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Protocol Cover Page

Protocol Title: A Multi-center, Two-Part, Single-Arm, Open Label, 25-Week Trial with PRO 140 in Treatment-Experienced HIV-1 Subjects.

Protocol Number: PRO 140_CD02_OpenLabel

Version: 3.0

Document Date: 11-Mar-2019

NCT Number: NCT03902522

A Multi-center, Two-Part, Single-Arm, Open Label, 25-Week Trial with PRO 140 in Treatment-Experienced HIV-1 Subjects.

Protocol Number:	**PRO 140_CD02_OpenLabel**
Version:	**3.0**
Date:	**11-Mar-2019**

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INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**PRO 140_CD02_OpenLabel**
Version:	**3.0**
Date:	**11-Mar-2019**

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 forobtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Address _____

Site Number _____

SPONSOR INFORMATION

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PROTOCOL SYNOPSIS

Name of Sponsor: CytoDyn, Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5)	
Protocol Number: PRO 140 _CD02_OpenLabel	**Therapeutic Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection
Title of Study: A Multi-center, Two-Part, Single-Arm, Open Label, 25-Week Trial with PRO 140 in Treatment-Experienced HIV-1 Subjects.	
Study Center(s): Up to 40 centers in the United States	
Planned Number of Subjects: Up to 25 subjects (or any number of subjects that can be enrolled by the time of Biologics Licence Application (BLA) submission for PRO 140).	
Indication for Use: PRO 140, in combination with other antiretroviral agents, is indicated for treatment experienced adult HIV-1 patients infected with CCR5-tropic virus. These patients must demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy and have documented genotypic or phenotypic resistance to at least one ART drug within three drug classes (or within two or more drug classes with limited treatment option). The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.	
Study Population: Study population includes treatment-experienced HIV-infected patients with CCR5-tropic virus who 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 option).	
Objectives: The primary objectives of the trial are to assess the efficacy, clinical safety and tolerability parameters of PRO 140 in combination with failing ART during the initial one-week treatment period, and in combination with Optimized Background Therapy during the subsequent 24-week treatment period.	
Endpoints: **Primary Efficacy Endpoint:**	

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- Proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the initial 1-week treatment period

Secondary Endpoints:

- Proportion of participants with ≥ 1 log10 reduction in HIV-1 RNA viral load from baseline at the end of the initial 1-week treatment period
- Mean change from Baseline in HIV-1 RNA levels (log_{10} copies/mL) at the end of the initial 1-week treatment period
- Percentage of participants achieving HIV-1 RNA < 400 copies/mL at week 25
- Percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 25
- Mean change from Baseline in HIV-1 RNA levels (log_{10} copies/mL) at week 25
- Mean change from Baseline in CD4 cell count at the end of the initial 1-week treatment period
- Mean change from Baseline in CD4 cell count at week 25

Safety Assessments:

- 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 study participants (using Visual Analogue Scale) and 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

Trial Design:

This is a multi-center, two part study, designed to evaluate the safety and tolerability of PRO 140 in conjunction with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks. The patient population for this trial are 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 option).

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

Screening Phase (up to 6 weeks):

This phase is designed to determine whether subjects are eligible to proceed to the Treatment Phase of the

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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 their existing ART (failing regimen) during the Screening Phase, Baseline, and first week (Part 1) of the Treatment Phase.

Baseline (1 week):

Potentially eligible subjects will confirm continued eligibility one week prior to the first treatment visit. HIV RNA will be tested at Baseline. Subjects whose result is >400 copies/mL will be enrolled one week later. Subjects with results <400 copies/mL will be designated as screen failure. The Baseline Visit (T0) will take place within 6 weeks of the Screening Visit.

Treatment Phase (25 weeks ± allowed windows):

The Treatment Phase is divided into two parts:

- **Part 1:** 1-week treatment period consisting of PRO 140 along with existing ART (failing regimen)
- **Part 2:** 24-week treatment period consisting of PRO 140 along with OBT

The injectable study treatment (PRO 140) will be administered starting at T1 visit and weekly there after:

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

Subjects will receive PRO 140 700 mg administered subcutaneously once per week.

Note: Subjects who are currently enrolled and receiving 350 mg dose will have the option to move to the 700 mg dose for the remainder of their participation in the trial.

Note: *Study treatment injections at T1, T2, T3, T7, T11, T15, T19 and T23 must be administered at clinic. The remaining study treatment injections may be self-administered by subjects outside the clinic.*

Part 1: One-week treatment period [PRO 140 + existing ART]

Part 1 of treatment phase begins with an evaluation of results of laboratory samples collected at the Screening Visit. 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, as per data gathered from Screening Visit,will be enrolled and receive PRO 140 for one week (Table 0-1). A visit to confirm HIV RNA continues to meet eligibility will be conducted one week pior to the first treatment.

Table 0-1: One-week period [PRO 140 + existing ART]

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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.) at T1 visit	SC injection

Part 2: 24-week treatment period [PRO 140 + OBT]

As shown in Table 0-2, after 7 days all subjects will enter the 24-week treatment period. During this period, all subjects will receive PRO 140 SC injection and Optimized Background Therapy. 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.

Table 0-2: 24-week treatment period [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 for up to 24 weeks (T2 – T25)	SC injection

Study participants will be regularly monitored for viral load following initiation of PRO 140, and will cease weekly study treatment injections should they experience treatment failure.

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

Treatment failure is defined in terms of virologic non-response and virologic rebound in the Open-Label Treatment Phase of the study.

(1) Virologic non-response is defined as two consecutive viral load results of:

- *< 0.5 $\log_{10}$ copies/mL decrease in HIV-1 RNA at Day 7 of Treatment Phase Part 2. [Assessment Timepoint: T3 and T4 visit]*
- *< 1.0 $\log_{10}$ copies/mL decrease in HIV-1 RNA at or after Week 4 of Treatment Phase Part 2 unless HIV-1 RNA <400 copies/mL [Assessment Timepoint: from T6 up to T25 visit].*
- *Confirmed plasma HIV-1 RNA levels ≥ 400 copies/mL at Week 25 of Treatment Phase Part 2. [Assessment Timepoint: T25 visit]*

(2) Virologic rebound is defined as two consecutive viral load results of:

- *≥ 1.0 $\log_{10}$ copies/mL increase in plasma HIV-1 RNA above nadir level* in Treatment Phase Part 2 [Assessment Timepoint: from T3 up to T25 visit] or*

**Note: This refers to "Nadir" level in the Treatment Phase which starts from T2 visit*

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- *≥ 400 copies/mL after suppression to < 50 copies/mL in Treatment Phase Part 2. [Assessment Timepoint: from T3 up to T25 visit]*

Safety Follow-up Visits:

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

- Subjects who experience treatment failure within Treatment Phase Part 2 will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels below level of detection) or upto 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 treatment failure at the end of Treatment Phase Part 2, will be followed up every 2 weeks for total of 4 weeks.

Duration of Study:

- **Screening Phase:**
  - up to 6 weeks*

    **Subject will move to Treatment Phase as soon as HIV-1 viral tropism, genotypic and phenotypic resistance results are available for review by Investigator, within 6 weeks of the Screening Visit.*
- **Baseline**
  - 1 week
- **Treatment Phase:**
  - 25 weeks (± allowed windows)
- **Follow-up Phase:**
  - 4 weeks** (± allowed windows)

    ***or up to maximum of 6 months after experiencing Treatment Failure (TF) if the treating physician does not feel that there is an antiretroviral regimen that will regain full viral suppression.*
- **Total Study Duration:**
  - 36 weeks [Does not include additional follow-up time for treatment failure subjects]

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

1. Males and females, age ≥ 18 years
2. Exclusive CCR5-tropic virus at Screening Visit as determined by Monogram Biosciences Trofile® Assay

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3. Have a history of at least 3 months on current antiretroviral regimen
4. Treatment-experienced HIV-infected patients with documented genotypic or phenotypic resistance to at least one ART drug within three drug classes

   OR

   Treatment-experienced HIV-infected patients with documented genotypic or phenotypic resistance to at least one ART drug within two drug classes and have limited treatment option. The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.
5. Be willing to remain on treatment without any changes or additions to the OBT regimen, except for toxicity management or upon meeting criteria for treatment failure
6. Plasma HIV-1 RNA ≥ 400 copies/mL at Screening Visit as determined by Human Immunodeficiency Virus 1 (HIV-1) Quantitative, RNA (Roche Taqman® Real-Time PCR) and documented detectable viral load (HIV-1 RNA >50 copies/ml) within the last 3 months prior to Screening Visit.
7. Laboratory values at Screening of:
   a. Absolute neutrophil count (ANC) ≥ 750/mm^3
   b. Hemoglobin (Hb) ≥ 10.5 gm/dL (male) or ≥ 9.5 gm/dL (female)
   c. Platelets ≥ 75,000 /mm^3
   d. Serum alanine transaminase (SGPT/ALT) < 5 x upper limit of normal (ULN)
   e. Serum aspartate transaminase (SGOT/AST) < 5 x ULN
   f. Bilirubin (total) < 2.5 x ULN unless Gilbert's disease is present or subject is receiving atazanavir in the absence of other evidence of significant liver disease
   g. Creatinine ≤ 1.5 x ULN
8. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator
9. 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).

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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.

10. 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.

    Note: Subjects diagnosed with either substance dependence or substance abuse or any history of a concomitant condition (e.g., medical, psychologic, or psychiatric) may be enrolled if in the opinion of site investigator these circumstances would not interfere with the subject's successful completion of the study requirements.

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

1. Documented CXCR4-tropic virus or Dual/Mixed tropic (R5X4) virus as determined by HIV-1 tropism assay
2. Patients with no viable treatment options (i.e., no fully active antiretroviral drug available which can be effectively combined to form a viable new OBT)
3. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)

   Note: Subjects infected by the hepatitis B virus or hepatitis C virus will be eligible for the study if they have no signs of hepatic decompensation and meet the liver function tests eligibility criteria.
4. Laboratory test values of ≥ grade 3 DAIDS laboratory abnormality with the exception of the absolute CD4+ count criterion of < 200/mm^3
5. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
6. Unexplained fever or clinically significant illness within 1 week prior to the first study dose
7. Any vaccination within 2 weeks prior to the first study dose.
8. Subjects weighing < 35kg
9. History of anaphylaxis to oral or parenteral drugs
10. History of Bleeding Disorder or patients on anti-coagulant therapy
11. Participation in an experimental drug trial(s) within 30 days of the Screening Visit
12. Any known allergy or antibodies to the study drug or excipients
13. Treatment with any of the following:

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a. Radiation or cytotoxic chemotherapy with 30 days prior to the Screening Visit

b. Immunosuppressants within 60 days prior to the Screening Visit

c. Immunomodulating agents (e.g., interleukins, interferons), hydroxyurea, or foscarnet within 60 days prior to the Screening Visit

d. Oral or parenteral corticosteroids within 30 days prior to the Screening Visit. Subjects on chronic steroid therapy > 5 mg/day will be excluded with the following exception:

- Subjects on inhaled, nasal, or topical steroids will not be excluded.

14. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety.

Statistical Considerations:

Sample Size Determination and Rationale:

Up to 25 subjects (or any number of subjects that can be enrolled by the time of BLA submission for PRO 140) will be enrolled. The sample size is based on clinical judgement with an intention to supplement the data for the target BLA indication.

