An extension of Protocol PRO 140_CD 01 to further evaluate the long-term Suppression of HIV-1 Replication following Substitution of Stable Combination Antiretroviral Therapy with a PRO 140 (Monoclonal CCR5 antibody) Monotherapy in Adult Subjects with HIV-1 infection

Protocol Number:	**PRO 140_CD 01-Extension**
Version:	**12.0**
Date:	**02 Apr 2021**

Sponsor:

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Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**PRO 140_CD 01-Extension**
Version:	**12.0**
Date:	**02 Apr 2021**

PROTOCOL APPROVAL FOR USE

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

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**PRO 140_CD 01-Extension**
Version:	**12.0**
Date:	**02 Apr 2021**

INVESTIGATOR'S SIGNATURE

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

Principal Investigator's Signature _____ Date _____

Print Name _____

Address _____

Site Number _____

SPONSOR INFORMATION

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CONTRACT RESEARCH ORGANIZATION INFORMATION

PROTOCOL SYNOPSIS

Name of Sponsor: CytoDyn Inc.	
Name of Study Product: PRO 140 (Humanized monoclonal antibody to CCR5) **Comparator:** Historical Control	
Protocol Number: PRO 140 _CD 01-Extension	**Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection
Title of Study: An extension of Protocol PRO 140_CD 01 to further evaluate the long-term suppression of HIV-1 replication following substitution of stable combination antiretroviral therapy with a PRO 140 (Monoclonal CCR5 antibody) monotherapy in adult subjects with HIV-1 infection	
Study Center(s): Site(s) participating in PRO 140 _CD 01 Protocol	
Planned Number of Subjects: Up to 28 subjects	**Study Development Phase:** Phase-2b
Indication for Use: Human Immunodeficiency Virus Type-1 (HIV-1) Infection	
Objectives: The primary objective is to assess the long-term efficacy of PRO 140 monotherapy for the maintenance of viral suppression in patients who have completed 12 weeks of treatment under Protocol PRO 140_CD 01 without experiencing virologic failure. The secondary objectives of the trial are to assess the long-term clinical safety and tolerability parameters of continued PRO 140 use in patients who have completed 12 weeks of treatment under Protocol PRO 140_CD 01 without experiencing virologic failure.	
Endpoints: **Primary Efficacy Endpoints:** Time to virologic failure after initiating PRO 140 monotherapy Virologic failure is defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days. **Secondary Efficacy Endpoints:** • Proportion of participants with virologic failure after initiating PRO 140 monotherapy. • Mean change in viral load (HIV-1 RNA levels) • Mean change in CD4 cell count • Change in Quality of Life metrics (up to TE107) **Safety Assessments:** • 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.	

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- 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 study is a Phase 2b, multi-center, extension study designed to evaluate the long-term efficacy, safety, and tolerability of PRO 140 monotherapy for the maintenance of viral suppression in patients who were stable on combination antiretroviral therapy and completed 12 weeks of treatment under PRO 140_CD 01 Treatment Substitution Study without experiencing virologic failure.

Consenting patients will continue to receive PRO 140 monotherapy until IP receives marketing approval or IND is withdrawn by Sponsor. There is one week overlap of existing retroviral regimen and PRO 140 at the end of the treatment extension phase in subjects who do not experience virologic failure.

PRO 140 will be administered as a 350 mg subcutaneous injection weekly during treatment extension phase. Study participants will be monitored for viral rebound on a weekly basis following initiation of PRO 140 monotherapy and will re-initiate their previous antiretroviral regimen if plasma HIV-1 RNA levels rise above 400 copies/ml on two consecutive blood draws at least 3 days apart.

NOTE: Patients that were enrolled under a previous Protocol version and are still receiving the 350 mg dose, have the option of increasing their dose to 700mg for the remainder of the Treatment Extension Phase.

The study will have three phases: Screening Phase, Treatment Extension Phase and Follow-up Phase.

Screening Phase (14 ± 3 days):

This phase is designed to determine whether subjects participating in PRO 140_CD 01 Treatment Substitution study are eligible to continue PRO 140 monotherapy in the Treatment Substitution Extension study. This phase consists of a series of screening 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.

This phase consists of two screening visits (SV1 and SV2) which correspond to Treatment Visits 12 and 13 of the PRO 140_CD 01 Treatment Substitution Study, respectively.

Subjects participating in PRO 140_CD 01 Treatment Substitution study that have not experienced virologic failure will be approached for study participation at Treatment Visit 12 (T12). A signed informed consent form will be obtained at the T12 visit which serves as Screening Visit 1 (SV1) for the PRO 140_Treatment Substitution Extension study.

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In addition to assessments scheduled at T12 for the PRO 140_CD 01 Treatment Substitution study, the following assessments will also be performed to determine eligibility for the PRO 140_Treatment Substitution Extension study:

- Medical History
- Physical Examination

The lab results of blood samples collected at SV1 (or T12 of the PRO 140_CD 01 Treatment Substitution study) will be reviewed at SV2 (or T13 of the PRO 140_CD 01 Treatment Substitution study).

