characteristics were similar for all treatment groups.

PRO 140 demonstrated potent, rapid, prolonged and dose-dependent antiviral activity (Figure 1-1 and Figure 1-2). A single 5mg/kg dose reduced viral loads by 1.83 log_{10} on average (Figure 1-2). These reductions represent the largest antiviral effects reported after just one dose of any HIV-1 drug [Jacobson JM, 2008]. In the 5 mg/kg group, mean viral load reductions of greater than 1 log_{10} were sustained for 2-3 weeks post-treatment (Figure 1-2).

Figure 1-1: PRO 140 1302 Study: Mean of the maximum (nadir) log_{10} reductions in HIV RNA

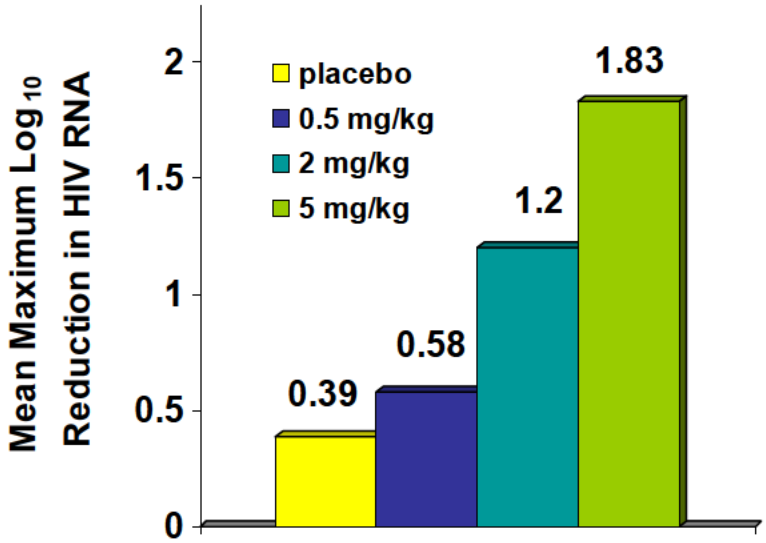
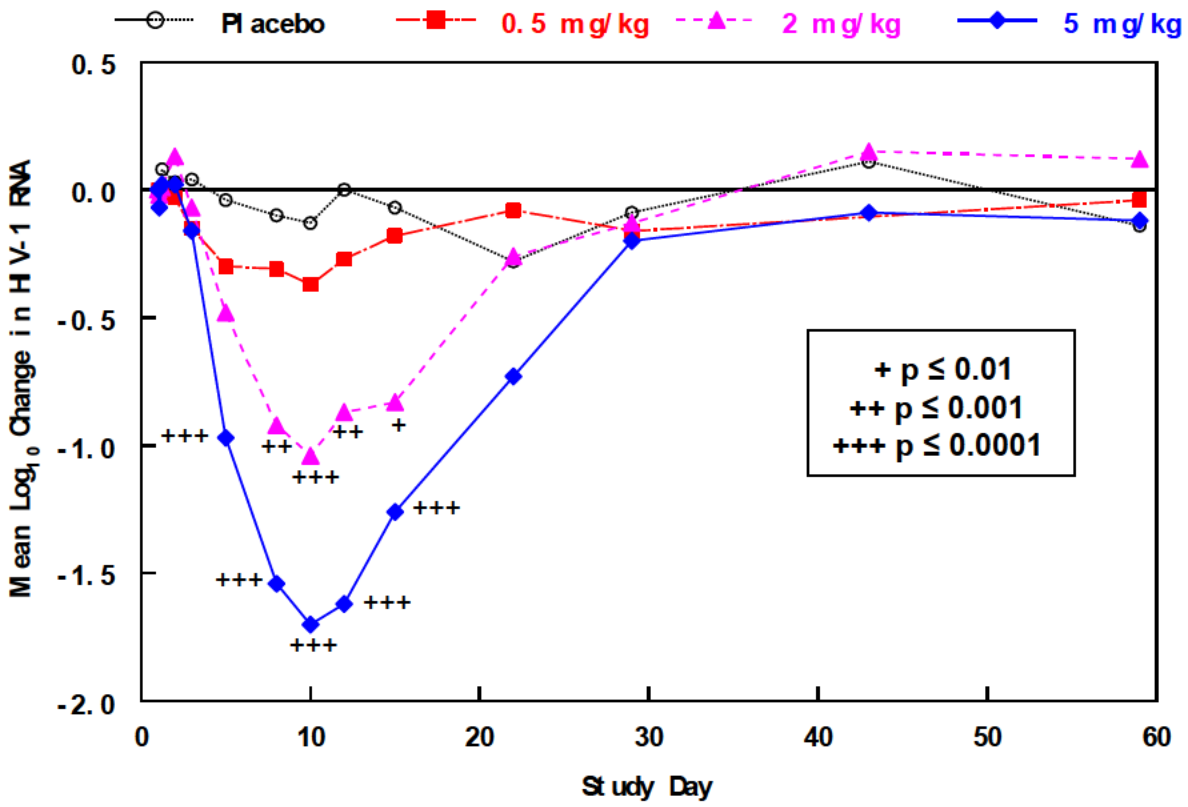


Figure 1-2: PRO 140 1302 Study: Mean log_{10} reductions in HIV RNA over time

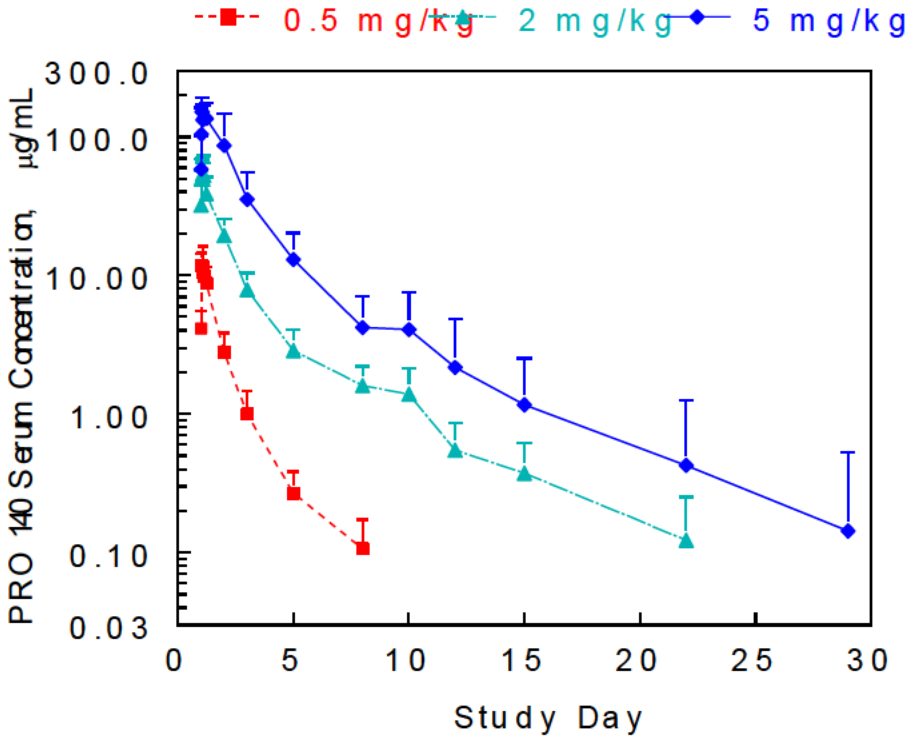


There was no change in CCR5 virus susceptibility to PRO 140 following treatment. All subjects had CCR5-only virus at screening in the first-generation Trofile assay. CCR5-only tropism results were observed in all subjects at all other timepoints, with two exceptions: One of nine (11%) of placebo subjects had dual/mixed virus at baseline and all subsequent timepoints, reflecting a spontaneous and stable switch in co-receptor tropism results. One of 30 (3%, 0.5 mg/kg group) had a dual/mixed tropism result on day 8 and CCR5-only results at all other timepoints, including the end of the day [Jacobson JM, 2008]. Clonal analysis of the dual/mixed virus revealed that it reflected outgrowth of pre-existing undetected virus rather than mutation of a CCR5 virus to a dual/mixed virus following treatment [Marozsan, 2008]. Therefore, no significant development of viral resistance to PRO 140 was observed despite potent and prolonged (2-3 weeks on average) viral suppression, followed by slow washout of the drug. Given that resistance to other classes of HIV-1 drugs can develop within one week of monotherapy [Demeter LM, 2000] [Saag, 1993][Richman, 1994], the findings indicate that PRO 140 presents a high barrier to viral resistance in vivo.

Figure 1-3 illustrates the mean serum concentrations of PRO 140 after IV injection. Serum levels increased with increasing dose. The mean Area Under Curve (AUC) from time zero to infinity (AUC_∞) values were 11.1, 74.3 and 278 mg x day/L for the 0.5, 2 and 5 mg/kg groups. The mean

serum half-life was 3.5-3.9 days in the two highest dose groups. In addition, PRO 140 significantly masked CCR5 on circulating lymphocytes for 2-4 weeks [Jacobson JM, 2008]. The PK and receptor occupancy data were broadly consistent with the duration of antiviral effects.

Figure 1-3: PRO 140 1302 Study: PRO 140 serum concentrations following a single intravenous injection in HIV- infected individuals.



The figure illustrates the mean serum concentrations over time by treatment group. The error bars depict standard deviations. The mean serum half-lives were 3.9 days and 3.5 days in the 2 mg/kg and 5 mg/kg dose groups, respectively.

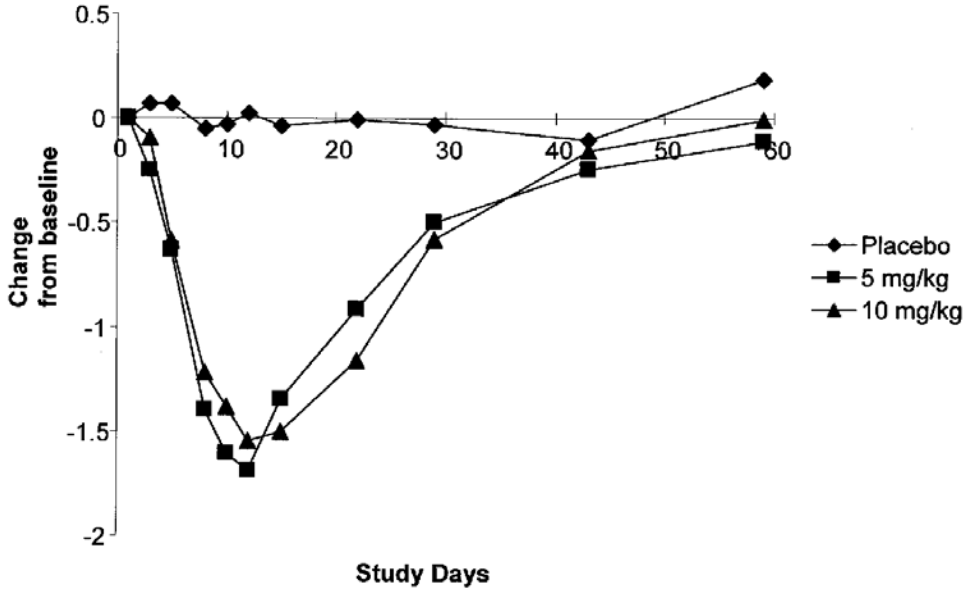
Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant effect on QTc interval intervals or other electrocardiographic parameters, and there were no remarkably laboratory findings. There was no loss or depletion of $CD4^+$ or $CCR5^+$ cells from the circulation. At the 5 mg/kg dose, there was a trend towards increased $CD4^+$ cell counts from baseline, with mean changes of +129, +96 and +83 cells/µL observed on days 8, 15, and 22, respectively.