Analysis Populations:

The **Intent-to-Treat (ITT)** population is defined as the set of subjects who are enrolled and have received at least one dose of PRO 140.

Subjects who discontinue from the study prior to their first post-baseline assessment will be included in the ITT population and analyzed as non-responders in the primary analysis.

The **Per Protocol (PP)** population is defined as the set of subjects who meet the ITT population requirements, and were not associated with a major protocol violation. This population will be identified before the database lock.

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

Efficacy Analysis

The primary analysis of primary and secondary endpoint will be conducted on the ITT population and PP population will be used for supportive analysis using the same analysis methodologies.

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

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- 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
BLA	Biologics Licence Application
°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
DMC	Data Monitoring Committee
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"
EOT	End of Treatment
°F	Fahrenheit
FDA	U.S. Food and Drug Administration
FDP	Fixed Dose Procedure
FU	Follow-Up

Abbreviation	Term
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
IA	Interim Analysis
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
MW	Molecular Weight
NCS	Not Clinically Significant
NP	Nurse Practitioner
NTF	Non-Treatment Failure
OBT	Optimized Background Therapy

Abbreviation	Term
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
TEAE	Treatment Emergent Adverse Events
TF	Treatment Failure
ULN	Upper limit of normal
USA	United States of America
VAS	Visual Analogue Scale
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 theprotocol, 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 Amarex Clinical Research 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 dueto 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 regimenis 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 chronicnucleoside 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 ofthe viral and cell membranes. PRO 140 has been administered intravenously or subcutaneouslyto 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 PRO140 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 mildlymphoid 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 highlysignificant.

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 relevanttoxicity. 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

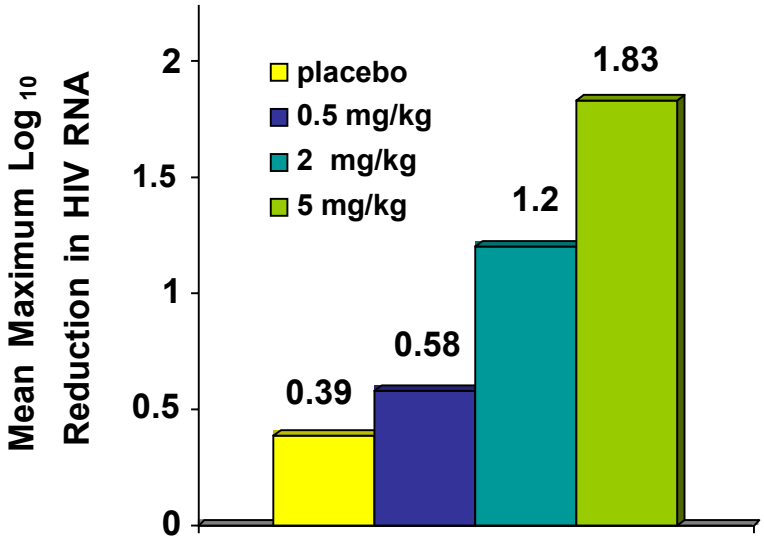
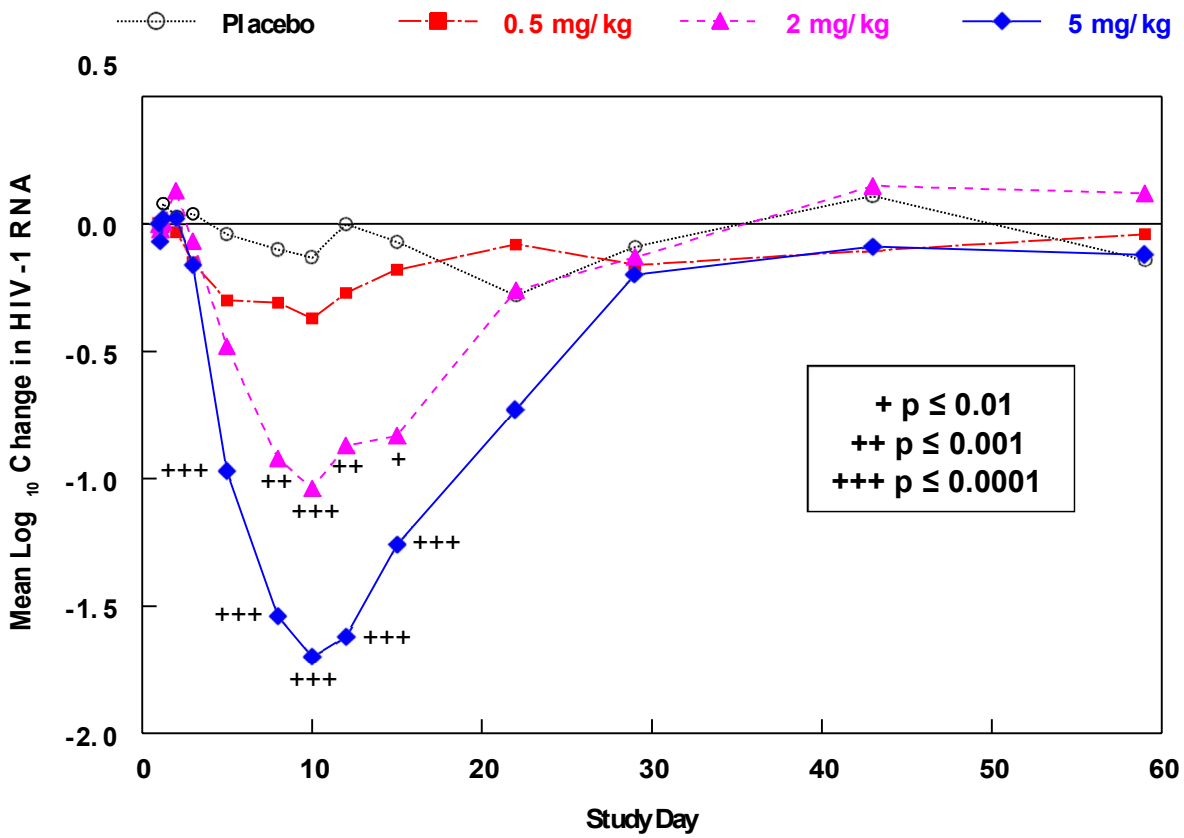


Figure 1-2: PRO 140 1302 Study: Mean log_{10} reductions in HIV RNA over time

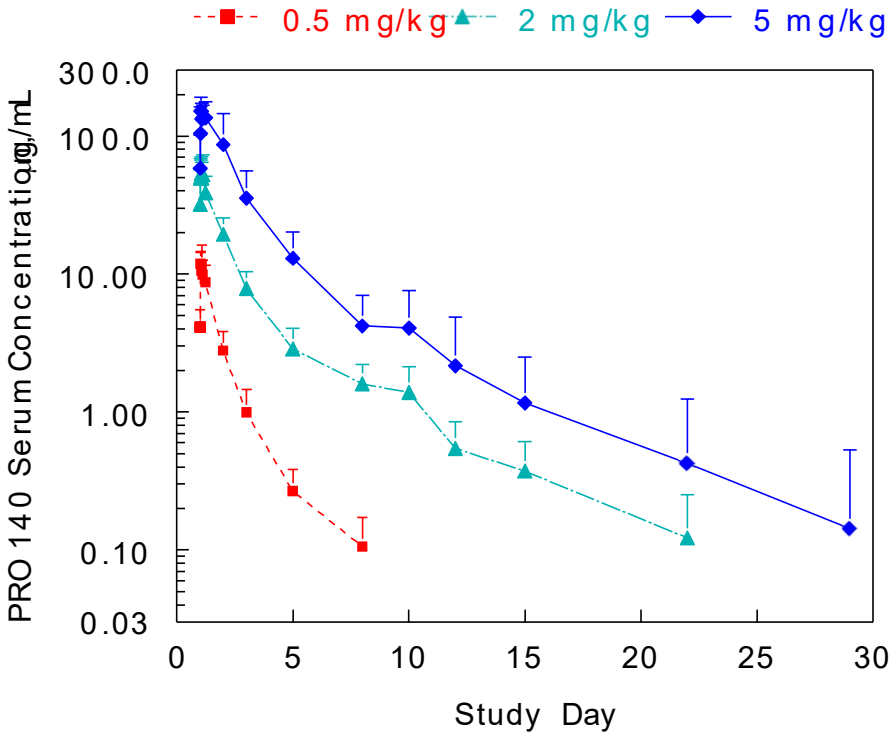


There was no change in CCR5 virus susceptibility to PRO 140 following treatment. All subjects had CCR5-only virus at screening in the first-generation Trofile assay. CCR5-only tropism results were observed in all subjects at all other timepoints, with two exceptions: One of nine (11%) of placebo subjects 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 an 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.

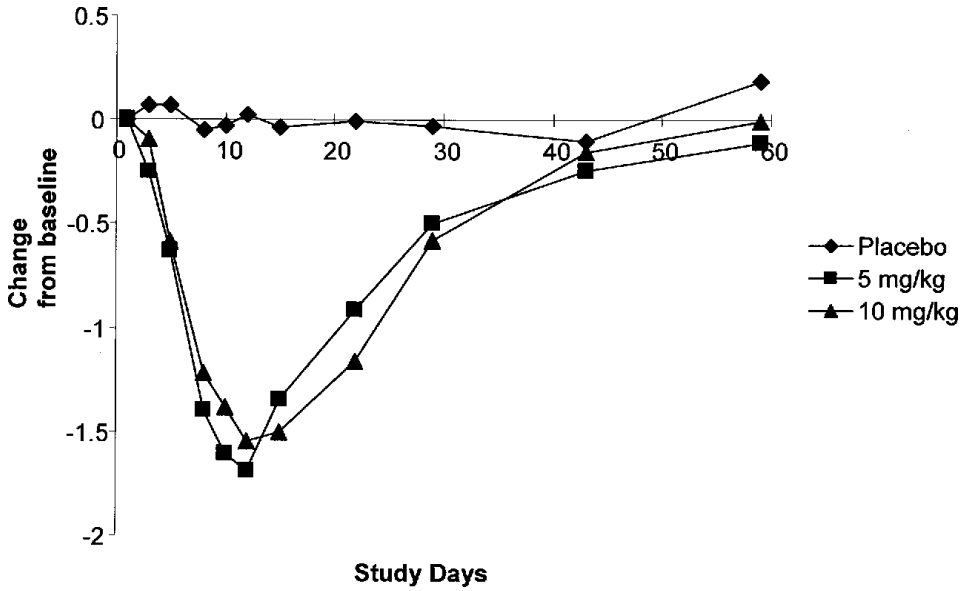
Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose- limiting toxicity was observed. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dosegroups. There was no significant 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 forone 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