Treatment Extension Phase (weekly ±3 days):

Treatment Extension (TE) 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 failures,
- will not be allowed to enter the extension study,
- will re-initiate their existing anti-retroviral therapy regimen at T13 visit under the existing PRO 140_CD 01 Treatment Substitution study, and
- will proceed to enter follow-up phase after T14 visit depending on viral status.

For subject who meets the eligibility criteria, the first Treatment Extension Visit (TE1) will take place 14 days from Screening Visit-1.

Eligible subjects will receive weekly treatments, given every week (± 3 days) or until virologic failure, whichever occurs first. Treatment Extension Phase visits will commence on TE1, i.e. the date of first treatment, with weekly visits (± 3 days) thereafter.

Efficacy assessments at each week will include assessment of viral load and CD4 cells count. Safety assessments will consist of physical exam, lab, and adverse event assessments at each Treatment Extension and Follow-Up Visits.

The study treatment (PRO 140 SC injections) will be administered by a licensed medical professional (MD, DO, PA, LPN, LVN, NP, RN, or CMA if permitted by state law) or by subjects trained to perform self-administration of study treatment.

All study subjects will re-initiate their previous antiretroviral regimen:

- One week prior to the end of Treatment Extension Phase, or

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- During the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in section 5.2 of the PRO 140_Treatment Substitution Extension Study protocol.

Subjects who experience virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days) at any time during the Treatment Extension Phase will undergo the Virologic Failure (VF) Visit assessments and then exit the Treatment Extension Phase to enter the Follow-up Phase of the study.

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

Follow-up Phase:

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

- Subjects who experience virologic failure will be followed up every 4 weeks until the viral suppression is achieved (i.e., plasma HIV-1 RNA levels return to <50 copies/mL)
- Subjects who do not experience virologic failure at the end of Treatment Extension Phase, will be followed up every 2 weeks for total of 4 weeks.

➢ ***Note**: Virologic failure subjects will have a long term safety follow up visit once a year within 2 years of completing the last VF-FU visit.*

Duration of Study:

- **Screening Phase:** 14 ± 3 days
- **Treatment Extension Phase:** Weekly ± allowed windows (±3 days).
- **Follow-up Phase:**
  - Virologic Failure: Until viral suppression is achieved
  - Non-Virologic Failure (NVF): 4 weeks

Total Study Duration:

Weekly until IP receives marketing approval or IND is withdrawn by Sponsor. [Does not include additional follow-up time for virologic failure subjects]

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

1. Subjects who have completed 12 weeks of treatment in PRO 140_CD 01 study without experiencing virologic failure.

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2. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods (birth control pills, barriers, or abstinence) throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative urine pregnancy test prior to receiving the first dose of study drug.
3. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

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

1. Not currently enrolled in PRO 140_CD 01 Treatment Substitution Study
2. Any acquired immune deficiency syndrome (AIDS)-defining illness according to the 1993 Centers for Disease Control and Prevention (CDC) AIDS surveillance definition
3. Laboratory test values ≥ grade 4 DAIDS laboratory abnormality.
4. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
5. Unexplained temperature >38.5^{o}C (101.3^{o}F) for seven consecutive days within 14 days prior to the first study dose
6. Diagnosed with either substance dependence or substance abuse or any history of a concomitant condition (e.g., medical, psychological, or psychiatric) that in the opinion of the primary care provider and/or site investigator would interfere with the subject's successful completion of the study requirements
7. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy

Statistical Considerations:

Sample Size Determination and Rationale:

Sample size determination is not applicable as only those subjects who are currently enrolled in PRO 140_CD 01 Treatment Substitution Study are allowed to participate in this extension study.

Analysis Populations:

The **Intent-to-Treat (ITT)** population is defined as the set of subjects who have received at least one dose of PRO 140 in the extension study and have at least one post-treatment efficacy assessment for viral load.

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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 PP population will be the primary analysis population for the analysis of primary and secondary endpoints.

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.

Interim Analysis:

There is no planned interim analysis (IA) for efficacy. IA for safety will be conducted after all enrolled subjects complete extended treatment with PRO 140 or until study treatment is discontinued, whichever comes first.

Virologic failure will be reported to the Data Monitoring Committee as the event occurs, allowing the DMC to review interim results and make recommendations to the Sponsor.

Statistical Analysis:

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

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

Efficacy Analysis

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

The primary efficacy endpoint for this study is time to virologic failure after initiating PRO 140 monotherapy. Virologic failure is defined as two consecutive HIV-1 RNA levels of $\geq$ 400 copies/ml separated by at least 3 days.

The time to virologic failure for the subjects treated with PRO 140 monotherapy will be compared to a historical data (i.e., time to HIV-1 RNA viral load > 500 copies/mL of 29 days). The statistical comparison will be conducted using Wilcoxon rank sum test and the median time to virologic failure for this study will be compared to 30 days.