1.4.2.5 PRO 140 2301 Study

PRO 140 2301 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in 30 male and female adult subjects infected with HIV-1. Subjects were randomized to one of three groups (N=10/group), each receiving one of three treatments: (i) a single IV dose of 5 mg/kg by 30-minute IV infusion; (ii) a single IV dose of 10 mg/kg by 30-minute IV infusion; (iii) a single placebo dose by 30-minute IV infusion. The objective of the study was to assess and characterize the PK and PD of PRO 140 administered by IV infusion, assess efficacy at a new dosage level, and safety and tolerability of single doses of PRO 140.

All PRO 140-treated subjects had more than 10-fold reduction in viral loads (mean max log_{10} reductions were 1.83 for treatment groups and 0.32 for placebo) (Figure 1-4). Both the 5 mg/kg and 10 mg/kg doses have shown favorable tolerability and no dose-limiting toxicity has been observed. High levels of receptor occupancy (>85% reduction in the number of cells detected) were observed for 29 days after treatment with both 5 and 10 mg/kg doses.

Figure 1-4: PRO 140 2301 Study: Mean change from baseline in HIV-1 RNA (Log_{10} copies/mL) over Time (ITT Subjects)



1.4.2.6 PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only CCR5 HIV-1 detectable, and no antiretroviral therapy for 12

weeks [Thompson, 2009]. Placebo (n=10) and three PRO 140 doses were examined: 162mg weekly for three weeks (n=11), 324mg weekly for three weeks (n=11), and 324mg biweekly (every other week) for two doses (n=12). Subjects were followed for 44 days after the final dose. The study enrolled 40 males and 4 females. The median age, weight, $CD4^+$ cell count and HIV-1 RNA at baseline were 42.3 years, 79.1 kg, 410 cells/μL and 20,000 copies/mL, respectively. Baseline characteristics were similar for the different treatment groups.

Potent, dose-dependent and highly statistically significant antiviral activity was observed (Figure 1-5 and Figure 1-6). The 324mg weekly dose resulted in a mean 1.65 log_{10} reduction in viral load, and highly significant reductions were observed for the other dose groups as well (Figure 1-5). There was no viral rebound between 324mg doses, and the antiviral effects persisted for one week after the final dose (Figure 1-6). The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection [Thompson, 2009].

Figure 1-5: PRO 140 2101 Study: Mean of the maximum (nadir) log_{10} reductions in HIV RNA

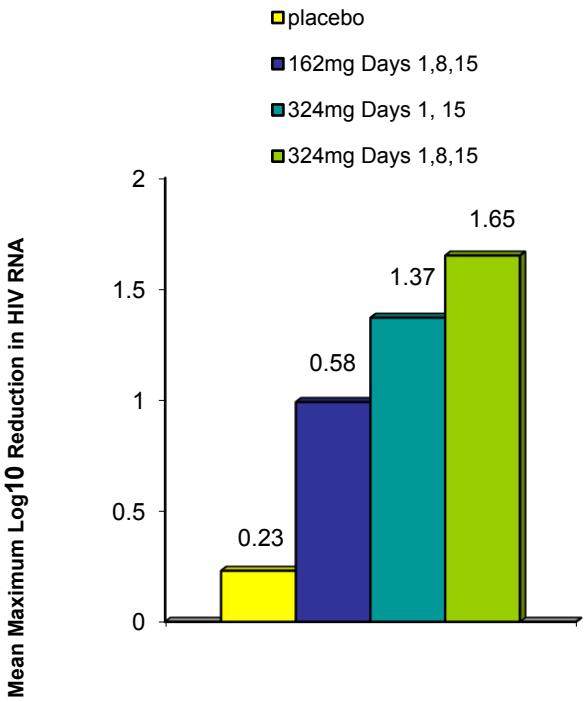
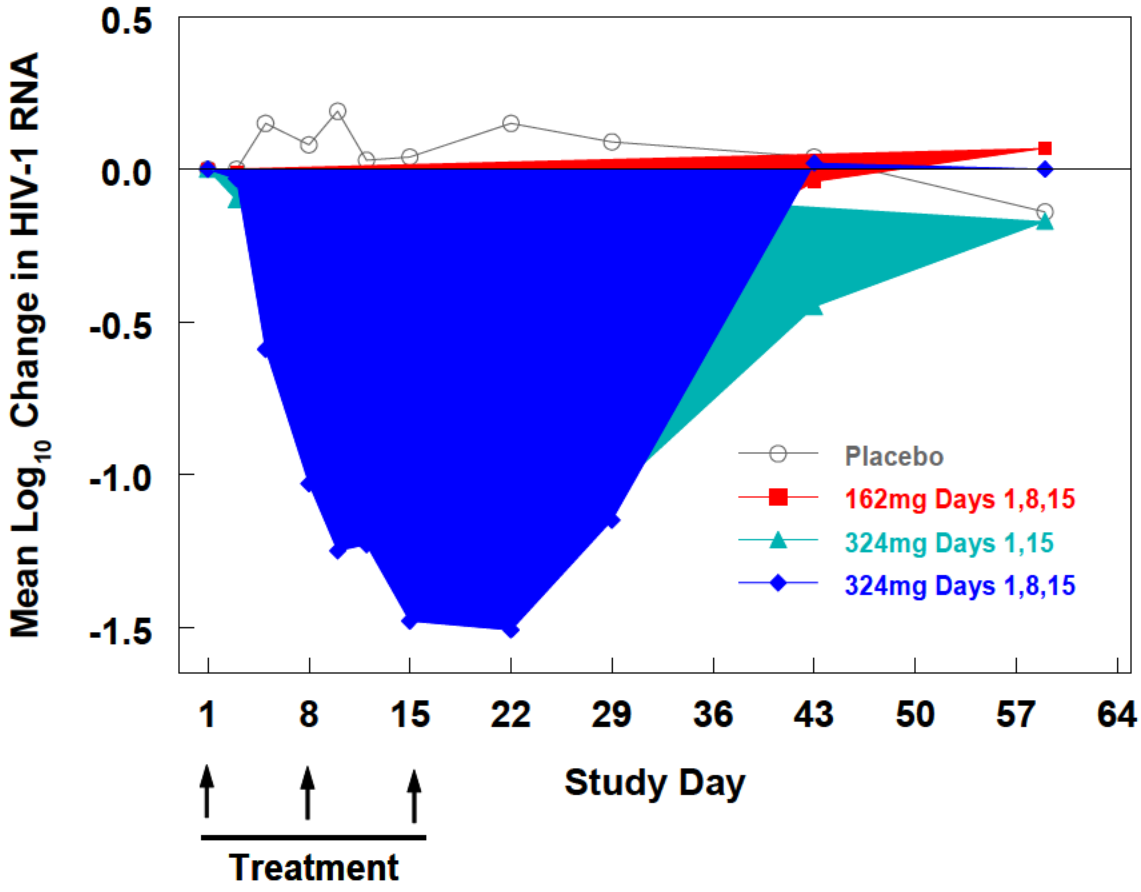


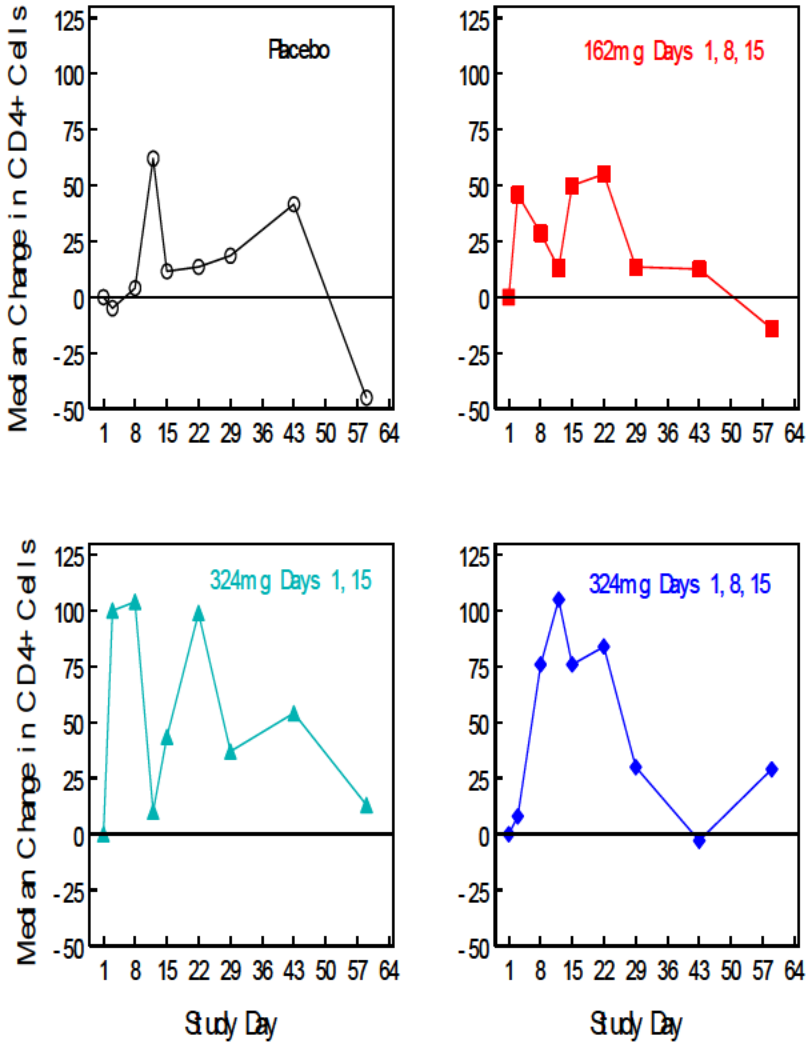
Figure 1-6: PRO 140 2101 Study: Mean change from baseline in HIV-1 RNA (Log_{10} copies/mL) over Time (ITT Subjects)



Subcutaneous PRO 140 was generally well tolerated both locally and systemically. There was no obvious dose-related pattern of toxicity. The most common adverse events (diarrhea, headache, lymphadenopathy and hypertension) were mild to moderate and self-resolving. These events are common in HIV infection and were reported with similar frequencies in the placebo and PRO 140 treatment groups. Administration-site reactions were mild, transient, and observed in a fraction of subjects. There was a trend towards increased CD4+ cell counts in subjects treated with PRO 140 (Figure 1-7). Based on its encouraging antiviral and tolerability profiles and the convenience of weekly self-administration, SC PRO 140 has been selected for further clinical development.

Figure 1-7: Change in CD4+ cell counts in subjects treated with subcutaneous PRO 140.

Subjects (n=10 to 12 per group) were randomized to received placebo weekly (Days 1, 8, 15), 162mg PRO 140 weekly (Days 1, 8, 15), 324mg PRO 140 biweekly (Days 1, 15, with placebo on Day 8), or 324mg PRO 140 weekly (Days 1, 8, 15). CD4+ cell counts were measured over time, and the median change from baseline was determined for each treatment group.