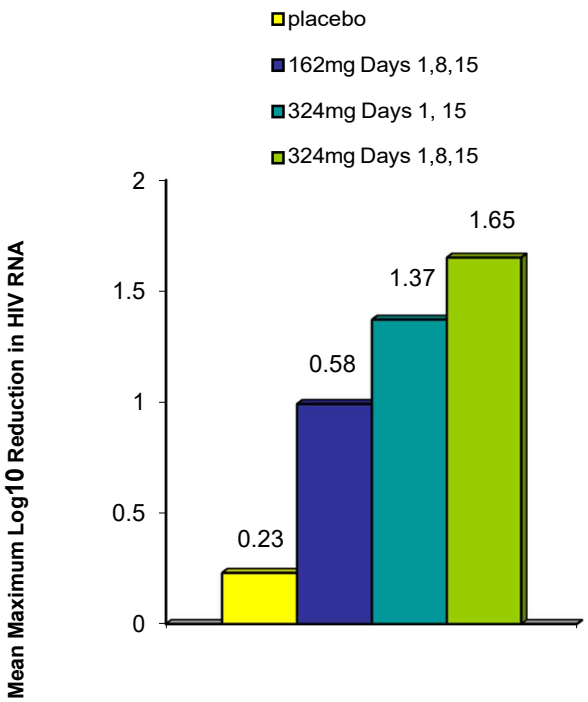
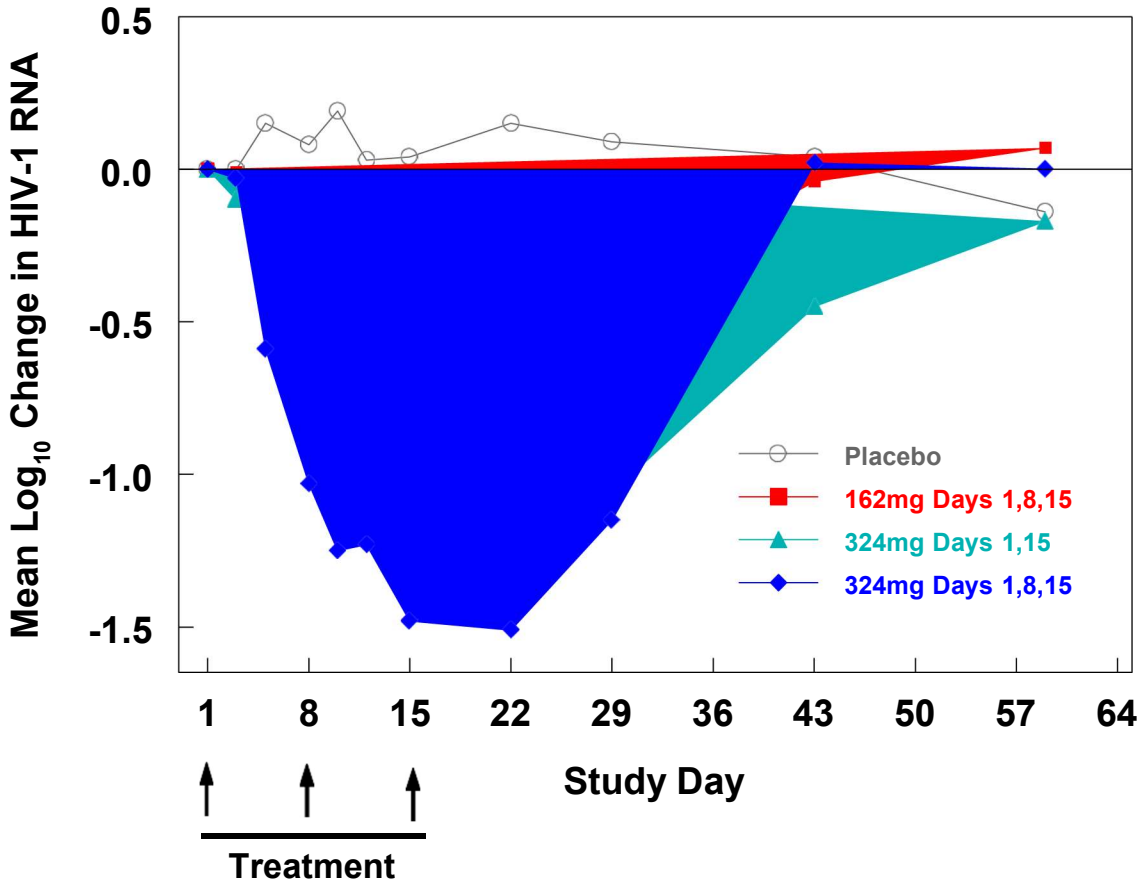


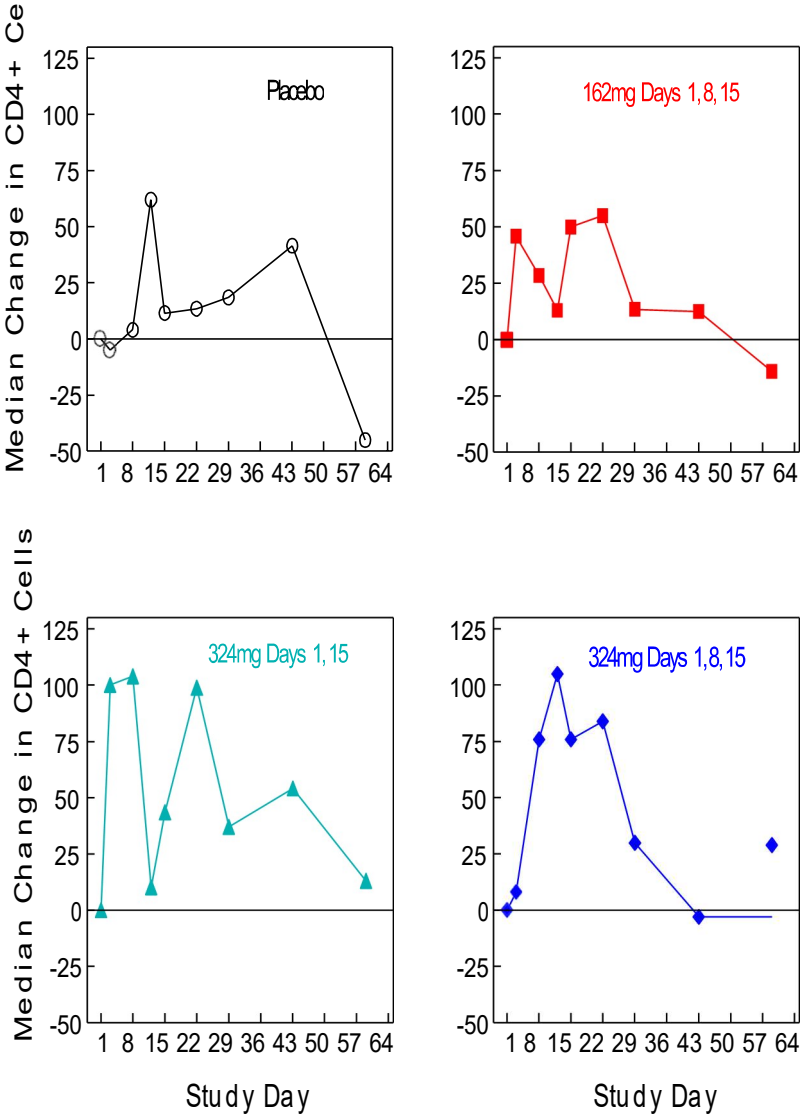
Figure 1-6: PRO 140 2101 Study: Mean change from baseline in HIV-1 RNA (Log_{10} copies/mL) over Time (ITT Subjects)



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) 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 (40) subjects (M/F: 37/3) with median age of 54.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-two out of 40 (55%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Of the 40 enrolled subjects, 3 subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37 subjects were found to have exclusive CCR5-tropic virus. Fifty-nine percent (59%) of CCR5-exclusive subjects compared to zero percent (0%) of D/M subjects experienced virologic success within 12 weeks of PRO140 monotherapy (p=0.0465). 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. As the aggregate analysis shows, the subjects who experienced virologic failure had higher IC90 value for PR0140 at baseline compared to subjects without virologic failure. The mean IC90 for subjects who experienced virologic failure was higher (10.84 µg/mL) than the IC90 for subjects without virologic failure (6.70 µg/mL) in the CD01 study (p=0.0115).

Anti-PRO140 antibodies were not identified in any 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 40 enrolled subjects. One (1) of 40 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-eight (28) of 40 subjects (70%) 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 40 (35%) subjects. The majority of the reported AEs (63/89; 70.7%) 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.

Additionally, a letter of amendment has been filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects (1 at baseline and 2 at the

time of virologic failure) enrolled in the study.

1.4.2.8 PRO 140_CD01-Extension Study

PRO 140_CD01-Extension study (open-label, 28 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 108 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 of ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy for up to 108 weeks.

A total of 16 subjects participated in the CD01-Extension study of which one subject was considered not eligible as subject experienced virologic failure prior to first extension treatment.

Fifteen (15) eligible subjects (M/F: 13/2) with median age of 55.3 years (26-68) and median CD4 T-cell count of 586 cells/mm3 (365-1059) were enrolled in an extension study. Eleven (11) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than one year of treatment (56 - 67 wks). One subject with undetectable viral load did not continue beyond 47 weeks due to relocation, and 3 subjects experienced virologic failure after a median time of 169 days (106-193).

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, 50 subjects, multi-center) seeks to evaluate 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 includes 50 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who demonstrates evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented history of genotypic or phenotypic resistance to at least one ART drug within two drug classes.

In double-blind treatment period, virally non-suppressed subjects will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days. The primary efficacy endpoint is proportion of participants with ≥ 0.5 log10 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 will receive PRO 140 along with OBT.

1.4.2.10 PRO 140_CD02 Extension study

PRO 140_CD02 Extension study (open label, 50 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 weekly injection in combination with Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 50 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who successfully completed PRO 140_CD02 study and continue to demonstrate HIV-1 viral suppression.

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 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 PRO 140 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 PRO140_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.

Protocol Number	Phase	No. of Subjects (Planned/Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
PRO 140 _CD01	2b	40/40	350 mg SC weekly dose for 12 Weeks of Monotherapy (total treatment duration 14 Weeks)	CHO	HIV-1 positive	Generally well tolerated, no drug-related SAEs, weekly dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity. Results are pending publication.
PRO 140 _CD01-Extension	2b	16/16	350 mg SC weekly monotherapy dose	CHO	HIV-1 positive	This clinical study is currently ongoing.
PRO 140 _CD02	2b/3	50/52	350 mg SC or placebo + ART for 1 week, then 350mg SC weekly + OBT for 24 weeks	CHO	HIV-1 positive	This clinical study has been completed
PRO 140 _CD02-Extension	2b/3	50/TBD	350 mg SC weekly + OBT	CHO	HIV-1 positive	This clinical study is currently ongoing.
PRO 140 _CD03	2b/3	500/TBD	350 mg SC weekly dose for up to 48 weeks of monotherapy	CHO	HIV-1 positive	This clinical study is currently ongoing..