All the data from the secondary endpoint will also be summarized according to the variable type.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADL	Activities of Daily Living
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ART	Antiretroviral Therapy
AST	Aspartate Transaminase
ATC	Anatomic Therapeutic Classification
AUC	Area Under Curve
BMI	Body Mass Index
°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
CMA	Certified Medical Assistant
CRA	Clinical Research Associate
CRF	Case Report Form
C_{max}	Maximal Concentration
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DO	Doctor of Osteopathic Medicine
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
Emax	Maximum drug effect
et al	et aliae; Latin for "and others"
°F	Fahrenheit

Abbreviation	Term
FDA	U.S. Food and Drug Administration
FDP	Fixed Dose Procedure
FU	Follow-Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HAART	Highly Active Antiretroviral Therapy
Hb	Hemoglobin
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
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
MoCA	Montreal Cognitive Assessment
MW	Molecular Weight
NCS	Not Clinically Significant

Abbreviation	Term
NP	Nurse Practitioner
NVF	Non-Virologic Failure
PA	Physician Assistant
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
Pr	Protease
QC	Quality Control
QoL	Quality of Life
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
TE	Treatment Extension
TEAE	Treatment Emergent Adverse Events
USA	United States of America
VAS	Visual Analogue Scale
VF	Virologic Failure
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

1.1 STATEMENT OF INTENT

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

1.2 THE PROBLEM STATEMENT

Substantial progress has been made over the past two decades in the development of effective and well tolerated combination antiretroviral regimens. Most HIV-1 infected persons who initiate antiretroviral therapy at early stages in the disease process and who are fully adherent to their antiretroviral regimens can anticipate life expectancies that are measured in decades. Although these advances have revolutionized antiretroviral therapy for most HIV-1 infected patients, contemporary lifelong daily adherence to treatment regimens remains challenging for a significant subset of patients. A number of studies have been conducted to evaluate the possibility of treatment simplification following control of viral replication with an induction regimen [Arribas JR, 2005][Pulido F, 2008][Moltó J, 2007] [Cameron DW, 2008][Nunes EP, 2009][Meynard JL, 2010][Katlama C, 2010][Gutmann C, 2010][Cahn P, 2011][Guiguet M et al., 2012]. Most of these simplification trials have involved the substitution of a boosted HIV-1 protease inhibitor such as lopinavir or darunavir for an effective combination regimen. Although the strategy has been successful in a substantial fraction of those who undergo regimen simplification, the overall body of evidence suggests that boosted protease inhibitor maintenance therapy is generally less effective than maintenance on a three drug regimen [Calza L, 2012][Thompson MA, 2012]. Factors influencing the likelihood of success include the duration of successful suppression prior to the regimen simplification and the extent to which patients are adherent to their simplified regimens [Calza L, 2012]. Although it has also been suggested that some patients may fail because of variability in trough concentrations of protease inhibitors, this has not been substantiated in rigorously conducted studies [Boffito M, 2003]. Other concerns that have been raised include the ability of HIV-1 protease inhibitors to achieve suppressive levels in the central nervous system [Thompson MA, 2012]. The current consensus appears to be that this approach should be reserved for specific patient populations in which considerations related to chronic nucleoside toxicity and/or adherence to complex antiretroviral regimens are dominant. In these situations, the importance of adherence and of close monitoring of plasma HIV-1 RNA levels has been

emphasized. In the case of HIV-1 protease inhibitor maintenance therapy, reestablishment of control of retroviral replication has generally been achieved by resumption of combination therapy.

The availability of an effective, simplified maintenance regimen would be of benefit to a subset of HIV-1 infected persons who are challenged by adherence and/or chronic nucleoside toxicity. Although PRO 140 would require either subcutaneous (SC) or intravenous (IV) administration, its favorable pharmacokinetics might allow dosing as infrequent as once or twice monthly. The ability to administer the drug infrequently under medical supervision could obviate one of the continuing challenges of close adherence to daily boosted protease inhibitor regimens that appear to be relatively unforgiving in maintenance settings when administered as the sole antiretroviral regimen. This is an open-label pilot study of PRO 140 monotherapy as maintenance therapy for those previously fully suppressed on combination antiretroviral regimens.

1.3 BACKGROUND AND HISTORICAL DATA

Based on published data from ACTG5197 trial entitled "A Phase II double-blind, randomized, placebo-controlled study to evaluate the antiretroviral effect of immunization with the MRY Ad5 HIV-1 GAG vaccine in HIV-1 infected individuals who interrupt antiretroviral drug therapy" the viral load will increase within 4 weeks after treatment interruption. The impact of treatment interruption on the CD4 cell count reduction is also observed after 4 weeks, actually the downward trend in CD4 cell counts can be observed by week 1, as it is depicted in Figure 1-3.

This study was conducted in HIV infected men and women of 18 to 55 year old (inclusive), who have maintained viral load suppression for at least 24 months and had a CD4 cell counts of greater than 500 cells/mm3 and HIV-1 RNA < 50 copies/mL.