1.4.2.7 PRO 140 _CD01 Study

PRO 140_CD01 study (open-label, 43 subjects, multi-center) (12-cohort 1, 28-cohort 2, 3-cohort 3) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution

of antiretroviral therapy in HIV-1 infected patients (with exclusive CCR5-tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty (43) subjects (M/F: 40/3) with median age of 55.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-three out of 43 (54%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels ≥ 400 copies/mL separated by at least 3 days.

Of the first 40 enrolled subjects enrolled under cohort 1 and cohort 2, three subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 40 subjects were found to have exclusive CCR5-tropic virus. A letter of amendment was filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects enrolled in the study.

All virologic failure subjects who had available lab data in both studies achieved viral suppression to < 400 HIV-1 RNA copies/mL, as well as viral suppression to 'Non Detectable' or < 50 HIV-1 RNA copies/mL after re-initiation of ART.

The by-subject analysis of PhenoSense® Entry Assay data for PRO140, maraviroc, and AMD3100 shows no significant changes in the post-treatment IC50 and IC90 values were noted when compared with baseline values in virologic failure and non-virologic failure groups of subjects.

Anti-PRO140 antibodies were not identified in any available post-treatment sample and data derived from the CD01 study further supports the favorable PRO140 PK profile data generated from both pre-clinical as well as prior Phase 1/2 clinical trials.

Safety data were analyzed for all 43 enrolled subjects. One (1) of 43 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-nine (29) of 43 subjects (67%) experienced one or more adverse events (AEs) after receiving at least one dose of PRO140. The most commonly occurring AEs were infections and infestation conditions which were reported by 14 of 43 (32.5%) subjects. The majority of the reported AEs (70/87; 80.4%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported AEs (72/89; 80.8%) were deemed mild in nature.

1.4.2.8 PRO 140 _CD01-Extension Study

PRO 140_CD01-Extension study (open-label, 17 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 160 weeks) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral

therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy for up to 160 weeks.

A total of 17 subjects are participating in the CD01-Extension study of which one subject was considered not eligible as subject experienced virologic failure prior to first extension treatment.

Sixteen (16) eligible subjects (M/F: 14/2) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled in an extension study. One patient discontinued at week 37 (with viral load of <40 copies/mL) due to relocation. Two subjects were withdrawn due to non-treatment related SAEs at week 140 and 149, respectively. One subject was withdrawn due to re-starting their ART at week 99. Two subjects withdrew consent at week 81 and 139, respectively. Five (5) subjects experienced virologic failure (VF) (two consecutive viral loads ≥400 copies/mL). The mean time to virologic failure was 329 days (106-691).

Five (5) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than three years of treatment (175-198 weeks). Overall, 12 subjects completed at least one year of treatment and 9 subjects completed at least two years of treatment in this study

PRO140 was generally well tolerated, and no drug-related SAEs were observed.

This clinical study is currently ongoing.

1.4.2.9 PRO 140 _CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 52 subjects, multi-center) evaluated the efficacy, safety, and tolerability of PRO 140 in combination with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks in patients infected with HIV-1. The study population included 52 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who demonstrated evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented history of genotypic or phenotypic resistance to at least one ART drug within three drug classes (or within two or more drug classes with limited treatment options). The options may be limited as a result of drug antiviral class cross-resistance or documented treatment intolerance.

In double-blind treatment period, virally non-suppressed subjects were randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days. The primary efficacy endpoint was proportion of participants with ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

During the 24-week open-label period, all subjects received PRO 140 along with Optimized Background Therapy (OBT).

This clinical study is completed.

1.4.2.10 PRO 140 _CD02 Open Label

PRO140_CD02 Open Label (open label, single-arm, 25 subjects, multi-center) seeks to evaluate the efficacy, clinical safety and tolerability parameters of PRO140 in combination with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks. The patient population for this trial is treatment-experienced HIV-infected patients with CCR5-tropic virus and demonstrates evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented genotypic or phenotypic resistance to ART drugs within three drug classes (or within two drug classes with limited treatment options).

This clinical study is currently ongoing.

1.4.2.11 PRO 140 _CD03 Study

PRO 140_CD03 study (open-label, two-arm comparator, 500 subjects, multi-center) seeks to evaluate the treatment strategy of using PRO 140 SC as a long-acting single-agent maintenance therapy versus continuing combination ART for 48 weeks in virologically suppressed subjects with CCR5-tropic HIV-1 infection. The first ~150 eligible subjects were enrolled to receive PRO 140 350mg SC weekly injection in a single-arm study. Subsequently, next ~150 subjects were randomized 1:1 to PRO140 350mg (Group A) or PRO 140 525mg (Group B).

An additional ~200 subjects will be randomized 1:1 to PRO 140 525mg (Group B) or PRO 140 700mg (Group C).

This clinical study is currently ongoing.

1.4.2.12 PRO 140 _CD03 Extension Study

PRO 140_CD03 Extension study (open label, 300 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 weekly injection as long-acting single-agent maintenance therapy versus continuing combination ART in patients infected with HIV-1. The study population includes treatment-experienced HIV-infected adult patients with CCR5-tropic virus who successfully completed PRO 140_CD03 study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

Table 1-1: Clinical Studies with PRO 140

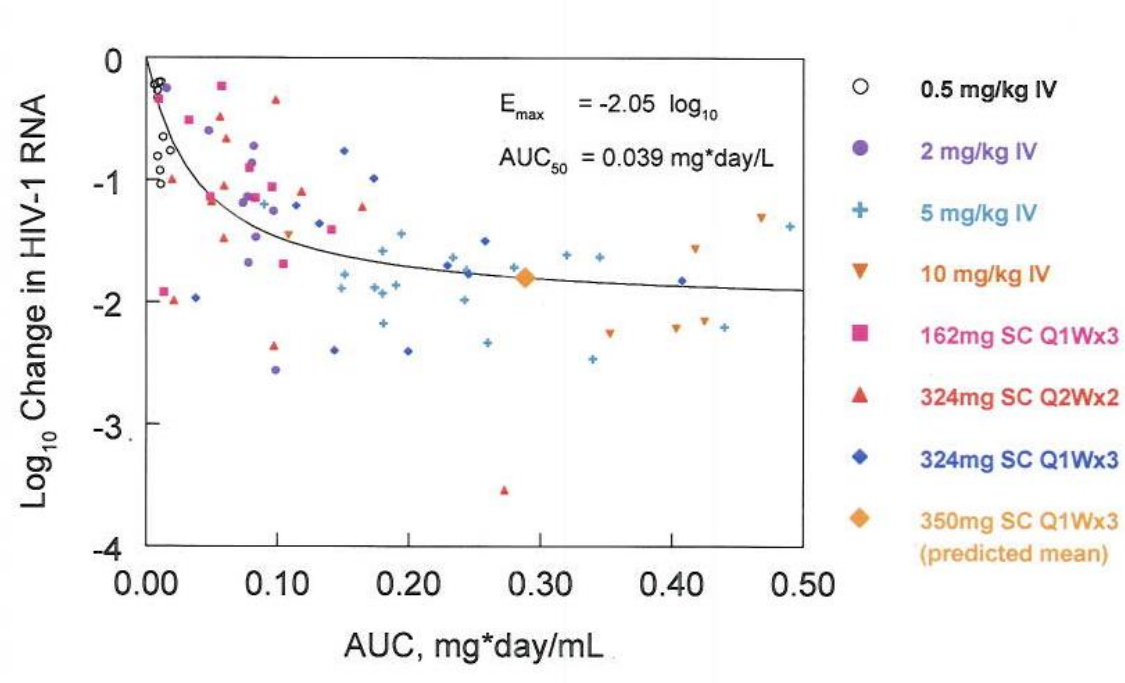
Protocol Number	Phase	No. of Subjects (Planned/Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
PRO 140 1101	1	20/20	Single 0.1, 0.5, 2.0, or 5.0 mg/kg	Sp2/0 myeloma	Healthy	Generally well tolerated; non-immunogenic; dose-dependent coating of CCR5; significant coating of CCR5 over placebo at 0.5, 2, and 5 mg/kg
PRO 140 1102	1	20/20	Either two or three doses totaling 200 or 350 mg respectively	CHO	Healthy	Generally well tolerated; drug derived from CHO cells well tolerated also; SC administration by Autoject® 2 better tolerated than manual injection
PRO 140 1103	1	15/14	Two doses, each of 350 mg	CHO	Healthy	More AEs associated with arm injection; trend of lower exposure in arm injections; thigh and abdominal administration preferred
PRO 140 1302	1b	40/39	Single 0.5, 2.0, or 5.0 mg/kg	Sp2/0 myeloma	HIV-1 positive	Generally well tolerated; antiviral suppression maintained for approx. 10 days with higher doses; favorable tolerability and potent, dose-dependent antiviral activity provide proof-of-concept
PRO 140 2301	2a	30/31	Single 5.0 or 10.0 mg/kg	CHO	HIV-1 positive	Generally well tolerated with no dose-limiting toxicities; potent antiviral suppression maintained for approx. 20 days when administered IV at 5 or 10 mg/kg. No dose-limiting toxicities at 10 mg/kg.
PRO 140 2101	2a	40/44	Three doses of 162 or 324 mg each	CHO	HIV-1 positive	Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; antiviral activity was statistically significant; two-fold exposure at higher dose; single dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity.
PRO 140	2b	43/43	350 mg SC weekly	CHO	HIV-1 positive	Generally well tolerated, no drug-related SAEs,

Protocol Number	Phase	No. of Subjects (Planned/Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
_CD01			dose for 12 Weeks of Monotherapy (total treatment duration 14 Weeks)			weekly dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity. Data under review and results are pending publication.
PRO 140 _CD01-Extension	2b	17/17	350 mg SC weekly dose for 160 Weeks of monotherapy (total treatment duration 161Weeks)	CHO	HIV-1 positive	This clinical study is currently ongoing.
PRO 140 _CD02	2b/3	50/52	350 mg SC weekly dose for up to 25 weeks in conjunction with existing ART followed by OBT	C HO	HIV-1 positive	This clinical study is completed
PRO140_CD 02 Open Label	2b/3	25/2	700mg SC + existing ART for 1 week followed by 700mg SC weekly OBT for 24 weeks	CHO	HIV-1 positive	This clinical study is currently ongoing
PRO 140 _CD03	2b/3	500/TBD	350 mg, 525mg, or 700mg SC weekly dose for up to 48 weeks of monotherapy	CHO	HIV-1 positive	This clinical study is currently ongoing
Pro140_CD0 3 Extension	2b/3	300/TBD	350mg SC weekly monotherapy dose	CHO	HIV-1 positive	This clinical study is currently ongoing

1.5 RATIONALE FOR DOSE SELECTION

The dose of 350 mg administered SC was chosen in light of a previous analysis suggesting that such a dose would be likely to provide maximal viral load suppression. In studies with antiviral agents that block viral entry through the CCR5 receptor, there is a general consensus that in order to achieve robust antiviral effects and minimize the potential for drug resistance in combination therapy, the dose of drug should result in exposures that fall on the plateau of a Maximum Drug Effect (Emax) plot.

Figure 1-8: Emax analysis of antiviral data generated with IV and SC PRO 140.



The maximal viral load reduction was analyzed with regard to drug exposure for PRO 140. Figure 1-8 above shows this relationship. Analysis shows that PR0 140 350mg weekly dose is expected to fall on the plateau of the Emax plot.