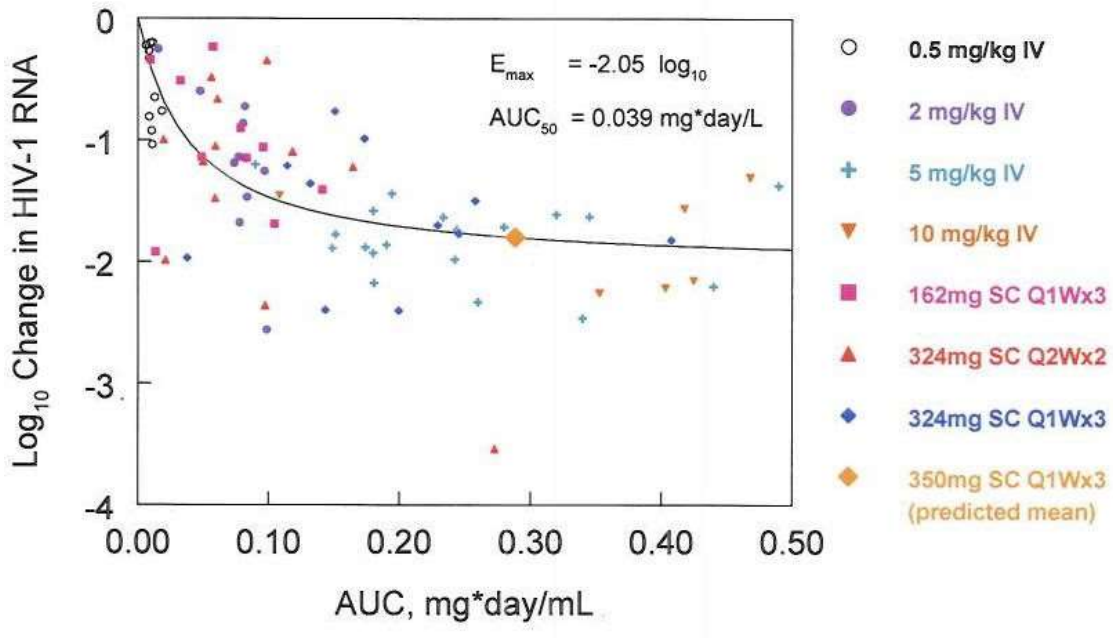
Protocol Number	Phase	No. of Subjects (Planned/Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
PRO 140 _CD03-Extension	2b/3	300/TBD	350 mg SC weekly monotherapy dose	CHO	HIV-1 positive	This clinical study is currently ongoing.

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 onthe 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).

1.6 RISKS / BENEFITS ASSESSMENT

1.6.1 RISKS/DISCOMFORT TO SUBJECTS AND PRECAUTIONS TO MINIMIZE RISK

1.6.1.1 Risks associated with continuation of Failing Antiretroviral Treatment Regimen

As per standard of care, patients who failing on their ART remain on failing regimen while waiting for the results of HIV-1 drug resistance tests. A new drug regimen is constructed by the Investigator based on the subject's resistance test results and treatment history. This duration corresponds with the screening phase of the study.

Once the results of resistance and tropism tests are available, the study treatment (PRO 140 700mg SC injection) will be added to the failing regimen for one week. After one week all subjects will receive PRO 140 SC injection and Optimized Background Therapy (OBT).

Addition of study treatment (PRO 140 700mg SC injection) to the failing regimen may not be effective in achieving a reduction in viral load for all subjects. Such cases could lead to an

increased risk of developing drug resistance, opportunistic infections and clinical progression of the disease.

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 administeredto 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 immuneresponse 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 concernis 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 supervised once weekly SC treatment with PRO 140 in addition to an optimized and simplified ART regimen. Subjects participating in the present short term combination therapy study for 25 weeks 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 assess the efficacy, clinical safety and tolerability parameters of PRO 140 in reducing HIV-1 viral load in patients on their current ART (failing regimen) during the 1-week treatment period, and in combination with Optimized Background Therapy during the subsequent 24-week treatment period.

The primary efficacy endpoint is proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the initial 1-week treatment period.

The secondary efficacy endpoints will be proportion of participants with ≥ 1 log10 reduction in HIV-1 RNA viral load from baseline at the end of the initial 1-week treatment period, mean change from Baseline in HIV-1 RNA levels (log10 copies/mL) at the end of the initial 1-week treatment period, percentage of participants achieving HIV-1 RNA < 400 copies/mL at week 25, percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 25, mean change from Baseline in HIV-1 RNA levels (log10 copies/mL) at week 25, mean change from Baseline in CD4 cell count at the end of 1-week treatment period, and mean change from Baseline in CD4 cell count at week 25.

Safety assessments include evaluation of 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 study participants (using Visual Analogue Scale) and 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 and frequency of treatment-emergent serious adverse events.

3 STUDY DESIGN

This is a multi-center, two part study, designed to evaluate the efficacy, safety and tolerability of PRO 140 in conjunction with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks respectively. The patient population for this trial are treatment-experienced 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 classes, or two drug classes with limited treatment options.

The study is divided into four phases: Screening, Baseline,Treatment, and Follow-up.

Screening Phase begins with signing of Informed Consent and lasts up to 6 weeks. Subject will enter the Treatment Phase as soon as HIV-1 viral tropism, genotypic and/or phenotypic resistance results are available for review by Investigator.

The Baseline visit is to confirm HIV RNA continues to meet eligibility and will be conducted one week pior to the first treatment.

The Treatment phase is divided into two parts:

- **Part 1:** One-week treatment period consisting of PRO 140 along with existing ART (failed regimen).
- **Part 2:** 24-week treatment period consisting of PRO 140 along with Optimized Background Therapy (OBT)

All subjects will continue taking their existing ART (failed regimen) during the Screening Phase and first week of the Treatment Phase (Part 1). After Treatment Phase Part 1, all subjects will enter the 24-week treatment period (Part 2). During this period, all subjects will receive PRO 140 SC injection and OBT.

Study participants will be regularly monitored for viral load following initiation of PRO 140, and will cease weekly study treatment injections should they experience treatment failure.

Subjects who experience treatment failure at any point during Treatment Phase Part 2 will undergo the Treatment Failure (TF) 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) orup to a maximum of 6 months after cessation of therapy if the treating physician does not feelthat there is an antiretroviral regimen that will regain full viral suppression. Subjects who do not experience treatment failure, will be followed up every 2 weeks for total of 4 weeks.

Note: Subjects who are currently enrolled and receiving 350 mg dose will have the option to move to the 700 mg dose for the remainder of their participation in the trial.

3.1 STUDY CENTER(S)

Up to 40 centers in the United States

3.2 STUDY POPULATION

Study population includes treatment-experienced HIV-infected patients with CCR5-tropic virus who 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 option). The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.

3.3 ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

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

1. Males and females, age ≥18 years
2. Exclusive CCR5-tropic virus at Screening Visit as determined by Monogram Biosciences Trofile® Assay
3. Have a history of at least 3 months on current antiretroviral regimen
4. Treatment-experienced HIV-infected patients with documented genotypic or phenotypic resistance to at least one ART drug within three drug classes

   OR

   Treatment-experienced HIV-infected patients with documented genotypic or phenotypic resistance to at least one ART drug within two drug classes and have limited treatment option. The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due topotential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.
5. Be willing to remain on treatment without any changes or additions to the OBT regimen, except for toxicity management or upon meeting criteria for treatment failure
6. Plasma HIV-1 RNA ≥ 400 copies/mL at Screening Visit as determined by Human Immunodeficiency Virus 1 (HIV-1) Quantitative, RNA (Roche Taqman® Real-Time PCR)

and documented detectable viral load (HIV-1 RNA >50 copies/ml) within the last 3 months prior to Screening Visit

7. Laboratory values at Screening of:
    a. Absolute neutrophil count (ANC) ≥750/mm3
    b. Hemoglobin (Hb) ≥10.5 gm/dL (male) or ≥ 9.5 gm/dL (female)
    c. Platelets ≥75,000 /mm3
    d. Serum alanine transaminase (SGPT/ALT) <5 x upper limit of normal (ULN)
    e. Serum aspartate transaminase (SGOT/AST) <5 x ULN
    f. Bilirubin (total) <2.5 x ULN unless Gilbert's disease is present or subject is receiving atazanavir in the absence of other evidence of significant liver disease
    g. Creatinine ≤1.5 x ULN
8. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator
9. 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
10. 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

    Note: Subjects diagnosed with either substance dependence or substance abuse or any history of a concomitant condition (e.g., medical, psychologic, or psychiatric) may be enrolled if in the opinion of site investigator these circumstances would not interfere with the subject's successful completion of the study requirements

3.3.2 Exclusion Criteria

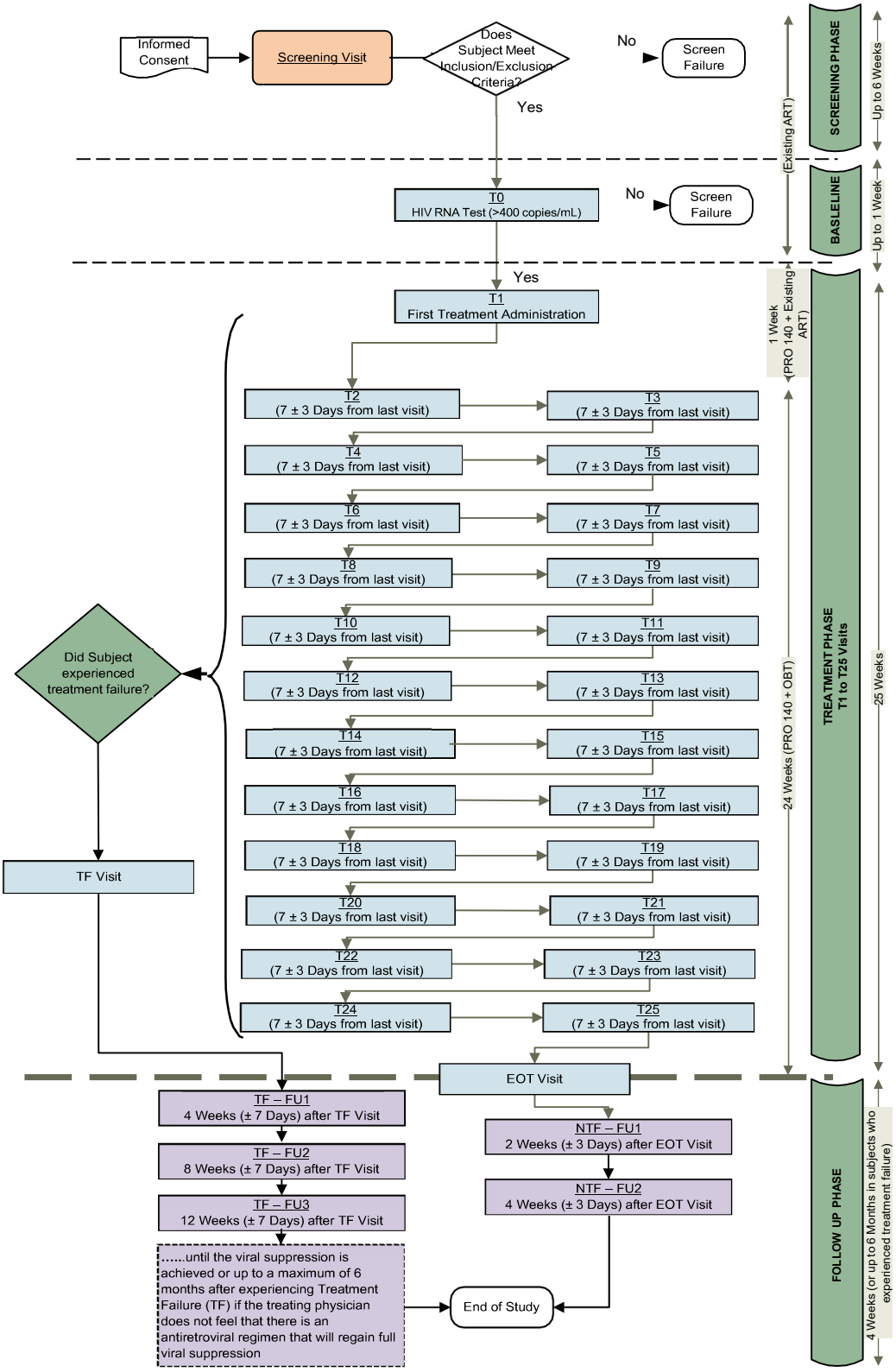
Subjects meeting any of the following criteria will be excluded from the study:

1. Documented CXCR4-tropic virus or Dual/Mixed tropic (R5X4) virus as determined by HIV-1 tropism assay

2. Patients with no viable treatment options (i.e., no fully active antiretroviral drug available which can be effectively combined to form a viable new OBT)
3. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)

   Note: Subjects infected by the hepatitis B virus or hepatitis C virus will be eligible for the study if they have no signs of hepatic decompensation and meet the liver function tests eligibility criteria
4. Laboratory test values of ≥ grade 3 DAIDS laboratory abnormality with the exception of the absolute CD4+ count criterion of <200/mm3
5. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
6. Unexplained fever or clinically significant illness within 1 week prior to the first study dose
7. Any vaccination within 2 weeks prior to the first study dose
8. Subjects weighing < 35kg
9. History of anaphylaxis to oral or parenteral drugs
10. History of Bleeding Disorder or patients on anti-coagulant therapy
11. Participation in an experimental drug trial(s) within 30 days of the Screening Visit
12. Any known allergy or antibodies to the study drug or excipients
13. Treatment with any of the following:
    a. Radiation or cytotoxic chemotherapy with 30 days prior to the screening visit
    b. Immunosuppressants within 60 days prior to the screening visit
    c. Immunomodulating agents (e.g., interleukins, interferons), hydroxyurea, or foscarnet within 60 days prior to the screening visit
    d. Oral or parenteral corticosteroids within 30 days prior to the Screening Visit. Subjects on chronic steroid therapy >5 mg/day will be excluded with the following exception:
        - Subjects on inhaled, nasal, or topical steroids will not be excluded
14. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy

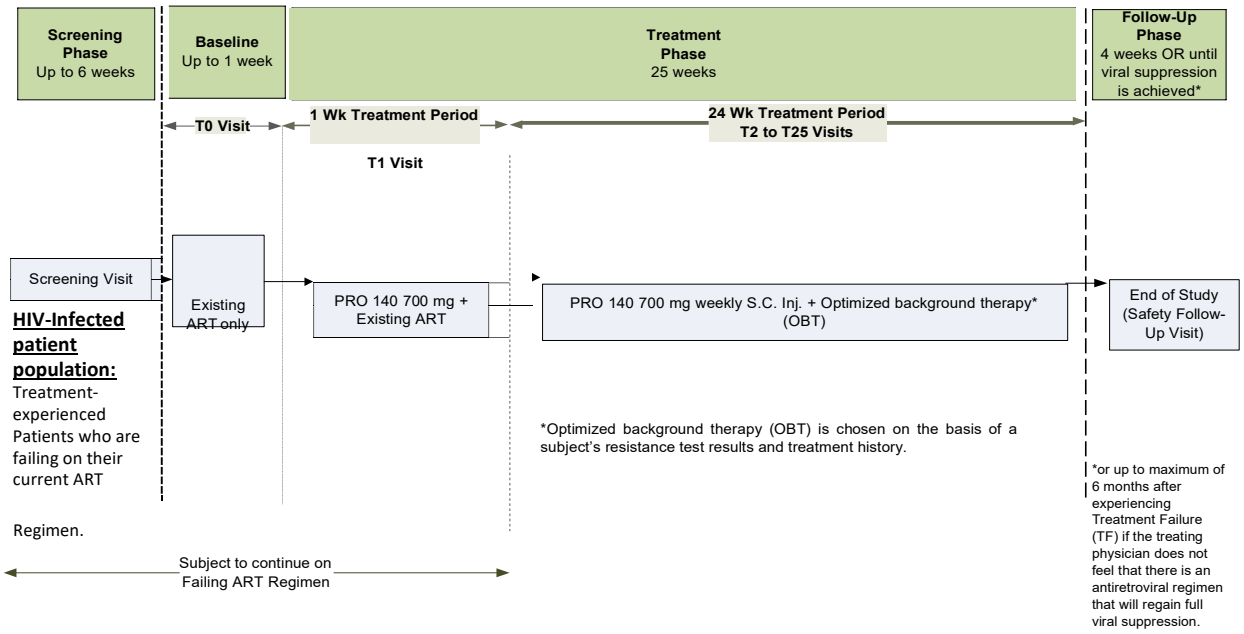
Figure 3-1: Study Flow Diagram



4 STUDY SCHEDULE

As shown in Figure 4-1, this study is divided into three phases: Screening, Treatment and Follow-up.

Figure 4-1: Study Schematic



(1) **Screening Phase:** This phase lasts up to 6 weeks, consists of Screening Visit (SV) and begins with signing of Informed Consent. Assessments performed during this phase determine the subject's final eligibility for study participation. First treatment will be administered within 42 days of Screening Visit.

All subjects will continue taking their existing ART (failed regimen) during the Screening Phase and first week of the Treatment Phase (Part 1).

(2) **Baseline:** The Baseline (T0) visit will take place within 6 weeks of the Screening Visit, as soon as HIV-1 viral tropism, genotypic and/or phenotypic resistance results are available for review by Investigator. HIV RNA and TruCount Assay will be performed to ensure continued eligibility prior to the first Treatment Visit (T1).

(3) **Treatment Phase:** Subjects will receive up to 25 treatments, given approximately every week (window period of ±3 days) or until treatment failure is experienced, whichever comes first.

The first Treatment Visit (T1) will take place within one week of the T0 visit.

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.

Note: *Study treatment injections at T1, T2, T3, T7, T11, T15, T19 and T23 must be administered at clinic. The remaining study treatment injections may be self- administered by subjects outside the clinic.*

Any time during Treatment Period Part 2, if treatment failure occurs, Investigator will readjust antiretroviral regimen based on HIV-1 genotypic and/or phenotypic drug resistance results obtained during the TF visit.

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

Treatment failure is defined in terms of virologic non-response and virologic rebound in Part 2 of the Treatment Phase of the study:

a) Virologic non-response is defined as two consecutive viral load results of:
   - <0.5 $\log_{10}$ copies/mL decrease in HIV-1 RNA at Day 7 of Treatment Period Part 2. *[Assessment Timepoint:T3 visit]*
   - <1 $\log_{10}$ copies/mL decrease in HIV-1 RNA at or after Week 4 of Treatment Period Part 2 unless HIV-1 RNA <400 copies/mL. *[Assessment Timepoint: from T6 up to T25 visit]*
   - Confirmed plasma HIV-1 RNA levels ≥400 copies/mL at Week 25 of the Treatment Period *[Assessment Timepoint: T25 visit]*

b) Virologic rebound is defined as two consecutive viral load results of:

   ≥1.0 $\log_{10}$ copies/mL increase in plasma HIV-1 RNA above nadir level* in Treatment Period Part 2 *[Assessment Timepoint: from T3 up to T25 visit]* or

   *Note: This refers to "Nadir" level in the Treatment Phase which starts from T2 visit

   - ≥400 copies/mL after suppression to <50 copies/mL in Treatment Period Part 2. *[Assessment Timepoint: from T3 up to T25 visit]*

(4) **Follow-Up Phase:** The duration of follow-up depends on whether or not subject has experienced treatment failure during Treatment Period Part 2.

- Subjects who experience treatment failure within Treatment Period Part 2 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 cessationof 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 treatment failure at the end of Treatment Period Part 2, 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

Procedure/Assessments	Screening Visit	Treatment Phase (26 weeks)																	In case of Treatment Failure
		ART only (1 week)	IP + ART (1 week)		IP + OBT (24 weeks)														
			T1																
Visit	SV	T0	(Pre-Rx)	(Post-Rx)	T2	T3	T4-6	T7	T8 - 10	T11	T12-14	T15	T16-18	T19	T20-22	T23	T24-25	EOT	TF
Window Period		Within 6 weeks of the Screening visit	Within 1 week ±3 days since T0		1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	
Informed Consent[1]	X																		
Eligibility Evaluation[2]	X																		
Subject Demographics	X																		
Medical History[3]	X		X																
HIV History	X		X																
Physical Examination	X		X[4]		X[4]	X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X	X
Neurological Examination[5]			X			X		X		X		X		X		X		X	X
Vital Signs[6]	X			X	X	X		X		X		X		X		X		X	X
Body Mass Index	X																	X	X
ECG	X																		
Complete Blood Count[7]	X							X				X						X	X
Biochemistry[8]	X							X				X						X	X
Coagulation Indices[9]	X							X				X						X	X
Serum Pregnancy Test[10]	X																		
Urinalysis[11]	X							X				X						X	X
HBsAg	X																		
Plasma HIV-1 RNA level	X	X	X		X	X		X		X		X		X		X		X	X
TruCount T assay[12]	X	X	X		X	X		X		X		X		X		X		X	X
PK conc. to PRO 140[13]			X					X				X						X	X

Procedure/Assessments	Screening Visit	Treatment Phase (26 weeks)																	In case of Treatment Failure
		ART only (1 week)	IP + ART (1 week)		IP + OBT (24 weeks)														
			T1																
Visit	SV	T0	(Pre-Rx)	(Post-Rx)	T2	T3	T4-6	T7	T8 - 10	T11	T12-14	T15	T16-18	T19	T20-22	T23	T24-25	EOT	TF
Window Period		Within 6 weeks of the Screening visit	Within 1 week ±3 days since T0		1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	
Serum conc. of ART Drugs[14]			X					X				X						X	X
Urine Pregnancy Test[10]			X																
Pre-enrollment Eligibility		X	X																
PRO 140 + Existing ART Regimen			X																
PRO 140 + OBT Administration					X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Reaction Assessment[15]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[16]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 Trofile® Assay[17]	X																		X
HIV-1 Drug Resistance Assay[18]	X		X		X	X		X		X		X		X		X			X
HIV-1 PhenoSense® Entry Assay[19]	X																		X
Anti-idiotypic antibodies to PRO 140			X					X				X						X	X
Blood sample collection for exploratory analysis[20]	X																		X
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Foot Notes:

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

[2] Initial evaluation of patient eligibility will be performed by Investigator.

[3] Medical history, past surgeries, disease history, history of substance abuse, social history, blood transfusion history, and current therapies (medications and non-medications).

[4] Symptom-directed physical examination

[5] The neurological assessment tool is based on the three question survey used by Simioni et al. (Simioni S, 2010) Additional neurological assessment modalities may be used as per Investigator's discretion.

[6] Post treatment vital signs will be recorded at T1-3, T7, T11, T15, T19, T23, EOT and TF visits (i.e.,blood pressure, heart rate, respiration rate, and temperature)

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

[8] 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)

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

[10] ONLY performed on women of childbearing potential.

[11] 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.

[12] Includes: CD3 %, CD4 %, CD8 %, Absolute Lymphocytes, CD3 cell count, CD4 cell count, and CD8 cell count

[13] PK samples for PRO 140 will be collected prior to IP administration at the T1, T7, T15, EOT and TF visits.