These changes in both viral load and CD4 counts are depicted in the following figures:

a. Viral Load: As it is depicted in Figure 1-1 if the subjects who have their viral load below 50 copies/mL and their CD4 cell counts > 500 cells/mm3 have a treatment interruption, then after 4 weeks approximately 50% of them will have a viral load of >500 copies/mL; and almost 100% of the subjects will have a viral load of >500 copies/mL by 10 weeks.

Figure 1-1: Historical Data: Kalpan-Meier Estimates for the time to HIV-1 RNA >500 copies/mL

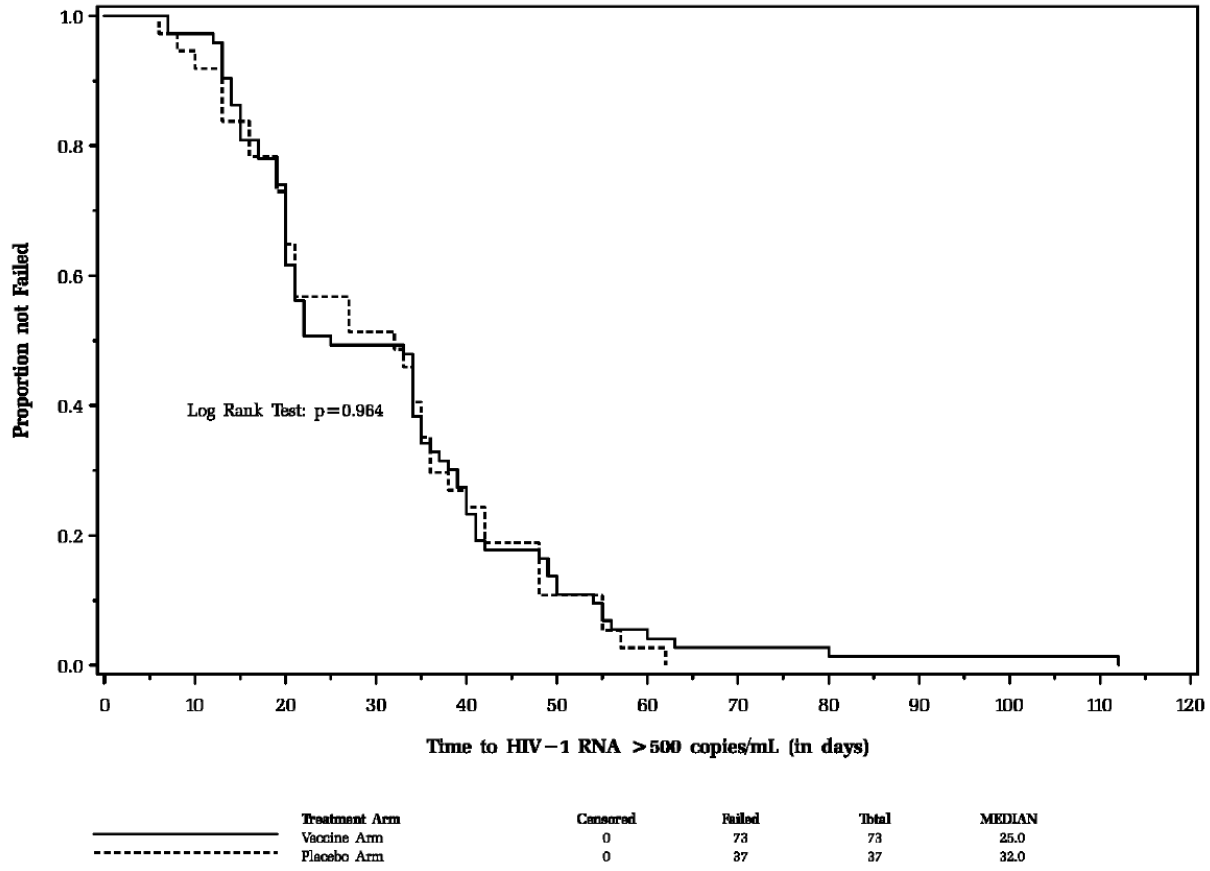
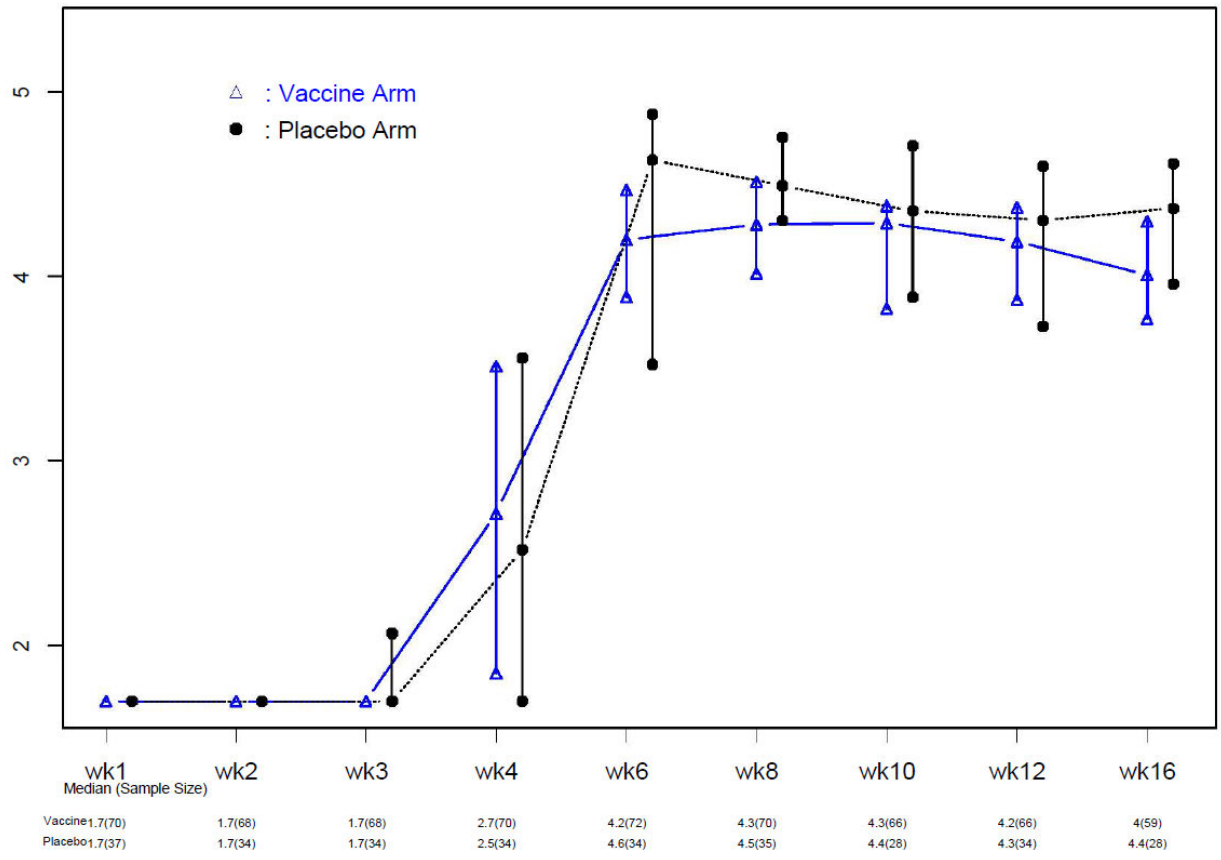