The maximal change in HIV-1 viral load from baseline was determined at any point 59 days after initiation of therapy. To allow approximate comparisons between the IV and SC doses, the overall AUC observed for repeat SC doses was conservatively estimated by multiplying the measured AUC0-7d by the number of doses administered. Viral load and AUC data were fit to an Emax equation: E = Emax x AUC/(AUC + AUC50). The orange diamond indicates projected data for three weekly 350 mg doses based on the mean exposure observed in the PRO 140 1103 study.

It is important to note that when larger proteins (MW> 10,000) are administered SC, they initially traffic through the lymphatic system. Uptake into the bloodstream occurs after the proteins reach the thoracic duct [Nishikawa M, 2005].

In addition, based on pharmacodynamic data from our prior SC and IV studies, maximum virologic suppression is expected to be achieved with trough concentrations that equal or exceed approximately 5 µg/mL.

Finally, the mean nadir reduction in viral load achieved with 3 weekly 324 mg SC doses (1.65 log_{10}) was similar to the mean nadir reductions observed with single 5 or 10 mg/kg IV doses (1.8 log_{10} in each case), and higher viral load reductions are expected in the present study based on the use of the 350 mg CHO formulation. Overall, several lines of evidence indicate that maximum virologic suppression will be achieved with 350 mg weekly dosing in the present study.

Majority of subjects receiving 350 mg weekly SC dosing in monotherapy setting experienced virologic failure in CD01-Extension study. Review of PRO 140 clinical data to date with 350mg SC weekly dosing, suggests no evidence of emergence of viral isolates with reduced susceptibility to PRO 140, no altered viral tropism or anti-PRO 140 antibodies formation suggesting the most likely cause of viral rebound is inadequate dosing to fully cover CCR5 receptor populations. Based on pharmacologic modeling studies, we anticipate that the 700mg dose will result in a lower fraction of study participants with trough levels below that which will 'uncoat' a significant number of CD4 cells (i.e., less than a certain multiple of the IC50 or IC90 for PRO 140).

As of Protocol v4.0, newly enrolled subjects will receive 700 mg. The dose of 700 mg administered SC was chosen to provide maximum viral load suppression in a heavily treatment experienced population to avoid developing resistance to current OBT therapies.

1.6 RISKS / BENEFITS ASSESSMENT

1.6.1 RISKS/DISCOMFORT TO SUBJECTS AND PRECAUTIONS TO MINIMIZE RISK

1.6.1.1 Risks associated with virologic failure

Subjects participating in the PRO140_CD02 or CD02 Open Label study will continue to receive study treatment (PRO 140 700mg SC injection) in addition to Optimized Background Therapy (OBT). Addition of study treatment (PRO 140 700mg SC injection) to OBT may not be effective for continued suppression of viral load for all subjects.

Note: Investigator will construct a new HAART regimen should viral rebound occur, where HIV-1 viral load meets virologic failure criteria.

Note: Subjects enrolled prior to Protocol v4.0 may still be receiving the original 350mg dose and

have the option of increasing their dose to 700mg.

1.6.1.2 Allergic Reaction

PRO 140 belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions (fatigue, diarrhea, fever, vomiting, headache, nausea, pain at the site of injection, low blood pressure, rash, itching, and chills) or flu-like reactions such as fever, chills, and aches. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of PRO 140, infusion of proteins always carries with it the theoretical risk for anaphylactic shock. Accordingly, whenever PRO 140 is initially administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

1.6.1.3 Immune Response

Subjects who take PRO 140 or other monoclonal antibodies can also develop an immune response to PRO 140 that may affect their ability to receive monoclonal antibodies, or to benefit from diagnosis or therapy with a monoclonal antibody in the future.

1.6.1.4 Pregnancy

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized).

1.6.1.5 Venipuncture

Blood sampling is required as part of the study protocol. Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

1.6.1.6 Risks to the Study Personnel and the Environment

The principal risk in the clinical setting is in the handling of needles that may be contaminated with HIV, or other human pathogens. Adherence to universal precautions for working with infectious agents will reduce the risk of exposure to these individuals. All bio-hazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site Standard Operating Procedures (SOPs).

1.6.1.7 Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

1.6.1.8 Theoretical risk for increased severity of West Nile virus infection

Individuals who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus [Thompson, 2009] Because of this, treatment with CCR5 co-receptor antagonists poses a theoretical risk for increased severity of West Nile virus infection. However, this concern is mitigated by several factors. First, no increased risk was observed for individuals who possess one functional and one non-functional CCR5 gene, indicating that an intermediate amount of CCR5 is sufficient for defense against West Nile virus [Thompson, 2009]. Second, use of CCR5 co-receptor antagonists is unlikely to completely abrogate CCR5 function, and there has been no association reported to date between CCR5 co-receptor use and severe West Nile virus. Additionally, PRO 140 weakly antagonizes the natural activity of CCR5 and thus is less likely to adversely affect immune function. Furthermore, this has not been established to be a risk with maraviroc, the anti-CCR5 drug already FDA-approved for the treatment of HIV.

Collectively, the experience with both IV and SC, simulation modeling and the recent confirmation that a higher concentration of PRO 140 synthesized using a highly efficient CHO cell line can be conveniently and safely administered has resulted in the design of the current study.

1.6.2 INTENDED BENEFIT FOR SUBJECTS

This study provides an opportunity for subjects to have once weekly SC treatment with PRO 140 in addition to an optimized and simplified ART regimen. Subjects participating in this combination therapy study will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

2 STUDY OBJECTIVES

The primary objective is to provide continued access to PRO 140 to subjects who complete participation in PRO140_CD02 or CD02_OpenLabel and continue to receive clinical benefit and would require PRO 140 to form a viable regimen, in the opinion of the treating physician.

Study endpoints include mean change in viral load (HIV-1 RNA levels) at the conclusion of the treatment period, mean change in CD4 cell count at the conclusion of the treatment period, emergence of Dual/Mixed (D/M)- and CXCR4-tropic virus in patients who had exclusive CCR5-tropic virus at study entry, tolerability of repeated subcutaneous administration of PRO 140 as assessed by investigator-evaluation of injection site reactions, frequency of treatment-related adverse events resulting in study drug discontinuation, frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale and frequency of treatment–emergent serious adverse events

3 STUDY DESIGN

This is an extension study, to provide continued access to PRO 140 to subjects who complete participation in PRO140_CD02 or CD02_OpenLabel and continue to receive clinical benefit and would require PRO 140 to form a viable regimen, in the opinion of the treating physician. The patient population for this trial is treatment-experienced HIV-infected patients with CCR5-tropic virus who demonstrate evidence of HIV-1 suppression after successfully completed 24 weeks of treatment in the PRO140_CD02 or CD02_Open Label study.

Subjects participating under Protocol versions 1.0-3.0 received 350 mg of PRO 140. Dose was increased from 350 mg to 700 mg weekly to provide maximum viral load suppression in a heavily treatment experienced population to avoid developing resistance to current OBT therapies.

Those that were enrolled under version 1.0-3.0 have the option of remaining on their current dose of 350mg or increasing their dose to 700 mg for the remainder of the trial.

The study is divided into three phases: Screening, Treatment Extension and Follow-up.

Screening Phase begins with signing of Informed Consent and lasts up to 21 days. All subjects will continue taking PRO 140 SC injection in addition to OBT during the Screening Phase.

Subject will enter the Treatment Extension Phase as soon as HIV-1 viral load results are available for review by Investigator. Treatment Extension Phase consists of weekly study treatment injections along with OBT. Study participants will be regularly monitored for viral load and will cease weekly study treatment injections should they experience virologic failure. Virologic failure is defined two consecutive HIV-1 RNA levels $\geq$ 400 copies/mL.

Note: Subjects will be allowed to continue PRO 140 with existing OBT regimen while waiting for new regimen to be constructed by the Investigator.

Subjects who experience virologic failure at any point during the Treatment Extension Phase will undergo the Virologic Failure (VF) Visit assessments and will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels below level of detection) or up to a maximum of 6 months after cessation of therapy if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression. Subjects who do not experience virologic failure, will be followed up every 2 weeks for total of 4 weeks.

3.1 STUDY CENTER(S)

Up to 30 centers in the United States

3.2 STUDY POPULATION

Study population includes treatment-experienced HIV-infected patients with CCR5-tropic virus that successfully complete 24 weeks of treatment with PRO140 in addition to Optimized Background Therapy within the PRO140_CD02 or CD02_OpenLabel protocol. Investigator believes subject requires continued access to PRO 140 in order to continue deriving clinical benefit and maintain HIV-1 viral suppression.

3.3 ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

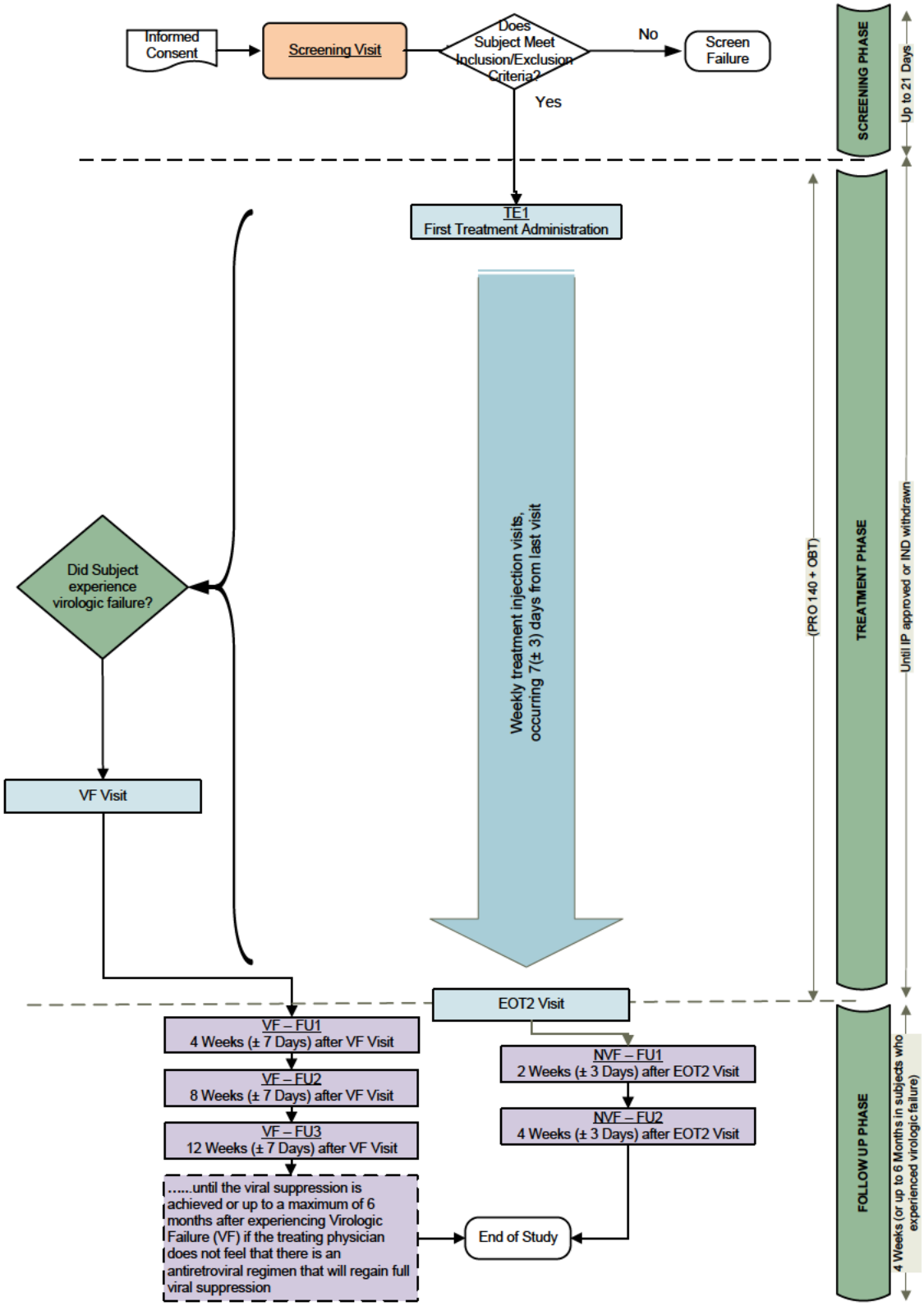
1. Subjects who have completed 24 weeks of treatment in PRO 140_CD 02 or CD02_OpenLabel study, and Investigator believes subject requires continued access to PRO 140 in order to continue deriving clinical benefit and maintain HIV-1 viral suppression.
2. HIV-1 RNA <50 at T23 Visit in PRO140_CD02 or CD02_Open Label study
3. Both male and female patients and their partners of childbearing potential must agree to use 2 medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative serum pregnancy test at Screening visit and negative urine pregnancy test prior to receiving the first dose of study drug.
4. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