[14] Serum conc. of ART Drugs prior to IP administration at the T1, T7, T15, EOT and TF visits.

[15] Injection Site Reaction Assessment as assessed by Investigator (or designee) at each treatment visit that occurs in the clinic.

[16] Subject-perceived injection site pain (average pain since last treatment) will be assessed using the Pain Visual Analog Scale (VAS) prior to each study treatment administration that occurs in the clinic.

[17] Monogram Biosciences Trofile® DNA and RNA

[18] Monogram Biosciences PhenoSense® GT and Gensosure Archive (and PhenoSense Integrase and GeneSeq Integrase testing, if applicable)

[19] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (CXCR4 inhibitor drug), Maraviroc and PRO 140 (CCR5 inhibitor drugs).

[20] Quest Diagnostics HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing and/or HIV-1 Proviral Tropism

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

(a) Subjects who do NOT experience treatment failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2
	NTF-FU1	NTF-FU2
Window Period	2 weeks (±3 days) after EOT visit	4 weeks (±3 days) after EOT 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
Anti-idiotypic Antibodies to PRO 140		X

[1] Symptom-directed physical examination

(b) Subjects who experience treatment failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2	Follow-Up Visit -3[1]
	TF-FU1	TF-FU2	TF-FU3
Window Period	4 weeks (±7 days) after TF visit	8 weeks (±7 days) after TF	12 weeks (±7 days) after TF
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
Anti-idiotypic Antibodies to PRO 140	X		

[1] Subject will be followed up till the viral suppression is achieved or up to a maximum of 6 months after experiencing Treatment Failure (TF) 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

4.1.1 Pre-Screening

Sites are encouraged to pre-screen subjects for study inclusion, evaluating HIV-1 RNA prior to performing a full screening visit.

The subject will sign and date the pre-screening informed consent form (ICF) prior to any study-related pre-screening procedures. A unique identification number (pre-screening number) will be assigned to each subject who has provided written pre-screening informed consent. The pre-screening number will incorporate a three-digit Study Center number (PS201, PS202, PS203….) and a two-digit numeric ID assigned in successive order of consenting to pre-screening procedures after signing the pre-screening ICF at each center, beginning with 001 at each site (e.g. PS201-01 or PS202-01).

Once the pre-screening ICF has been signed, the following procedures and information will be obtained to confirm pre- eligibility including:
• Review of prior medical records for ART history and resistance to ART drugs
• Blood sample collection for HIV-1 RNA and TruCount assay

A pre-screening log will be maintained to capture the following information:
• Pre-screening number
• Patient initials
• Date pre-screened
• Initial eligibility
• Date of re-consent (for the full consent form) or reason for ineligibility

4.1.2 Screening Visits

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informedconsent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent. The subject screening number will incorporate a three-digit Study Center number (001, 002 or 003….) and a three-digit numeric ID assigned in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site (e.g. 001- 001 or 002-001).

Subject Screening # : **XXX - YYY**

XXX=Study Center YYY=Subject Numeric ID

All study centers will be instructed to maintain the study-specific pre-screening, screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

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

- Detailed medical history (see section 7.4),
- Detailed history of HIV infection and treatment (see section 7.5),
- Demographic information (see section 7.3),
- Prior and current medications review (see section 7.6),
- Physical examination (see section 7.7),
- Electrocardiogram (ECG) (see section 7.8),
- Body Weight & Height measurements (see section 7.10)
- Vital Signs (see section 7.10),
- Collection of Blood Specimens (see section 7.11) for
    - Complete Blood Count
    - Biochemistry
    - Coagulation Indices [Prothrombin time (PT) and INR]
    - Hepatitis B surface antigen (HBsAg)
    - Plasma HIV-1 RNA level
    - TruCount T Assay
    - HIV-1 viral tropism (Trofile® DNA or RNA Assay)
    - HIV-1 Drug Resistance Assay
    - HIV-1 PhenoSense® Entry (*Monogram BioSciences*)
    - Serum pregnancy test, 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.

- Blood sample collection for Exploratory/Confirmatory analysis

- Collection of Urine Specimen for Urinalysis (see section 7.11.13)

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 additionalinformation 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.

Eligible subjects that are not enrolled within 42 days of Screening Visit will have screening lab assessments repeated, with the exception of HIV-1 viral tropism, genotypic and/or phenotypic resistance, to reconfirm eligibility.

4.2 BASELINE

The Baseline (T0) visit will be performed for subjects who have met all eligibility criteria within 6 weeks of the Screening Visit, as soon as HIV-1 viral tropism, genotypic and/or phenotypic resistance results are available for review by Investigator. HIV RNA and TruCount Assay will be performed to ensure continued eligibility prior to the first Treatment Visit (T1). Subjects who have an HIV RNA result >400 copies/mL will be enrolled at the T1 visit. Subjects who have an HIV RNA result <400 copies/mL will be designated as screen failure.

The following assessments will be performed at the T0 visit:

- Change in concomitant medications (see section 7.5)
- Collection of Blood Specimens (see section 7.11) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay

4.3 TREATMENT PHASE

Treatment Phase begins with an evaluation of results of laboratory samples 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.

Eligible subjects will receive up to 25 treatments injections, given once per week (± 3 days) or until treatment failure, whichever occurs first. Eligible subjects will receive PRO 140 700mg administered as two subcutaneous injections within the first week of the Treatment Phase, followed by two subcutaneous injections of PRO 140 700mg, given once per week (± 3 days) for up to 24 weeks.

Treatment Phase is divided into two parts:

- Part 1: One-week treatment period [PRO 140 + failing ART]Part 2: 24-week treatment period [PRO 140 + OBT]

Note: A confirmatory HIV RNA test will be completed one week prior to initiation of treatment with PRO 140.

As shown in Table 4-3, enrolled subjects will have IP along with failing ART for one week.

Table 4-3 Part 1: One week period [IP (PRO 140) + existing ART]

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.) at T1 visit	SC injection

As shown in Table 4-4, all enrolled subjects will receive PRO 140 along with optimized background therapy (OBT) for up to 24 weeks after completing the initial 7-day treatment period.

Table 4-4 Part 2: 24-week treatment maintenance period [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 for up to 24 weeks (T2 – T25)	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.

Note: *Study treatment injections at T1, T2, T3, T7, T11, T15, T19 and T23 must be administered at clinic. The remaining study treatment injections may be self-administered by subjects outside the clinic.*

All study subjects will continue or adjust their current Optimized Background Therapy:

- At the end of 25-week Treatment Phase, or
- Anytime during the Treatment Phase, if treatment 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 levels, per the discretion of the Investigator.
- Subjects who experience treatment failure at any time during the Treatment Phase will undergo the Treatment Failure (TF) Visit assessments and enter the Follow-up Phase of the study.
- Subjects who meet any criteria (other than treatment failure) for discontinuation of study treatment as specified in section 5.2.1 of the protocol, will undergo End of Treatment Phase (EOT) Visit assessments and enter the Follow-up Phase of the study.
- Subjects who do not experience treatment failure will enter the Follow-up Phase of the study at the end of 25-week Treatment Phase.

Visits during the Treatment Phase will commence on T1, i.e. the date of first treatment, with weekly visits (± 3 days) thereafter. The first Treatment Visit (T1) will take place as soon as HIV-1 viral tropism, genotypic and/or phenotypic resistance results are available for review by Investigator, within 6 weeks of the Screening Visit.

4.3.1 Treatment Visit (T1) - Part 1 of Treatment Phase

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 at Screening Visit (see section 7.2)
- Neurological assessment (see section 7.9)
- Symptom-directed physical examination (see section 7.7),
- Change in concomitant medications (see section 7.5)
- Any changes in medical history since Screening Visit (see section 7.4),
- Collection of Blood Specimens (see section 7.11) for

- Plasma HIV-1 RNA level
- TruCount T Assay
- PK sample for PRO 140
- Anti-idiotypic antibodies to PRO 140
- Serum concentration of ART drugs
- HIV Drug Resistance Assay

➢ **Note:** *Blood sample for Plasma HIV-1RNA level, TruCount T Assay and HIV-1 Drug Resistance Assay will be collected at SV, T1, T2, T3, T7, T11, T15, T19, T23, EOT and TF visits.*

➢ **Note:** *PK sample for PRO 140 and Anti-idiotypic antibodies to PRO 140 will be performed at T1, T7, T15, EOT and TF visits*

➢ **Note:** *Serum concentration for ART will be performed at T1, T7, T15, visits, EOT and TF visits, as well as any Unscheduled Visit within the Treatment Phase as per discretion of the Investigator.*

- Urine Pregnancy Test (see section 7.11.6)

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 1 mL injections on opposite sides of the abdomen.

Note: All study treatments (PRO 140) 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 depending on the study visit week.

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).*

- Assessment of Adverse Events (AE) (see section 9)
- Vital Signs (see section 7.10) will be assessed within 15 minutes of study treatment administration.

Note: Investigator should determine the Optimized background therapy (OBT) regimen based on genotypic and/or phenotypic results obtained during Screening Phase and provide the appropriate prescription to the study subject at Treatment Visit 1 (T1).

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. The use of another experimental agent (e.g., ibalizumab) to create a viable HIV suppressive OBT regimen in certain subjects with severely limited approved and available therapeutic options will be allowed with the prior approval from sponsor.

4.3.2 Treatment Visit-2 (T2) to Treatment Visit-25 (T25) - Part 2 of Treatment Phase

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

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.5),
- Symptom-directed physical examination (see section 7.7),
- Neurological Assessment (see section 7.9)
  - **Note:** *Neurological assessment will be performed at T3, T7, T11, T15, T19, T23 visits*
- Vital Signs (see section 7.10)
  - **Note:** *Post-treatment vital signs will be assessed within 15 minutes following study treatment administration when performed inside clinic.*
- Collection of Blood Specimens (see section 7.11) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - HIV-1 Drug Resistance Assay
  - PK sample for PRO 140
  - Serum concentration of ART drugs
  - Anti-idiotypic antibodies to PRO 140
  - **Note:** *Blood sample for Plasma HIV-1RNA level, TruCount T Assay, and HIV-1 Drug Resistance Assay will be performed at SV, T1, T2, T3, T7, T11, T15, T19, T23, EOT and TF visits*
  - **Note:** *PK sample for PRO 140 and Anti-idiotypic antibodies to PRO 140 will be performed at T1, T7, T15, EOT and TF visits*

- **Note:** *Serum concentration for ART will be performed at T1, T7, T15, visits, EOT and TF visits, as well as any Unscheduled Visit within the Treatment Phase as per discretion of the investigator.*

- 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).*
- Subject-perceived Injection Site Pain Assessment (see section 7.14)
  - **Note:** *Subject-perceived injection site pain will be assessed using the Pain Visual Analog Scale (VAS) prior to study treatment administration assessing average pain at injection site since last treatment.*

4.3.3 End of Treatment (EOT) Visit

The following assessments will be performed for subjects who do not experience treatment 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 7.14),
- Collection of Blood Specimens (see section 7.11) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - Complete Blood Count
  - Biochemistry
  - Anti-idiotypic antibodies to PRO 140
  - PK sample for PRO 140
  - Serum Conc. of ART Drugs

4.3.4 Treatment Failure (TF) Visit

Treatment failure is defined in terms of virologic non-response and virologic rebound in Part 2 of the Treatment Phase:

(1) Virologic non-response is defined as two consecutive viral load results of:

- <0.5 $\log_{10}$ copies/mL decrease in HIV-1 RNA at Day 7 of Treatment Phase Part 2. *[Assessment Timepoint:T3 visit]*
- <1 $\log_{10}$ copies/mL decrease in HIV-1 RNA at or after Week 4 of Treatment Phase Part 2 unless HIV-1 RNA <400 copies/mL. *[Assessment Timepoint: from T6 up to T25 visit]*
- Confirmed plasma HIV-1 RNA levels ≥400 copies/mL at Week 24 of Treatment Phase Part 2. *[Assessment Timepoint: T25 visit]*

(2) Virologic rebound is defined as two consecutive viral load results of:

≥1.0 $\log_{10}$ copies/mL increase in plasma HIV-1 RNA above nadir level* in Treatment Phase Part 2 *[Assessment Timepoint: from T3 up to T25 visit]* or

*Note: This refers to "Nadir" level in Treatment Phase Part 2 which starts from T2 visit.