Figure 1-2 depicts the actual change in the median viral load and their 95% Confidence Intervals over a period of 16 weeks. After week 3 there is a clear increase in the viral load and by week 6 the viral load reaches the highest level and was maintained through week 16.

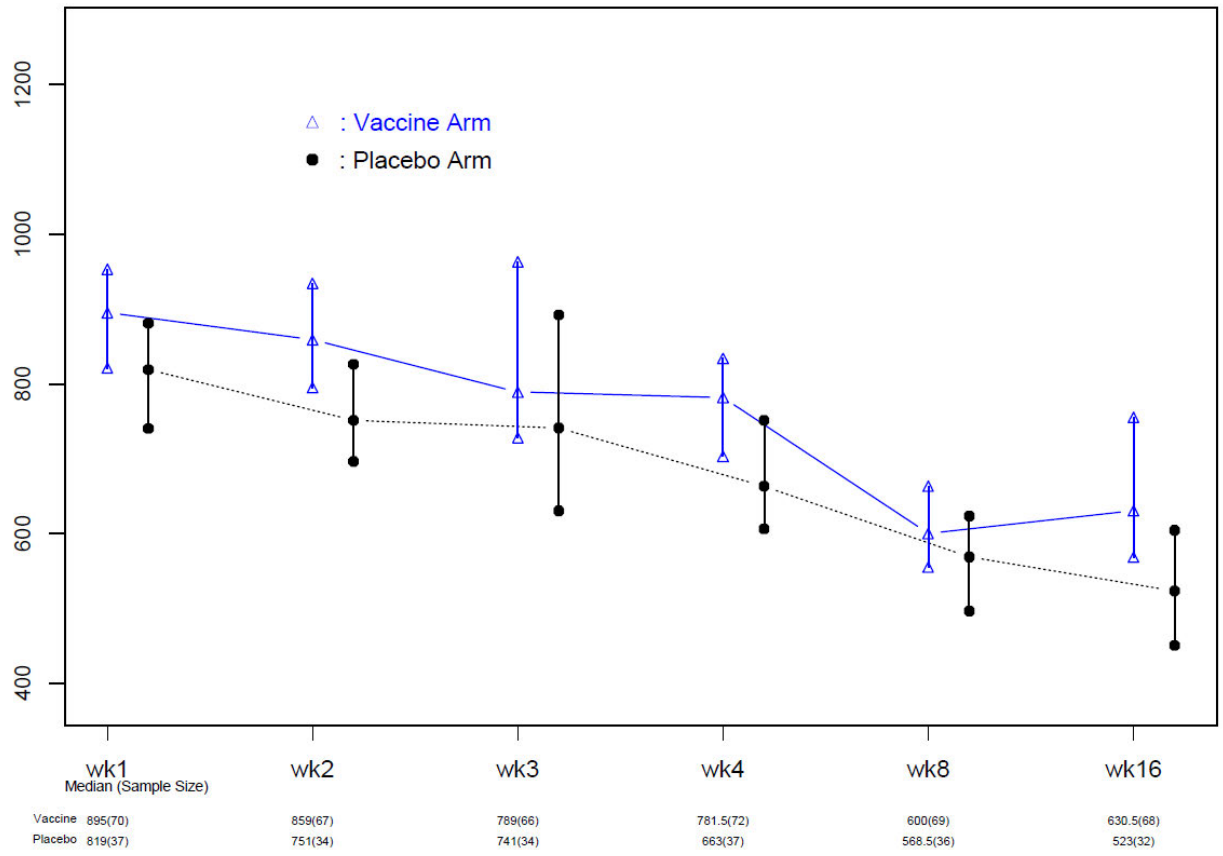
Figure 1-2: Historical Data: Median (95% C.I.) ATI *log*$_{10}$ HIV-1 RNA copies by treatment arm