3.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Not currently enrolled in PRO 140_CD 02 or CD02_OpenLabel study
2. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi’s sarcoma)
3. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
4. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety measures

Figure 3-1: Study Flow Diagram



4 STUDY SCHEDULE

This study is divided into three phases: Screening, Treatment and Follow-up.

(1) **Screening Phase:** This phase lasts up to 21 days and begins with signing of Informed Consent. Assessments performed during this phase determine the subject's final eligibility for study participation. Subjects who meet all eligibility criteria will receive first treatment injection at Treatment Extension Visit 1 (*which corresponds to EOT from PRO140_CD02 or CD02_OpenLabel study*).

All subjects will continue taking PRO 140 along with OBT during the Screening Phase.

Note: Subject consent and screening assessments should be completed prior to EOT visit in the PRO140_CD02 or CD02_OpenLabel study.

(2) **Treatment Extension Phase:** Subjects will receive weekly treatments (window period of ±3 days) until virologic failure is experienced, consent is withdrawn, the study drug is approved, or the trial is completed/ended by CytoDyn, whichever comes first.

Virologic failure is defined as two consecutive HIV-1 RNA levels ≥ 400 copies/mL.

Subjects who meet all eligibility criteria will receive first treatment injection at Treatment Extension Visit 1 (*which corresponds to EOT from PRO140_CD02 or CD02_OpenLabel study*).

PRO 140 will be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or self-administered by subjects.

Any time during the Treatment Extension Phase, if virologic failure occurs, Investigator will readjust antiretroviral regimen based on HIV-1 genotypic and/or phenotypic drug resistance results obtained during the VF visit.

Subjects will be allowed to continue PRO 140 with existing OBT regimen while waiting for new regimen to be constructed by the Investigator.

(3) **Follow-Up Phase:** The duration of follow-up depends on whether or not subject has experienced virologic failure during the Treatment Extension Phase.

- Subjects who experience virologic failure within Treatment Extension Phase will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels below level of detection) or up to a maximum of 6 months after cessation of therapy if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.
- Subjects who do not experience virologic failure at the end of Treatment Extension Phase, will be followed up every 2 weeks for total of 4 weeks.

Procedures to be performed during each of these study phases are described below and provided as a Schedule of Assessments in Table 4-1 and Table 4-2.

Table 4-1: Schedule of Assessments – Screening and Treatment Phase[a]

Procedure/Assessments	Screening	Treatment Phase				
Visit	Screening (T23/24/25)	TE1[b] (EOT)		Subsequent TE Visits (weekly ±3 days)	EOT2	VF
		Pre-treatment	Post-treatment			
Informed Consent[1]	X					
Subject Demographics	X					
Medical & HIV History[2]	X					
Eligibility	X	X				
Physical Examination	X[3]	X		X[3]	X	X[3]
Neurological Examination[4]	X	X			X	X
Vital Signs[5]	X	X	X	X	X	X
ECG	X				X	
Complete Blood Count[6]		X		X[15]	X	X
Biochemistry[7]		X		X[15]	X	X
Coagulation[8]		X		X[15]	X	X
Urinalysis[9]		X		X[15]	X	X
Urine pregnancy test[10]		X				
Plasma HIV-1 RNA level[11]	X	X		X	X	X
TruCount T assay[11]	X	X		X	X	X
PRO 140 + OBT Regimen	X	X		X	X	
Injection Site Reaction Assessment - Investigator[12]	X		X	X	X	
HIV-1 Trofile® RNA + PhenoSense Entry Assay[13]						X
HIV-1 Drug Resistance Assay[14]						X
CCR5 Receptor Occupancy [16]				X		
Adverse Events	X		X	X	X	X
Concomitant Medications	X	X		X	X	X

X (red bold with yellow highlight): Activities performed under PRO 140_CD02 or CD02_OpenLabel study protocol

[a] Schedule of assessment (Screening/Treatment Phase) can be modified by the Investigator based on clinical judgment and in the best interest of the subject.
[b] Subject eligibility should be confirmed prior to study treatment administration at TE1.

Foot Notes:

[1] Informed consent must be obtained prior to subject participation in any protocol-related activities that are not part of routine care.

[2] Medical history, past surgeries, disease history, history of substance abuse, social history, blood transfusion history, and current therapies (medications and non-medications) will be brought forward from PRO140_CD02 or CD02_OpenLabel.

[3] Symptom-directed physical examination. Complete physical examination at TE1, EOT2 and VF.

[4] The screening tool for this assessment is based on the three question survey used by Simioni et al. (Simioni S, 2010). Additional modalities may be used for this assessment at the discretion of the Investigator.

[5] Vital signs (i.e., blood pressure, heart rate, respiration rate and temperature) will be recorded post-treatment whenever IP administered at the clinic.

[6] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets.

[7] Serum Biochemistry

Hepatic function indicators: total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, Lactate dehydrogenase (LDH)

Renal function indicators: BUN, creatinine

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total)

[8] Prothrombin time (PT) and International Normalized Ratio (INR)

[9] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment.

[10] ONLY performed on women of childbearing potential. Subject will not be allowed to participate if the result is positive.

[11] Plasma HIV-1 RNA and TruCount T Assay will be performed once every 4 weeks when subject comes to clinic. TruCount T Assay includes: CD3 %, CD4 %, CD8 %, Absolute Lymphocytes, CD3 cell count, CD4 cell count, and CD8 cell count

[12] Injection Site Reaction will be assessed by the Investigator whenever IP administered at the clinic.

[13] Monogram Biosciences Trofile® RNA and PhenoSense® Entry Assays [AMD3100 (CXCR4 inhibitor drug), Maraviroc and PRO 140 (CCR5 inhibitor drugs)]

[14] Monogram Biosciences PhenoSense® GT Assay

[15] Every 12 weeks during Treatment Extension.

[16] Refer to Section 7.11.10.

Table 4-2: Schedule of Assessments –Follow-Up (FU) Phase

(a) Subjects who do NOT experience virologic failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2
	NVF-EFU1	NVF-EFU2
Window Period	2 weeks (±3 days) after EOT2 visit	4 weeks (±3 days) after EOT2 visit
Physical Examination	X[1]	X[1]
Vital Signs	X	X
Plasma HIV-1 RNA level	X	X
TruCount T assay	X	X
Adverse Events	X	X
Concomitant Medications	X	X

[1] Symptom-directed physical examination

(b) Subjects who experience virologic failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2	Follow-Up Visit -3[1]
	VF-EFU1	VF-EFU2	VF-EFU3
Window Period	4 weeks (±7 days) after VF visit	8 weeks (±7 days) after VF	12 weeks (±7 days) after VF
Physical Examination	X[2]	X[2]	X[2]
Vital Signs	X	X	X
Plasma HIV-1 RNA level	X	X	X
TruCount T assay	X	X	X
Adverse Events	X	X	X
Concomitant Medications	X	X	X

[1] Subject will be followed up till the viral suppression is achieved or up to a maximum of 6 months after experiencing Virologic Failure (VF) if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.

[2] Symptom-directed physical examination

4.1 SCREENING PHASE

The subject will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. The unique identification number (screening number) assigned to each subject under PRO140_CD02 or CD02_OpenLabel study will be retained.

All study centers will be instructed to maintain the study-specific screening and enrollment logs at their sites.

Once the ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility including:

- Demographic information (see section 7.3),
- Prior and current medications review (see section 7.6),
- Symptom-directed physical examination (see section 7.7),
- Electrocardiogram (ECG) (see section 7.8),
- Vital Signs (see section 7.10),
- Collection of Blood Specimens (see section 7.11) for
    - Plasma HIV-1 RNA level
    - TruCount T Assay

All screening information will be fully documented in the subject's medical records (i.e., source documents).

- For consented subjects who do not meet eligibility criteria, a Screen Failure electronic Case Report Form (eCRF) will be completed. The Screen Failure eCRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.
- For consented subjects who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the eCRF.

4.2 TREATMENT EXTENSION PHASE

Treatment Extension Phase begins with an evaluation of viral load–results collected during the Screening Phase. Subjects who meet all eligibility criteria, as per data gathered from Screening

Phase are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failure and exit the study without further evaluation.

As shown in Table 4-3, eligible subjects will receive weekly treatment injections (± 3 days) until virologic failure or another reason for discontinuation, occurs, whichever occurs first. Eligible subjects will receive PRO 140 700mg* administered as two subcutaneous injections along with Optimized Background Therapy (OBT).

Note: Subjects enrolled prior to Protocol v4.0 may still be receiving the original 350mg dose and have the option of increasing their dose to 700mg.

Table 4-3: Treatment Extension Phase [PRO 140 + OBT]

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 X 2 mL/inj.) per week	SC injection

The study treatment (PRO 140 SC injections) will be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or self-administered by subjects depending on the study visit week.

All study subjects will continue their current Optimized Background Therapy:

- Throughout the Treatment Extension Phase, or
- Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in section 5.2.1 of the protocol. Subjects will be allowed to continue PRO 140 with existing OBT regimen while waiting for new regimen to be constructed by the Investigator.

Note:

- Subjects may return to clinic for an additional blood draw in-between the clinic visits for plasma HIV-1 RNA or CD4+ levels, per the discretion of the Investigator.
- Subjects who experience virologic failure at any time during the Treatment Extension Phase will undergo the Virologic Failure (VF) Visit assessments and enter the Follow-up Phase of the study.
- Subjects who meet any criteria (other than virologic failure) for discontinuation of study treatment as specified in section 5.2.1 of the protocol, will undergo End of Treatment

Extension Phase (EOT2) Visit assessments and enter the Follow-up Phase of the study.

- Subjects who do not experience virologic failure will enter the Follow-up Phase of the study at the end of Treatment Extension Phase.