- ≥400 copies/mL after suppression to <50 copies/mL in Treatment Phase Part 2. *[Assessment Timepoint: from T3 up to T25 visit]*

The following assessments will be performed for subjects who experience treatment 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 7.14),
- 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

- Anti-idiotypic antibodies to PRO 140
- PK sample for PRO 140
- Serum Conc. of ART drugs
- Blood sample collection for Exploratory/Confirmatory analysis

- Change in Optimized Background Therapy based on genotypic and phenotypic results obtained at TF visit.

4.4 FOLLOW-UP PHASE

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

- Subjects who experience treatment failure within Treatment Phase Part 2 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 treatment failure at the end of Treatment Phase Part 2, will be followed up every 2 weeks for total of 4 weeks.

4.4.1 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 7.5),
- 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
  - Anti-idiotypic antibodies to PRO 140 (only at Treatment Failure - FU1 and Non Treatment Failure - FU2)

4.5 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 Treatment Phase Part 2 (without treatment failure) and 4- week Non-Treatment Failure Follow-Up Phase will be considered as having completed the study.
- A subject who experiences treatment failure during the Treatment Phase, undergoes the Treatment Failure (TF) Visit assessments and is followed up until viral suppression is achieved or up to a maximum of 6 months after experiencing treatment 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 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 MedicalMonitor 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 treatment failure

  Defined in terms of virologic non-response and virologic rebound in the Open-Label Treatment Phase (Part 2) of the study:

  (1) Virologic non-response is defined as two consecutive viral load results of:

  - *<0.5 log_{10} copies/mL decrease in HIV-1 RNA at Day 7 of Treatment Phase Part 2. [Assessment Timepoint:T3 visit]*
  - *<1 log_{10} copies/mL decrease in HIV-1 RNA at or after Week 4 of Treatment Phase Part 2 unless HIV-1 RNA <400 copies/mL. [Assessment Timepoint: from T6 up to T25 visit]*
  - *Confirmed plasma HIV-1 RNA levels ≥400 copies/mL at Week 24 of Treatment Phase Part 2. [Assessment Timepoint: T25 visit]*

  (2) Virologic rebound is defined as two consecutive viral load results of:

  - *≥1.0 log_{10} copies/mL increase in plasma HIV-1 RNA above nadir level* in Treatment Phase Part 2 [Assessment Timepoint: from T3 up to T25 visit] or*

    **Note: This refers to "Nadir" level in Treatment Phase Part 2 which starts from T2 visit*
  - *≥400 copies/mL after suppression to <50 copies/mL in Treatment Phase Part 2. [Assessment Timepoint: from T3 up to T25 visit]*

  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 requiretreatment 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 continueto 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 used during Part 1 and Part 2 of the Treatment Phase 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. One study injection kit will be assigned per subject per treatment visit.

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 and Table 6-2 provide the unit strength, dosing frequency and mode of administration for the study drug.

Table 6-1: Investigational Product - PRO 140 at T1 visit

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 2mL/inj.) per week on opposite sides of abdomen at T1 visit	SC injection

Table 6-2: Investigational Product - PRO 140 at T2 - T25 visit

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 2mL/inj.) per week on opposite sides of abdomen for up to 24 weeks (T2 – T25)	SC injection

Note: Patients with low body fat percentages may find subcutaneous injections uncomfortable. In such cases, PRO 140 700 mg can be injected as four 175mg/ml injections of 1 mL each and/or can be placed at different areas other than abdomen as per discretion of the Investigator.

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

Study drug will be prepared by Ajinomoto Althea, Inc. and will be packaged, labeled, and shipped by Sherpa Clinical Packaging, LLC.

The contents of each vial are described in Section 6.1. PRO 140 kits will be labeled withinformation 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, Fixed Dose Procedure (FDP) individual vial (

Figure 6-1), syringe label (Figure 6-2), and kit labels (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

Part 1: One-week treatment period (T1)

Protocol: PRO 140_CD02 Kit No. xxx 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. xxx 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

Part 2: 24-week treatment period (T2 – T25)

Protocol: PRO 140_CD02 Kit No. xxx 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. xxx 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

Part 1: One-week treatment period (T1)

Protocol: PRO 140_CD02 Contents of Kit No. xxx

This syringe contains 1 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

Part 2: 24-week treatment period (T2 – T25)

Protocol: PRO 140_CD02 Contents of Kit No. xxx

This syringe contains 1 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

Part 1: One-week treatment period (T1)

Protocol: PRO 140_CD02 Kit No. xxx

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

Part 2: 24-week treatment period (T2 – T25)

Protocol: PRO 140_CD02 Kit No. xxx

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

The pharmacy manual 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 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 1.0 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.

Note: Patients with low body fat percentages may find subcutaneous injections uncomfortable. In such cases, PRO 140 700 mg can be injected as four 175mg/ml injections of 1 mL each and/or can be placed at different areas other than abdomen as per discretion of the Investigator.

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.

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 accountabilitycan 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 besent 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 T1 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

A medical history will be recorded during the Screening Phase and will include:

- All ongoing medical conditions
- Disease history (HIV), history of substance abuse, social history, blood transfusion history and any past surgeries
- All previously resolved medical conditions related to HIV or which are relevant in the judgment of the Investigator
- Any prior medical conditions that have resolved within the last year

Events that emerge prior to the first treatment (T1) will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to the patient's receiving investigational product (IP) treatment.

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Genitourinary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing)

7.5 HIV HISTORY

A detailed HIV history will be recorded during the Screening Phase and will include:

- Date of diagnosis
- Most recent viral load and CD4 count
- Nadir CD4 and peak viral load, if known
- ART-related history

- Current and previous ART regimens
- Date of initiation of ART
- Reasons for changes in ART
- Previous adverse drug reactions, including hypersensitivity reactions to prior therapies
- Challenges with adherence to therapy
- History of drug resistance, if known
- Opportunistic infections, malignancies, and previous adverse reactions to drugs used for opportunistic infections prophylaxis

7.6 PRIOR / CONCOMITANT MEDICATIONS AND NON-STUDY TREATMENTS

A complete history of 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 beginning 30 days prior to first Screening Visit and 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.

7.6.1 Excluded Medications and Therapies

1. Use of Maraviroc or any other CCR5 antagonist
2. Use of oral or parenteral corticosteroids (>5 mg/day) is NOT allowed during the study, with the following exceptions:
    - Use of chronic systemic corticosteroids at replacement doses (e.g., < 5mg/day prednisone) AND use of inhaled, nasal, or topical steroids are allowed.
    - Use of short course of systemic corticosteroids (Medrol pack) after T2 will only beallowed with prior approval from the sponsor.
3. Use of radiation or cytotoxic chemotherapy, immunosuppressants and immunomodulating agents (e.g., interleukins, interferons) or agents with known anti-HIV activity (i.e., hydroxyurea, foscarnet) are NOT allowed during the study.
4. Use of any non-FDA approved/investigational therapy

7.6.2 Allowable Medications and Therapies

All other medications/therapies that are not otherwise prohibited and, in the judgment of the Investigator, are required for proper medical care of the subject may be prescribed.

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 Screening Visit (SV), End of Treatment (EOT) Visit, and at Treatment Failure (TF) Visit. Only symptom-directed physical examination will be performed 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 the Screening Visit (SV) 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 at Treatment Visits 1, 3, 7, 11, 15, 19 and 23 (T1, T3, T7, T11, T15, T19, T23), End of Treatment (EOT) and at Treatment Failure (TF) 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 (INC. HEIGHT AND WEIGHT)

Vital signs will be collected at all study visits performed at the clinic. Vital signs collected during the Treatment Phase 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:

- Height (at Screening Visit)
- Weight (at SV, EOT and TF visits)
- BMI (derived from the height and weight measurements; at SV, EOT and TF visits)

- 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

Blood and urine samples will be collected 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 Screening Visit, T7, T15 End of Treatment Phase Visit or Treatment 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 Screening Visit, T7, T15, End of Treatment Phase Visit or Treatment 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 PK sample for PRO 140

- Frequency of testing: At the T1, T7, T15, EOT and TF visits.

7.11.4 Anti-idiotypic antibodies to PRO 140

- Frequency of sample collection*: At the T1, T7, T15, EOT and TF visits in addition to Treatment Failure Follow-up Visit 1 (TF-FU1) and Non-Treatment Failure Follow-up Visit 2 (NTF-FU2)

  ****Note:** Sera will be collected from study subjects and stored at -80°C for future analysis.*

7.11.5 Serum pregnancy test

- Frequency of testing: At Screening Visit
- Only 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.

7.11.6 Urine pregnancy test

- Frequency of testing: At Treatment Visit 1 prior to first 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.

7.11.7 Plasma HIV-1 RNA level and TruCount T Assay

- Frequency of testing: At SV, Treatment Visits 1, 2, 3, 7, 11, 15, 19 and 23, as well as EOT and TF visits. In addition, blood sample will also be collected at all Treatment Failure Follow-up (TF-FU) Visits or Non-Treatment Failure Follow-up (NTF-FU) 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 (Abbott RealTime) test.*

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

7.11.8 HIV-1 Trofile® Assay

- Includes:

  a. Trofile® RNA Assay

  b. Trofile® DNA Assay

  Trofile® RNA is the primary assay used to assess HIV-1 co-receptor tropism status. However, Trofile® DNA can be used at the discretion of the Investigator when lastrecorded viral load is less than 1000 copies/mL.

- Frequency of testing: At SV and TF visits

7.11.9 HIV-1 Drug Resistance Assay

- Includes:

  a. PhenoSense® GT

b. PhenoSense Integrase and GeneSeq Integrase testing

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).

PhenoSense Integrase and GeneSeq Integrase testing will be additionally performed if subject has past exposure to an integrase or in cases where complex drug resistance patterns is known or suspected.

- Frequency of sample collection: At SV, T1, T2, T3, T7, T11, T15, T19, T23 and TF

Samples for PhenoSense® GT (and PhenoSense Integrase and GeneSeq Integrase testing, if collected) during visits T1, T2, T3, T7, T11, T15, T19, and T23 will be stored at Lab and will be analyzed only if subject experiences Treatment Failure.

7.11.10 HIV-1 PhenoSense® Entry assay

- Frequency of testing: At SV and TF visits
- With AMD3100 (CXCR4 inhibitor drug), Maraviroc and PRO 140 (CCR5 inhibitor drugs).