b. CD4 Cell count: As it is depicted in Figure 1-3, subjects who have CD4 cell count of greater than 500 cells/mm^3 and have a treatment interruption, a trend toward a decline in CD4 observed by week 1. This downward trend in CD4 cell count continued and after 4 weeks of treatment

interruption approximately 10% and by week 16 more than 30% reduction in their viral load was observed.

Figure 1-3: Historical Data: Median (95% C.I.) ATI CD4+ cell count by treatment arm



1.4 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 therapy for human immunodeficiency virus (HIV) infection.

PRO 140 is directed at an ECL2 domain of the CCR5 cell surface receptor for HIV-1. Binding of this domain of the CCL5 molecule interferes with viral entry by interfering with the final phase of viral binding to the cell surface prior to fusion of the viral and cell membranes. PRO-140 has been administered intravenously or subcutaneously to 114 HIV-1 infected individuals in Phase I/II studies of safety, tolerability, pharmacokinetics and pharmacodynamics [Jacobson JM, 2010][Jacobson JM, 2010]. The drug has been well tolerated following administration of single

doses of 0.5 to 5 mg/kg or up to three weekly doses of up to 324 mg. Single subcutaneous doses of 324 mg have resulted in drops in plasma HIV-1 RNA levels of approximately 1.0 $\log_{10}$. Repetitive weekly administration of this dose of PRO 140 has been associated with drops in plasma HIV-1 RNA levels of approximately 1.5 $\log_{10}$. Serum concentrations of PRO 140 above the IC_{50} for clinical isolates of HIV-1 are maintained for at least 2 weeks following a single dose of 324 mg. Plasma HIV-1 RNA levels rise to baseline levels as PRO 140 is cleared from the plasma and, presumably, other compartments.

1.5 SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES

1.5.1 Pre-Clinical Studies with PRO 140

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

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

1.5.2 Clinical Studies with PRO 140

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

1.5.2.1 PRO 140 1101 Study

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

1.5.2.2 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 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.

1.5.2.3 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.

1.5.2.4 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 R5 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 the different treatment groups.

PRO 140 demonstrated potent, rapid, prolonged and dose-dependent antiviral activity (Figure 1-4 and Figure 1-5). A single 5mg/kg dose reduced viral loads by 1.83 $\log_{10}$ on average (Figure 1-5). 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 1-5).

Figure 1-4: PRO 140 1302 Study: Mean of the maximum (nadir) log_{10} reductions in HIV RNA