Visits during the Treatment Extension Phase will commence on TE1, i.e. the date of first treatment, with weekly visits (± 3 days) thereafter. Subjects who meet all eligibility criteria will receive first treatment injection at Treatment Extension Visit 1 (*which corresponds to EOT from PRO140_CD02 or CD02_OpenLabel study*).

4.2.1 Treatment Extension Visit (TE1)

The following assessments will be performed at the first treatment visit, unless otherwise specified:

Pre-Treatment

- Confirmation of eligibility criteria by reviewing test results and other criteria assessments performed during Screening Phase (see section 7.2)
- Neurological assessment (see section 7.9)
- Complete physical examination (see section 7.7),
- Assess for any changes in Concomitant medications (see section 7.6)
- Collection of Blood Specimens (see section 7.11) for
    - Complete Blood Count
    - Biochemistry
    - Plasma HIV-1 RNA level
    - TruCount T Assay
    - Urine Pregnancy Test (see section 7.11.5), for female subjects of childbearing potential. Childbearing potential is defined as someone who is not surgically sterile or is not more than one year past complete cessation of menstrual cycles.

Administration of study treatment [PRO 140]

Study treatment will be administered weekly as a subcutaneous injection in the abdomen.

Subjects will receive the study treatment delivered as two 2 mL injections on opposite sides of the abdomen.

Note: IP must be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or self-administered by subjects.

Post-Treatment

- Injection Site Reaction Assessment (see section 7.13)
  - **Note:** *To assess injection site reactions, the investigator will use the DAIDS AE grading table (refer to section 16.3).*
- Assess for any Adverse Events (see section 9)
- Vital Signs (see section 7.10) will be assessed within 15 minutes of study treatment administration.

4.2.2 Subsequent Treatment Extension Visits

The following assessments will be performed at each treatment extension visit beyond TE1, unless otherwise specified:

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.6),
- Neurological assessment (see section 7.9) [*at EOT2*],
- Symptom-directed physical examination (see section 7.7),
- Electrocardiogram (ECG) (see section 7.8) [*at EOT2*],
- Vital Signs (see section 7.10)
  - **Note:** *Post-treatment vital signs will be assessed within 15 minutes following IP administration performed at clinic.*
- Collection of Blood Specimens (see section 7.11) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - **Note:** *Occurs once every 4 weeks when subject is at clinic.*
  - Complete Blood Count (CBC)
  - Biochemistry
  - Coagulation indices
  - Urinalysis

- **Note:** *Occurs once every 12 weeks when subject is at clinic.*

- Study Treatment Administration (PRO 140)
- Injection Site Reaction Assessment (see section 7.13)
  - **Note:** *To assess injection site reactions, the investigator will use the DAIDS AE grading table (refer to section 16.3).*

4.2.3 Virologic Failure (VF) Visit

Virologic failure is defined as two consecutive HIV-1 RNA levels ≥ 400 copies/mL.

The following assessments will be performed for subjects who experience virologic failure at any time during the Treatment Phase:

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.5),
- Complete Physical Examination (see section 7.7),
- Vital Signs (see section 7.10),
- Neurological Assessment (see section 7.9),
- Subject-perceived Injection Site Pain Assessment (see section 7.13),
- Collection of Blood Specimens (see section 7.11) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - Complete Blood Count
  - Biochemistry
  - HIV Drug Resistance Assay
  - HIV PhenoSense Entry® Assay
  - HIV Trofile® Assay
- Change in Optimized Background Therapy based on genotypic and phenotypic results obtained at VF visit.

4.3 FOLLOW-UP PHASE

The duration of follow-up depends on whether subject experiences virologic failure.

- Subjects who experience virologic failure within the Treatment Extension Phase will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels below level of detection) or up to a maximum of 6 months after cessation of therapy if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.
- Subjects who do not experience virologic failure at the end of the Treatment Extension Phase, will be followed up every 2 weeks for total of 4 weeks.

4.3.1 Follow-Up Visits

The following assessments will be performed at each follow-up visit, unless otherwise specified:

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.6),
- Symptom-directed physical examination (see section 7.7),
- Vital Signs (see section 7.10),
- Collection of Blood Specimens (see section 7.11) for
    - Plasma HIV-1 RNA level
    - TruCount T Assay

4.4 UNSCHEDULED VISITS

In the event that the patient returns to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator.

5 SUBJECT COMPLETION AND WITHDRAWAL

5.1 SUBJECT COMPLETION

- A subject who completes the Treatment Extension Phase (without virologic failure) and 4-week Non-Virologic Failure Follow-Up Phase will be considered as having completed the study.
- A subject who experiences virologic failure during the Treatment Extension Phase, undergoes the Virologic Failure (VF) Visit assessments and is followed up until viral suppression is achieved or up to a maximum of 6 months after experiencing virologic failure if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression will be considered as having completed the study.

5.2 SUBJECT WITHDRAWAL

A subject who enters the Treatment Extension Phase but does not complete the study, as defined in Section 5.1, is considered to have prematurely withdrawn from the Study.

All subjects have the right to withdraw at any point during treatment without prejudice to future care. It will be documented whether or not each subject completed the clinical study. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded.

The Investigator can discontinue a subject at any time if it is considered medically necessary.

In addition, subjects WILL be withdrawn from the study, in consultation with the Medical Monitor and the Investigator, if any of the following are met:

- A subject is significantly non-compliant with the requirements of the protocol.
- The investigator determines that it is in the best interest of the subject.
- Subject chooses to withdraw or is withdrawn due to an adverse event
- A subject becomes pregnant

  Note: *The pregnancy will be followed to term for safety follow-up. Relevant safety information collected after the study has completed will be reported as supplemental information.*
- Discontinuation of study by Sponsor

Premature withdrawal from the study MAY occur if, in consultation with the Medical Monitor and the Investigator, any of the following are met:

- A subject is treated with a prohibited medication.

- Major protocol violation

5.2.1 Discontinuation of Study Treatment

Discontinuation of study treatment (PRO 140) and continuation of HAART as per standard of care is recommended if:

- Subject experiences virologic failure, defined as two consecutive HIV-1 RNA levels ≥ 400 copies/mL

  Note: Subjects will be allowed to continue PRO 140 with existing OBT regimen while waiting for new regimen to be constructed by the Investigator.

- Develops AIDS-defining conditions as specified in Appendix I (Section 16.1) under which subject is unable to continue treatment with study drug (PRO 140), or subject require treatment with prohibited concomitant medications.
- Shows signs or symptoms of clinically significant immunosuppression
- Subject or the subject's clinician wishes to adjust OBT (except in the event of toxicity management).
- Subject becomes pregnant.

5.2.2 Data Collected for Withdrawn Subjects

Patients may withdraw from the study or discontinue study treatment at any time; however, CytoDyn is dedicated to minimizing missing data in this study. It is therefore suggested that all patients, regardless of whether they continue to receive study treatment, continue within the study.

Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Patients who have study treatment discontinued will continue to be followed, per protocol, whenever possible. Patients who have study treatment discontinued due to a serious adverse event will be followed until resolution or stabilization of the event.

In the event that a subject is withdrawn from the study at any time due to an adverse event or serious adverse event (SAE), the procedures stated in Section 9.1.1 or 9.3, respectively must be followed.

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the eCRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

5.3 SCREEN FAILURES

A subject who has signed a consent form, has been assigned a screening number, but is not treated is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

6 STUDY TREATMENT

6.1 INVESTIGATIONAL PRODUCT DESCRIPTION

PRO 140 is a humanized IgG4,κ monoclonal antibody (mAb) to the chemokine receptor CCR5. PRO 140 is provided at a concentration of 175 mg/mL and is intended for SC route of administration.

Kits will be labeled with a unique identification number. Each kit will contain two vials of PRO 140 for SC injection. One milliliter (1 mL) of PRO 140 solution will be drawn from each vial and loaded into the syringe. A total of 700 mg (175 mg/mL) of PRO 140 is delivered as two (2) mL injections administered subcutaneously on opposite sides of the abdomen. Two study injection kits will be assigned per subject per treatment visit.

Note: Subjects enrolled prior to Protocol v4.0 may still be receiving the original 350mg dose and have the option of increasing their dose to 700mg.

Each vial of the PRO 140 product contains ~1.4 mL antibody at 175mg/ml in a buffer containing 5 mM L-histidine, 15.0 mM glycine, 95 mM sodium chloride, 0.3% (w/v) sorbitol, 0.005% (w/v) polysorbate 20 (Tween 20®), and sterile water for injection, at pH of 5.5.

Note: *1 mL injection will be drawn from 1.4 mL solution in a vial. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

Table 6-1 provide the unit strength, dosing frequency and mode of administration for the study drug.

Table 6-1: Investigational Product - PRO 140

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 X 2 mL/inj.) per week on opposite sides of abdomen	SC injection

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

Study drug will be prepared by Ajinomoto Althea, Inc. and will be packaged, labeled, and shipped by PCI Clinical Services

The contents of each vial are described in Section 6.1. PRO 140 kits will be labeled with information such as: study protocol #; fill volume; concentration; storage condition; a "use as per study protocol" statement; a cautionary statement; sponsor's name and address; and the kit number.

Below are representative samples of the Investigational Product, FDP individual vial (Figure 6-1), syringe label (Figure 6-2), and kit label (Figure 6-3) designated for use in this clinical protocol. Each kit contains two labeled vials and two syringe labels.

Figure 6-1: Investigational Product - Vial Label

Protocol: PRO 140_CD02 Kit No. 2-xxxxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA	Protocol: PRO 140_CD02 Kit No. 2-xxxxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-2: Investigational Product - Syringe Label

Protocol: PRO 140_CD02 Contents of Kit No. 2-xxxxx This syringe contains 2 mL PRO 140 (175 mg/mL) solution for subcutaneous injection USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-3: Investigational Product - Kit Label

Protocol: PRO 140_CD02 Kit No. 2-xxxxx
Site No. _____ Subject No. _____
This kit contains 2 single-use vials
Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection
Store at 2°C to 8°C (36°F to 46°F)
USE AS PER STUDY PROTOCOL
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use
CytoDyn Inc., Vancouver, WA, USA

Pharmacy manual for PRO140_CD02 study provides the criteria regarding vial acceptance or rejection, as well as instructions for the preparation of the IP syringes to be used to administer drug.

6.3 INVESTIGATIONAL PRODUCT STORAGE

Study drug will be shipped at 2°C to 8°C (refrigerated [36°F to 46°F]) to the investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (refrigerated [36°F to 46°F]). The contents of the vial should appear as a clear to opalescent, colorless to yellow solution; fine translucent particles may be present. This is normal.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

6.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

Guidelines for dose preparation can be found in the PRO140_CD02 or CD02_OpenLabel Pharmacy Manual.

PRO 140 will be provided to the administering personnel in single-use syringes prepared from vials of study drug stored at 2-8°C at the site pharmacy prior to use. Each of two syringes is filled to deliver 2.0 mL of study drug.

Equivalent volumes of study drug will be administered subcutaneously on opposite sides of the abdomen.

A 25-guage needle should be used to remove IP from vial and for administration to subjects.

IP should be administered slowly over 15 seconds per mL. IP should not be kept in syringe for longer than 60 minutes.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as described in Section 16.3.

All doses of study drug will be prepared by either the credentialed pharmacist or qualified medical professional and will be administered as SC injection by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or self-administered by subjects depending on the study visit week.