7.11.11 Serum Concentration of ART drugs

- Frequency of sample collection: At Treatment Visits 1, 7, 15, EOT and TF.
- Sample collected at T1 visit is to identify serum concentration for ART drugs (failing regimen) at the time of first study dose while sample collected at T7, T15, EOT and TF visit is to confirm subject compliance to OBT regimen during Part 2 of the Treatment Phase.

7.11.12 Blood sample collection for Exploratory/Confirmatory analysis

- Includes:

a. HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing or

b. HIV-1 Proviral Tropism

The Quest Diagnostics HIV-1 coreceptor tropism test begins with standard Sanger sequencing of the third variable (V3) loop of the HIV-1 gene, the primary determinant of viral tropism. The next-generation DNA sequencing (ultradeep sequencing [UDS]) is performed if standard sequencing detects only CCR5 virus. HIV-1 Coreceptor Tropism, Proviral DNA test is used when the plasma viral load is <1000 copies/mL.

- Frequency of testing: At SV and TF visits

7.11.13 Urinalysis

- Frequency of testing: At the Screening Visit, T12, EOT and TF.
- 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

7.11.14 Coagulation Indices

- Frequency of testing: At the Screening Visit, T12, EOT and TF.
- Prothrombin time (PT) and International Normalized Ratio (INR)

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 (or designee) starting after the first injection is given. Refer to sections 9.1.8 and 16.3 for more details.

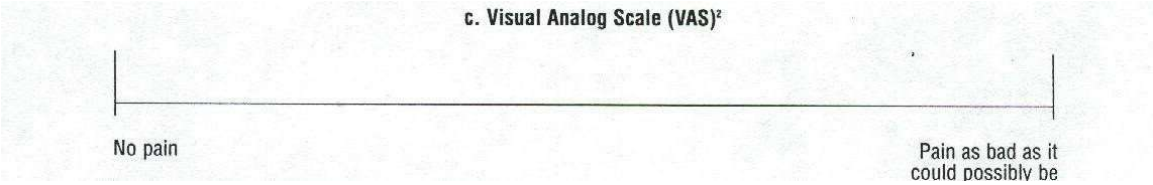
7.14 Pain Assessment using Visual Analog Scale (VAS)

Tolerability of repeated subcutaneous administration of PRO 140 is evaluated based on assessment of subject-perceived injection site pain using the Pain Visual Analog Scale (VAS). This assessment will be performed each time subjects arrive to the clinic for the study visit.

Beginning at Treatment Visit 2, subjects will be asked to mark the point that best represents the average pain intensity **over the past week** at the injection site on a horizontal line (100 mm in length) anchored by the following word descriptors at each end, “no pain" on the left side and "pain as bad as it could possibly be" on the right side of the line. The subject marks on the line or by pointing to a position on the line the point that they feel represents their perception of their

pain state. The VAS score is determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks.

Figure 7-1: Visual Analog Scale



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 an open label study. All eligible subjects will receive study treatment within 6 weeks of Screening Visit, followed by weekly subcutaneous injections of study treatment for up to 24 weeks.

8.2 DESCRIPTION OF STUDY ENDPOINTS

8.2.1 Primary Endpoint

The primary endpoint for this study is proportion of participants with a ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline to the end of the initial 1-week treatment period.

8.2.2 Secondary Endpoint

The secondary endpoints will be as follows:

1. Proportion of participants with ≥ 1 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline to the end of the initial 1-week treatment period
2. Mean change from Baseline in HIV-1 RNA levels ($\log_{10}$ copies/mL) to the end of the initial 1-week treatment period
3. Percentage of participants achieving HIV-1 RNA < 400 copies/mL at week 25
4. Percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 25
5. Mean change from Baseline in HIV-1 RNA levels ($\log_{10}$ copies/mL) at week 25
6. Mean change from Baseline in CD4 cell count at the end of the initial 1-week treatment period
7. Mean change from Baseline in CD4 cell count at week 25

8.2.3 Safety Assessments

Safety measurements will include:

- 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 study participants (using Visual Analogue Scale) and 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

8.3 SAMPLE SIZE DETERMINATION AND RATIONALE

Up to 25 subjects (or any number of subjects that can be enrolled by the time of BLA submission for PRO 140) will be enrolled in this study. The sample size is based on clinical judgement with an intention to supplement the data for the target BLA indication.

8.4 RANDOMIZATION AND BLINDING

No randomization or blinding requirement.

8.5 INTERIM ANALYSIS

No interim analysis planned for this study.

8.6 GENERAL STATISTICAL CONSIDERATIONS

8.6.1 Analysis Populations

8.6.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as the set of subjects who are enrolled and have received at least one dose of PRO 140.

Subjects who discontinue from the study prior to their first post-baseline assessment will be included in the ITT population and analyzed as non-responders in the primary safety analysis.

8.6.1.2 Per Protocol Population

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, and were not associated with a major protocol violation. This population will be identified before the database lock.

8.6.1.3 Safety Population

The Safety population is defined as all 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 9.4 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 efficacy and 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

For the per protocol analysis of efficacy endpoints there will be no imputation of missing data. However, missing data will be imputed using different methods that will be detailed in the SAP for the ITT population of the primary and secondary endpoints.

8.7 DATA SUMMARY

8.7.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The number of subjectsscreened, received treatment, completed, and discontinued during the study, as well as the reasonsfor 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 Screening Visit, 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 Efficacy Analysis

8.7.4.1 Primary Analysis

The primary analysis will be conducted on the ITT population.

All data from the primary and secondary endpoints 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.

8.7.4.2 Supportive Analysis

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the PP population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used.

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 besummarized 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 study participants (using Visual Analogue Scale) and 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 visit and continue up until the final study visit (i.e. up to NTF-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 onsetand 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 relationshipof 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 judgement, 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 childis 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 Amarex Safety Department within 24 hours:

CRO Medical Monitor	Attn: Shide Badri, MD Amarex LLC 20201 Century Boulevard, Suite 450 Germantown, MD 20874 Email: saereporting@amarexcro.com Phone: +1 (240) 454-6844 Fax: +1 (240) 454-6602

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 andeach 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 protocoladherence 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 willbe 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.

For the IA, a cut-off date for data collection and monitoring will be determined and sites will be requested to provide current information up to the cut-off date.

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 ofthe 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 alsohas 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. Allprotocol 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 thePrincipal Investigator and Sponsor or Sponsor designee. The Investigator will not participate inthe 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 correspondenceto 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 beobtained 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 fromthe 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 researchrecords 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.

15 REFERENCES

Demeter LM Shafer RW, Meehan PM, Holden-Wiltse J, Fischl MA, Freimuth WW, Para MF, Reichman RC. Delavirdine susceptibilities and associated reverse transcriptase mutations in human immunodeficiency virus type 1 isolates from patients in a phase I/II trial of delavirdine monotherapy (ACTG 260). Antimicrob.Agents Chemother.. - 2000. - Vol. 44. - pp. 794-797.

Gulick RM Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, Nadler J, Clotet B, Karlsson A, Wohlfeiler M, Montana JB, McHale M, Sullivan J, Ridgway C, Felstead S, Dunne MW, van der Ryst E, Mayer H. Maraviroc for Previously Treated Patients with R5 HIV-1 Infection NEJM. - October 2, 2008. - Vol. 359 : 14. - pp. 1429-1441.

Jacobson JM Lalezari JP, Thompson MA, Fichtenbaum CJ, Saag MS, Zingman BS, D'Ambrosio P, Stambler N, Rotshteyn Y, Marozsan AJ, Maddon PJ, Morris SA, Olson WC. study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. Antimicrob Agents Chemother.. - 2010. - Vol. 54. - pp. 4137-42..

Jacobson JM Saag MS, Thompson MA, Fischl MA, Liporace R, Reichman RC, Redfield RR, Fichtenbaum CJ, Zingman BS, Patel MC, Murga JD, Pemrick SM, D'Ambrosio P, Michael M, Kroger H, Ly H, Rotshteyn Y, Buice R, Morris SA, Stavola JJ, Maddon PJ, Kremer AB, Ols Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. J Infect Dis.. - 2008. - Vol. 198. - pp. 1345-52..

Jacobson JM Thompson MA, Lalezari JP, Saag MS, Zingman BS, D'Ambrosio P, Stambler N, Rotshteyn Y, Marozsan AJ, Maddon PJ, Morris SA, Olson WC. Anti-HIV-1 activity of weekly or biweekly treatment with subcutaneous PRO 140, a CCR5 monoclonal antibody. J Infect Dis.. - 2010. - Vol. 201. - pp. 1481-7.

Marozsan A. J., T. Parsons, W. Huang, E. Stawiski, J. M. Whitcomb, P. J. Maddon, and W. C. Olson. Clonal analysis of HIV-1 co-receptor tropism change following treatment with PRO 140, a CCR5 monoclonal antibody. 48th Annual ICAAC / IDSA 46th Annual Meeting. - Washington, DC. : [s.n.], 2008. - Vols. Abstract H-1218.

Moyle G Gatell J, Perno CF, Ratanasuwan w, Schechter M, Tsoukas C Potential for new antiretrovirals to address unmet needs in the management of HIV-1 infection. AIDS Patient Care STDS. - 2008. - pp. 459-471.

Nishikawa M Takashima K, Nishi T, Furuta RA, Kanzaki N, Yamamoto Y et al. Analysis of binding sites for the new small-molecule CCR5 antagonist TAK-220 on human CCR5. Antimicrob Agents Chemother. - 2005. - Vol. 49(11). - pp. 4708-4715..

Office of AIDS Research Advisory Council AIDSinfo Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [Online] AIDS Info. - Nov 13, 2014. - Dec 29, 2014. - http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Richman D. D., D. Havlir, J. Corbeil, D. Looney, C. Ignacio, S. A. Spector, J. Sullivan, S. Cheeseman, K. Barringer, D. Pauletti. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. J Virol.. - 1994. - Vol. 68. - pp. 1660-1666..

Saag M. S., E. A. Emini, O. L. Laskin, J. Douglas, W. I. Lapidus, W. A. Schleif, R. J. Whitley, C. Hildebrand, V. W. Byrnes, J. C. Kappes. A short-term clinical evaluation of L-697,661, a non-nucleoside inhibitor of HIV-1 reverse transcriptase. N.Engl.J Med.. - 1993. - Vol. 329. - pp. 1065-1072..

Simioni S Cavassini M, Annoni J, Abraham AR, Bourquin I, Schiffer V, Calmy A, Chave J, Giacobini E, Hirschel B, Du Pasquier RA Cognitive dysfunction in HIV patients despite long-standing suppression of viremia.. - 2010. - Vol. 24. - pp. 1243-1250.

Tang MW Shafer RW HIV-1 Antiretroviral Resistance: Scientific Principles and Clinical Applications Drugs. - 2012. - pp. e1-e25.

Thompson M., Lalezari, J., Saag, M., Jacobson, J., Zingman, B., Stambler, N., D'Ambrosio, P., Maddon, P., Olson, W., and Morris, S. Weekly and bi-weekly subcutaneous PRO 140 demonstrates potent, sustained antiviral activity. 16th Conference on Retroviruses and Opportunistic Infections. - Montreal QE, Canada, : [s.n.], 2009. - Vol. Abstract #571a.

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.