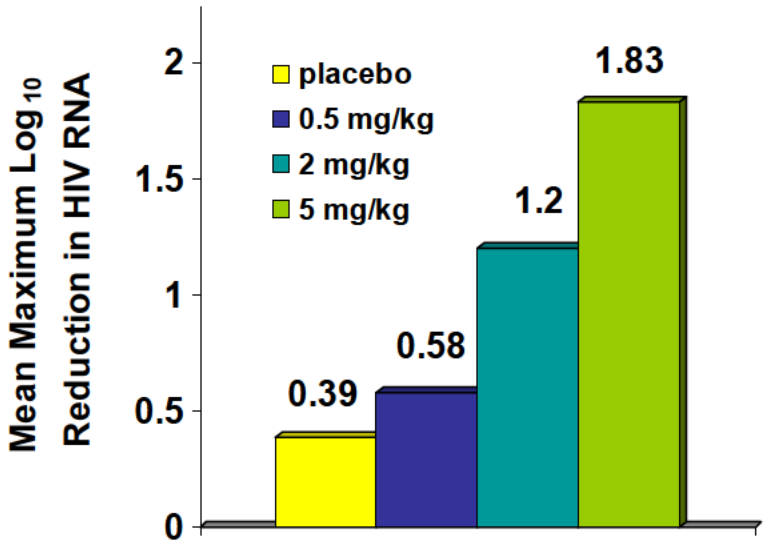
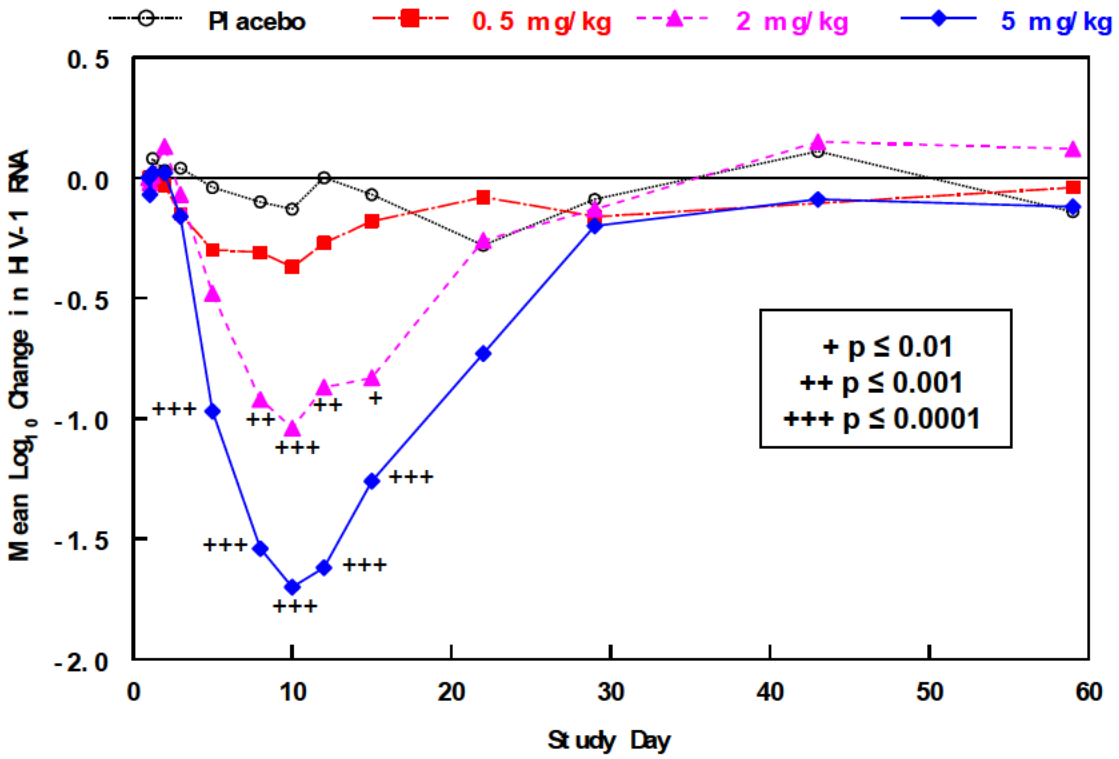