Note: It is preferred that the same injection site be used throughout the study. At the same time, it is not recommended to inject the study drug into areas where skin shows signs of a previous injection site reaction. It is advised to change the injection site if any previous injection site reaction remains unresolved. Alternatively, the 700 mg dose may be delivered as four 1mL doses (two SC injections on opposite sides of abdomen) for those that experience discomfort with the 2mL injections (i.e. subjects with low body fat percentages).

6.5 INVESTIGATIONAL PRODUCT RECEIPT AND ACCOUNTABILITY

Study drug must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study drug, including master records listing the date of receipt, the number and nature of medication units received, and a dispensing record which includes each quantity dispensed, identification of the staff member/subject to whom dispensed, the date of dispensing, the intended study participant, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until drug accountability can be confirmed by study CRA during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

6.6 INVESTIGATIONAL PRODUCT DISPOSITION

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels or any partially used or unused drug supply until instructed by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers and drug labels to the drug distributor as directed by the Sponsor. A copy of the completed drug disposition form will be sent to CytoDyn, Inc. or to its designee.

7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1 INFORMED CONSENT

Written informed consent will be obtained for this study by the Investigator or designee from all subjects before the performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2 ASSESSMENT OF ELIGIBILITY

During the Screening Phase and at TE1 Visit (prior to treatment administration), the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and Exclusion criteria of this Protocol are described in Sections 3.3.1 and 3.3.2. If the subject is not suitable or eligible for the trial then the subject will be a screen failure.

7.3 DEMOGRAPHIC INFORMATION

For the purposes of this study, demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

7.4 MEDICAL HISTORY

Medical history obtained within PRO140_CD02 or CD02_OpenLabel study will be brought forward.

Events that emerge after first treatment (TE1) will be recorded as AE under this protocol.

7.5 HIV HISTORY

HIV history obtained within PRO140_CD02 or CD02_OpenLabel study will be brought forward.

7.6 PRIOR / CONCOMITANT MEDICATIONS AND NON-STUDY TREATMENTS

A complete record of current antiretroviral therapies will be recorded in the source documents and on the appropriate page of the eCRF.

In addition to this, all other medications and therapies administered or taken by the subject throughout the study will be recorded. Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing)

Please refer to Exclusion Criteria (Section 3.3.2) for a list of prohibited treatments and/or procedures. All other medications that are appropriate for the care of the subject may be prescribed. If concomitant medications are started during the study, the indication for the concomitant medication should be considered an AE.

7.7 PHYSICAL EXAMINATION

The complete physical examination will include routine examinations for the following:

- General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Lymph Nodes
- Heart/Cardiovascular abnormalities
- Respiratory
- Abdomen
- Genitourinary
- Musculoskeletal and Extremities
- Neurologic abnormalities Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety results for the subject; i.e., the abnormality is clinically significant (CS).

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

The complete physical examination will be conducted at the TE1, EOT2 and at Virologic Failure (VF) visit. Only symptom-directed physical examination will be performed during Screening Phase, at treatment and follow-up visits conducted within the clinic, and at unscheduled visits within the Treatment and Follow-up Phases.

7.8 ELECTROCARDIOGRAM

A 12-lead ECG will be conducted at EOT2 and results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded.

7.9 NEUROLOGICAL ASSESSMENT

Neurological assessment will be performed by the Principal Investigator (or delegated personnel) or a Neurologist during Screening Phase, at TE1, EOT2 and Virologic Failure (VF) visit.

The neurological assessment tool is based on the three question survey used by Simioni et al. [Simioni S, 2010]. Refer to section 16.4 for further details. Additional assessment modalities can be used for further assessment as per Investigator's discretion.

7.10 VITAL SIGNS

Vital signs will be collected at all study visits performed at the clinic. Vital signs collected during the Treatment Extension Phase (*except for TE1*) will be performed post-treatment, assessed within 15 minutes following study treatment administration.

The following vital signs will be collected at all visits, unless otherwise stated:

- Seated blood pressure (taken after the subject has been seated for at least 5 minutes)
- Heart Rate
- Respiration Rate
- Temperature

7.11 CLINICAL LABORATORY ASSESSMENTS

Unless stated otherwise, blood and urine samples will be collected once every eight weeks according to the time points in the schedule of assessments for analysis of the following parameters:

7.11.1 Routine CBC

- Frequency of testing: At TE1, once every 12 weeks during Treatment Extension, EOT2 or Virologic Failure visit
- Includes hemoglobin, hematocrit (HCT), red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count (%), absolute neutrophils count and platelets count.

7.11.2 Biochemistry

- Frequency of testing: At TE1, once every 12 weeks during Treatment Extension, EOT2 or Virologic Failure visit
- Biochemistry profile includes assessment of

  Hepatic function indicators: total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, LDH

  Renal function indicators: BUN, creatinine

  Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total)

7.11.3 Coagulation indices

- Frequency of testing: At TE1, once every 12 weeks during Treatment Extension, EOT2 or Virologic Failure visit.
- Prothrombin time (PT) and International Normalized Ratio (INR)

7.11.4 Urinalysis

- Frequency of testing: At TE1, once every 12 weeks during Treatment Extension, EOT2 or Virologic Failure visit.
- Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment

7.11.5 Urine pregnancy test

- Frequency of testing: At first treatment visit (TE1) prior to treatment administration
- A urine sample will be collected from female subjects of childbearing potential. This test will be performed at the study site using a commercially available kit.

7.11.6 Plasma HIV-1 RNA level and TruCount T Assay

- Frequency of testing: During Screening, at first treatment visit (TE1) prior to treatment administration, at least once every four weeks during Treatment Extension Phase, EOT2, at VF, and at all Virologic Failure Follow-up (VF-EFU) or Non- Virologic Failure Follow-up (NVF-EFU) visits.
- To assess antiretroviral therapeutic response to PRO 140

  Note: *Plasma HIV-1 RNA level will be measured using Human Immunodeficiency Virus 1 (HIV-1), Quantitative, RNA (Taqman®) test.*

  TruCount T Assay includes measurement of Absolute Lymphocytes, CD3 cell count, CD4 cell count, CD8 cell count, CD3%, CD4% and CD8%

7.11.7 HIV-1 Trofile® Assay

- Includes:

  a. Trofile® RNA Assay

  Trofile® RNA is the primary assay used to assess HIV-1 co-receptor tropism status.

- Frequency of testing: At Virologic Failure visit

7.11.8 HIV-1 Drug Resistance Assay

- Includes:

  a. PhenoSense® GT

  PhenoSense® GT is a combination resistance test for three classes of antiretroviral drugs (i.e., nucleoside/nucleotide, non-nucleoside, and protease inhibitors), that provides both phenotypic and genotypic results from the same blood sample (viral load ≥500 copies/ml).

- Frequency of sample collection: At Virologic Failure visit

7.11.9 HIV-1 PhenoSense® Entry assay

- Frequency of testing: At Virologic Failure visit, in conjunction with HIV-1 tropism testing
- With AMD3100 (CXCR4 inhibitor drug), Maraviroc and PRO 140 (CCR5 inhibitor drugs).

7.11.10CCR5 Receptor Occupancy

- To assess the number CCR5 receptors on patients' CD4 cell surface. Of those CCR5 receptors, the test will also assess the number and percentage of CCR5 receptors that are covered by PRO 140.
- Frequency of testing: This assessment will be performed up to 5 times at different treatment visits. Blood will be taken prior to PRO 140 injection (trough sample) and 24-48 hours (peak sample) after the PRO 140 injection to check for CCR5 occupancy, and correlative analysis will be performed with PRO 140 PK concentration and HIV-1 RNA levels.

All laboratory reports will be reviewed by the Investigator.

Post-treatment abnormal results that are considered by the Investigator to be clinically significant will be recorded as adverse events. If the Investigator judges it necessary, testing may be repeated in order to make the determination of clinical significance. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

7.12 INVESTIGATIONAL PRODUCT ADMINISTRATION

Refer to Section 6.4 for details.

7.13 INJECTION SITE REACTION ASSESSMENT

At each treatment visit that occurs at the clinical site, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded

by the Investigator starting after the first injection is given. Refer to sections 9.1.8 and 16.3 for more details.

7.14 COVID-19 GUIDANCE

The purpose of this guidance is to inform sites how to proceed in light of the challenges faced by patients and clinical trial sites as a result of COVID-19 shelter-in-place mandates from state governments. The content of this letter is based on FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (18 Mar 2020).

- The current schedule of assessments requires subjects to visit the clinic at least once every four weeks for lab assessments. Subjects may still continue to receive treatment with PRO 140 if they are unable to visit the clinic.
- Site staff may visit subjects' homes to conduct study assessments and/or deliver PRO 140.
- Sites may ship PRO 140 to subjects' homes if subjects are unable to visit the clinic.
- If subjects are unable to visit the clinic at least once every four weeks lab assessments will be missed. If this occurs site staff should contact subjects weekly by phone to assess:
    - Compliance to study treatment
    - Potential adverse events
    - Changes in concomitant medications
- Sites should document phone calls and include confirmation of compliance to study treatment, and report any adverse events and/or changes in medications.
- Subjects who report positive tests results for COVID-19 should have the diagnosis recorded as an adverse event.
- Sites should clearly document reasons for failing to obtain required assessments (e.g., limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).
- Any changes in the study visit schedule or missed visit should be entered as protocol deviation in the EDC and reason should be documented as missed study visit or visit performed out of window period due to COVID-19.
- If subject is early withdrawn from the study due to COVID-19, the reason should be clearly documented in the End of Study (EOS) section in EDC as "study discontinuation due to COVID-19".

- Monitoring activities will be performed remotely until Centers for Disease Control (CDC) recommendations allow travel to resume.

8 STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1 TREATMENT GROUPS

This is a single arm study. All eligible subjects will receive PRO 140 as a 700mg subcutaneous injection weekly until one of the following occurs:

- virologic failure
- consent withdrawn
- PRO 140 is approved
- CytoDyn decides to discontinue its development

Note: Subjects enrolled prior to Protocol v4.0 may still be receiving the original 350mg dose and have the option of increasing their dose to 700mg.

8.2 DESCRIPTION OF SAFETY MEASURES

The following safety measures will be assessed in this study.

1. Mean change in viral load (HIV-1 RNA levels) at the conclusion of the treatment period
2. Mean change in CD4 cell count at the conclusion of the treatment period
3. Emergence of Dual/Mixed (D/M)- and CXCR4-tropic virus in patients who had exclusive CCR5-tropic virus at study entry.
4. Tolerability of repeated subcutaneous administration of PRO 140 as assessed by investigator-evaluation of injection site reactions
5. Frequency of treatment-related adverse events resulting in study drug discontinuation
6. Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale
7. Frequency of treatment–emergent serious adverse events

8.3 SAMPLE SIZE DETERMINATION AND RATIONALE

Sample size determination is not applicable as only those subjects who are currently enrolled in PRO 140_CD 02 or CD02_OpenLabel study are allowed to participate in this study.

8.4 RANDOMIZATION AND BLINDING

No blinding or randomization requirement.

8.5 INTERIM ANALYSIS

No interim analysis planned.

8.6 GENERAL STATISTICAL CONSIDERATIONS

8.6.1 Analysis Populations

8.6.1.1 Safety Population

The Safety population is defined as the set of subjects who received at least one dose of PRO 140. This population will be used for the analysis of safety parameters.

8.6.2 Statistical Methods

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later.

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the safety data from this trial including details of appropriate statistical tests to examine underlying assumptions.

8.6.3 Prognostic Factors/Covariates

There are no pre-planned covariates analyses of the data from this study.

8.6.4 Handling of Missing Data

The methodology of imputing missing data, if applicable, will be detailed in the SAP.

8.7 DATA SUMMARY

8.7.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The number of subjects screened, received treatment, completed, and discontinued during the study, as well as the reasons for all post treatment discontinuations will be summarized. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Gender, Time since HIV diagnosis, Viral load at T1, etc.) will be summarized using appropriate descriptive statistics.

Medical history of the subjects will also be provided as a by-subject listing.

8.7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Safety population. All prior and concomitant medications recorded in the eCRFs will be coded to generic term and all matching Anatomic Therapeutic Classification (ATC) codes using WHO Drug Summaries will be prepared using the coded terms. All prior and concomitant medications recorded in the eCRFs will also be listed.

8.7.4 Safety Measures

The following safety measures will be evaluated:

- Mean change in viral load (HIV-1 RNA levels) at the conclusion of the treatment period
- Mean change in CD4 cell count at the conclusion of the treatment period
- Emergence of Dual/Mixed (D/M)- and CXCR4-tropic virus in patients who had exclusive CCR5-tropic virus at study entry.
- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by investigator-evaluation of injection site reactions
- Frequency of treatment-related adverse events resulting in study drug discontinuation
- Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale
- Frequency of treatment–emergent serious adverse events

All safety data measures will be summarized and tabulated according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include:
  - Frequency counts and percentages.
  - Logit model will be used for inferential statistics.

8.7.5 Safety Analysis

The Safety population will be used for the analysis of safety assessments.

For continuous variables data will be summarized using n, mean, Standard Deviation (SD), minimum and maximum values. For categorical variables data will be summarized using frequency and percentage. No inferential statistics are planned.

8.7.5.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of SAEs, and AEs resulting in discontinuation of study treatment will be presented.

8.7.5.2 Tolerability Assessment

All data from tolerability assessments of repeated subcutaneous administration of PRO 140 as assessed by investigator-evaluation of injection site reactions will be summarized.

8.7.5.3 Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized.

8.7.5.4 Physical Examination

All physical examination findings will be listed and any abnormality will be summarized.

8.7.5.5 Vital Signs

All vital sign assessment findings will be listed and summarized.

8.7.5.6 ECG Examination

All ECG examination findings will be listed and any abnormality will be summarized.

8.7.5.7 Neurological Assessment

All neurological assessment findings will be listed and any abnormality will be summarized.

9 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

9.1 ADVERSE EVENT

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the Investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant (NCS) should not be recorded as an AE.

9.1.1 Reporting of Adverse Events

Report initiation for all AEs and SAEs will begin at the time of the first treatment extension visit and continue up until the final study visit (i.e. up to NVF-FU2 for subject who do not experience virologic failure or until viral suppression is achieved for subjects who experience virologic failure). All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the eCRFs. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.2), the impact the event had on study treatment (see Section 9.1.2), the DAIDS AE grade (intensity) of the event (see Section 9.1.3), the causality of the event (see Section 9.1.4), whether treatment was given as a result of the event (see Section 9.1.5), and the outcome of the event (see Section 9.1.6).

9.1.2 Impact of Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol, or if the outcome of the event was "death".

9.1.3 DAIDS AE Grade (Severity) Assessment

The investigator will carefully evaluate the comments of each subject and the response to treatment in order to judge the true nature and severity of the AE. The question of the relationship of AEs to study drug should be determined by the investigator after thorough consideration of all available facts. To assess severity, the investigator will use the DAIDS AE grading table (for adverse events as well as any injection site reactions refer to Section 16.2 and Section 16.3).

The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.

Table 9-1: DAIDS AE Grading Table v2 General Guidelines

Grade	Description
Grade 1	indicates a mild event
Grade 2	indicates a moderate event
Grade 3	indicates a severe event
Grade 4	indicates a potentially life-threatening event
Grade 5	Death related to AE.

DAIDS AE Grading Table Version 2.0- November 2014

9.1.4 Causality Assessment

Adverse events will be assigned a relationship (causality) to the study treatment. The Principal Investigator (PI) must review each AE and make the determination of relationship of the event to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3)

Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Remotely related**: In general this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.1.5 Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-medication therapy administered, surgery, or other (with a specification).

9.1.6 Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.1.7 Expected / Anticipated Adverse Events

The most common potential study drug-related adverse reaction reported is mild headache. Other adverse events likely to be related to the drug include mild to moderate diarrhea, nausea, and fatigue.

9.1.8 SC Injection-related Events

SC and IV injections of concentrated protein materials can be associated with injection-related AEs that impact the ability to safely and successfully deliver the drug. Local injection-site reactions may include pain/discomfort, induration, erythema, nodules/cysts, pruritus, ecchymosis, etc. For SC injections, bleeding, absorption of the drug, leakage of drug, and induration at the local injection site can be additional complications. Other AEs that are common to monoclonal antibody-based therapies are chills, headache, backache, malaise, fever, pruritus, rash, nausea, tingling, and hypertension.

SC injection-related events will be monitored according to the guidelines provided in Section 16.2 (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS AE Grading Table]). Injection-site reactions thought to be directly related to the injection are considered to be AEs of special interest, and a separate guideline for the acquisition of data related to this AE of special interest is provided in Section 16.3.

For subjects who develop grade 1 or grade 2 events, continue therapy as per protocol. If a subject chooses to discontinue study treatment, the site should notify the protocol team leadership, and encourage the subject to complete any remaining study visits until the toxicity resolves.

For subjects who develop grade 3 events following study drug injection, the subject should be reevaluated closely until the AE returns to Grade ≤2, at which time study treatment may be reintroduced at the discretion of the site investigator. If the *same* Grade 3 AE recurs following the next administration of study drug, study treatment must be permanently discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely for resolution of the AE to Grade ≤ 2 and the team leadership must be notified.

Subjects with Grade 3 asymptomatic laboratory abnormalities in cholesterol, creatine kinase (CK) or triglycerides may continue study treatment.

For grade 4 events permanently discontinue therapy.

9.2 SERIOUS ADVERSE EVENTS (SAE)

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the AE)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If a pregnancy occurs in a subject or partner of a male subject during a clinical study this must also be reported to CytoDyn, Inc. The Investigator should discuss the case with the Medical Monitor. Any pregnant subject must be followed up by the Investigator or designee until the child is born. Any AEs of the subject during pregnancy, that meets serious criteria, must be documented and reported CytoDyn, Inc. Participants who become pregnant will be entered into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

9.3 REPORTING OF SERIOUS ADVERSE EVENTS

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.1.1. Once the Investigator becomes aware of an SAE, he/she must report the SAE to [redacted] within 24 hours:

CRO Medical Monitor	[redacted]

The Amarex Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, ECG reports, discharge summary, hospital notes, etc.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified. Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)).

9.3.1 SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The monitors, auditors, personnel authorized by the Sponsor, the local IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 MONITORING REQUIREMENTS

In an effort to fulfill the obligations outlined in 21 Code of Federal Regulations (CFR) Part 312 and ICH guidelines which requires the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all eCRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to, study, laboratory and diagnostic reports, neurological examination results, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the case report forms, in accordance with federal regulations. A Monitoring Log will be maintained at each study site which the monitor will sign, date and state the type of visit.

The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2 ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

Electronic CRFs must be completed for each subject who has signed an informed consent form. For subjects who are screen failures, this would be limited to the screen failure eCRF page. All source documents and eCRFs will be completed as soon as possible after the subject's visit. Corrections to data on the eCRFs will be documented. The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Electronic CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4 REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the eCRFs.

12 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR Part 312, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable GMP and the products provided for this study will be used only in accordance with this protocol.

12.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator at the site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

12.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

12.3 SUBJECT INFORMED CONSENT REQUIREMENTS

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the Investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form ICF is to be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

13 DATA HANDLING AND RECORD KEEPING

13.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to the approved eCRFs. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and eCRFs will be completed as soon as possible after the subject's visit.

The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and eCRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject’s study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject’s case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

13.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control (QC) of the data. Data management will be carried out as described in the Sponsor’s or CRO’s standard operating procedures (SOPs) for clinical studies.

The handling of data, including data QC, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor’s or the CRO’s SOPs as well as provisions of the study-specific Data Management Plan.

13.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- Product (e.g., IP supplies) and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening and enrollment log
- SAE reports
- IRB approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator.

14 PUBLICATION PLAN

All information supplied by CytoDyn in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure (IB), clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of CytoDyn, shall not be disclosed to others without the written consent of CytoDyn, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of PRO 140. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: Because this is a multi-center trial, the site and Investigator shall not independently publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities conducted under this protocol until such multi-center publication is released with the written approval and under the direction of Sponsor. Notwithstanding the foregoing, if a multi-center publication is not released within eighteen (18) months after completion of analysis of all study data from all studies conducted within the multi-center trial, both the site and Investigator shall have the right to publish the results of and information pertaining to the site's and Investigator's activities conducted under this protocol and the clinical trial agreement, subject to the prior review and written approval of Sponsor. The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the multi-center trial or the study is terminated before its completion and the final clinical

study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

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16 APPENDIX

16.1 APPENDIX I: AIDS-DEFINING CONDITIONS

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)†
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary,†§ disseminated,† or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- *Pneumocystis jirovecii* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent

- Toxoplasmosis of brain, onset at age >1 month†
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)
† Condition that might be diagnosed presumptively.
§ Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm

16.2 APPENDIX II: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (DAIDS AE GRADING TABLE)

http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf

16.3 APPENDIX III: ADVERSE EVENTS OF SPECIAL INTEREST: INJECTION SITE REACTIONS

The following table should be used to characterize injection-site reactions and provide appropriate grading of severity (DAIDS and modified additions).

Injection-site Reactions

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Injection-site pain	Pain without touching or pain when area is touched: no or minimal limitation of use of limb	Pain without touching or pain when area is touched limiting use of limb OR causing greater than minimal interference with usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform basic self-care function OR hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Characterization of the injection site, if not normal	Erythema OR induration of 5x5 cm - 9x9 cm (or 25 cm2-81 cm2)	Erythema OR induration OR Edema >9 cm any diameter (or >81 cm2)	Ulceration OR secondary infection OR Phlebitis or Sterile abscess OR drainage	Necrosis (involving dermis and deeper tissue)
Pruritus associated with injection	Itching localized to injection site AND relieved spontaneously or <48 hours of treatment	Itching beyond the injection site but not generalized OR itching localized to injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social and functional activities	N/A
Bleeding	Initial bleed that does not exceed bandage and spontaneously stops	Bleeding that exceeds bandage and spontaneously stops	Continued bleeding that requires change of dressing and alternative injection site	N/A
Absorption of drug	Minor elevation of skin at injection site but no leakage of injection material	Leakage at injection site ceases with decrease in injection rate	Leakage at injection site that does not cease with decrease in injection rate	

16.4 APPENDIX V: NEUROLOGICAL ASSESSMENT

Three Question Screening Survey (Simioni, et al, 2010)

1. 'Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)'?
2. 'Do you feel that you are slower when reasoning, planning activities, or solving problems'?
3. 'Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)'?

For each question, subjects should provide one of the following answers: 'never', 'hardly ever', or 'yes, definitely'.

If subject answers "yes, definitely" to any question, Investigator may use additional neurological assessment modalities at its discretion.