Figure 1-5: PRO 140 1302 Study: Mean log_{10} reductions in HIV RNA over time

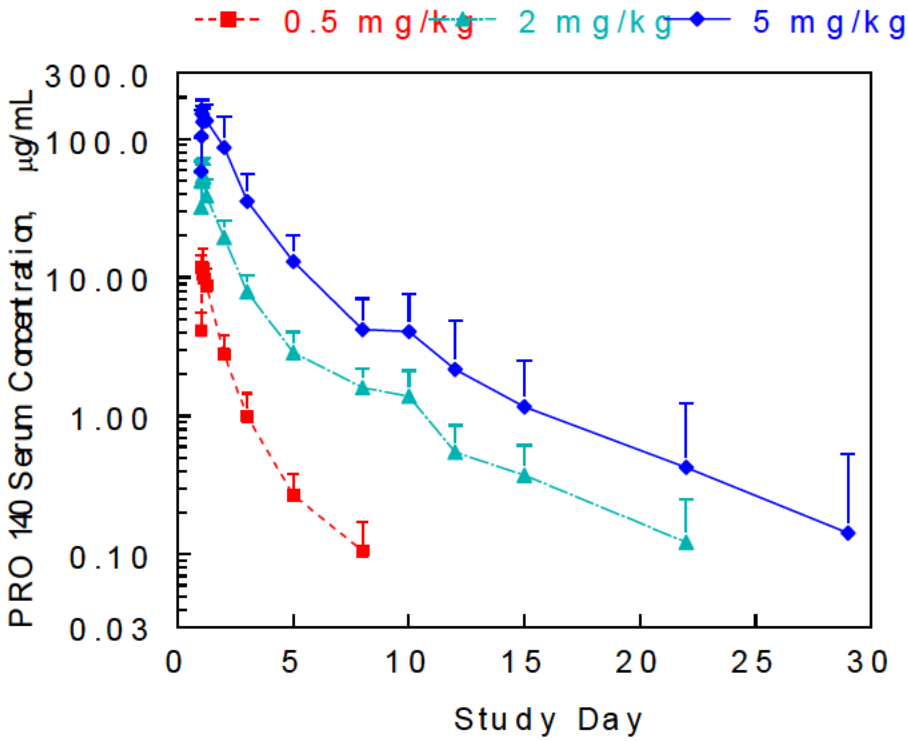


There was no change in R5 virus susceptibility to PRO 140 following treatment. All subjects had R5-only virus at screening in the first-generation Trofile® assay. R5-only tropism results were observed in all subjects at all other timepoints, with two exceptions: One of nine (11%) of placebo subjects 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 R5-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 R5 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 1-6 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 1-6: PRO 140 1302 Study: PRO 140 serum concentrations following a single intravenous injection in HIV- infected individuals.



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

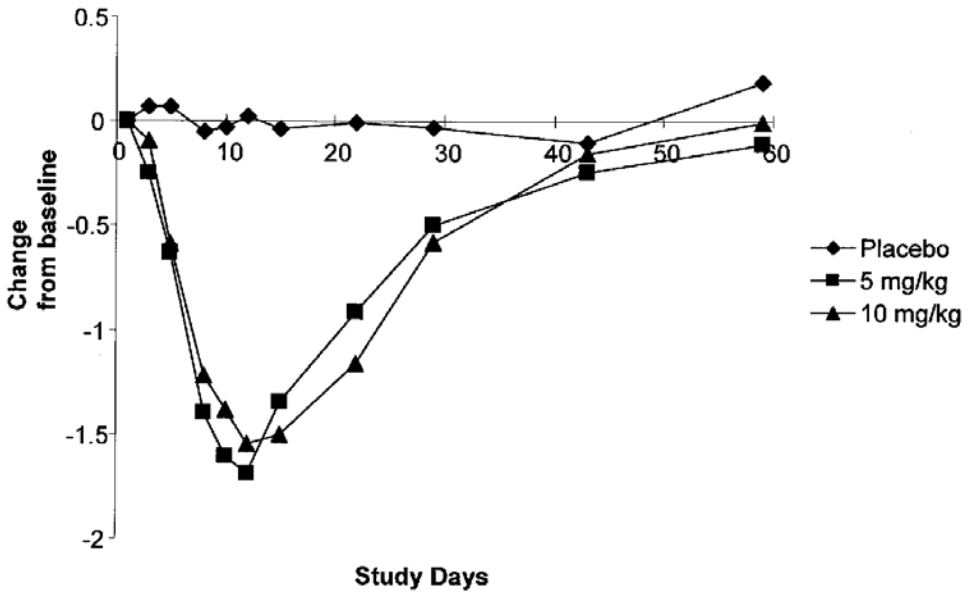
Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant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

1.5.2.5 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 log10 reductions were 1.83 for treatment groups and 0.32 for placebo) (Figure 1-7). 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 1-7: PRO 140 2301 Study: Mean change from baseline in HIV-1 RNA (Log10 copies/mL) over Time (ITT Subjects)



1.5.2.6 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 R5 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 1-8 and Figure 1-9). 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 1-8). There was no viral rebound between 324mg doses, and the antiviral effects persisted for one week after the final dose (Figure 1-9). The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection [Thompson, 2009].

Figure 1-8: PRO 140 2101 Study: Mean of the maximum (nadir) log_{10} reductions in HIV RNA

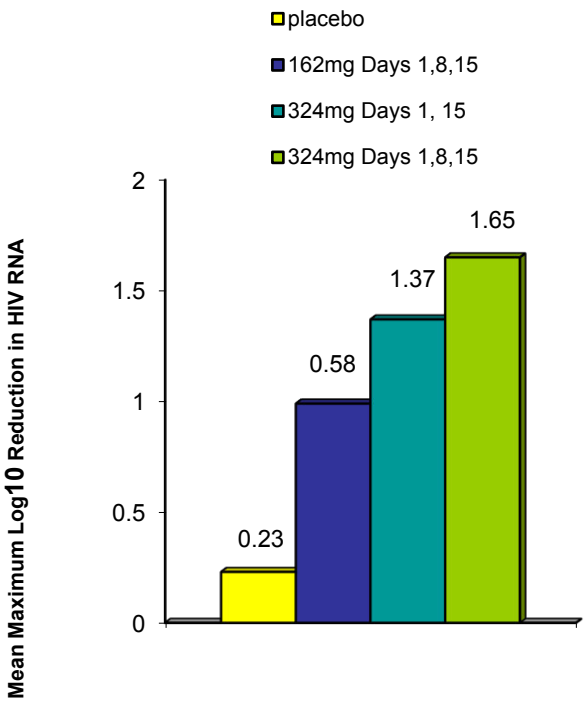
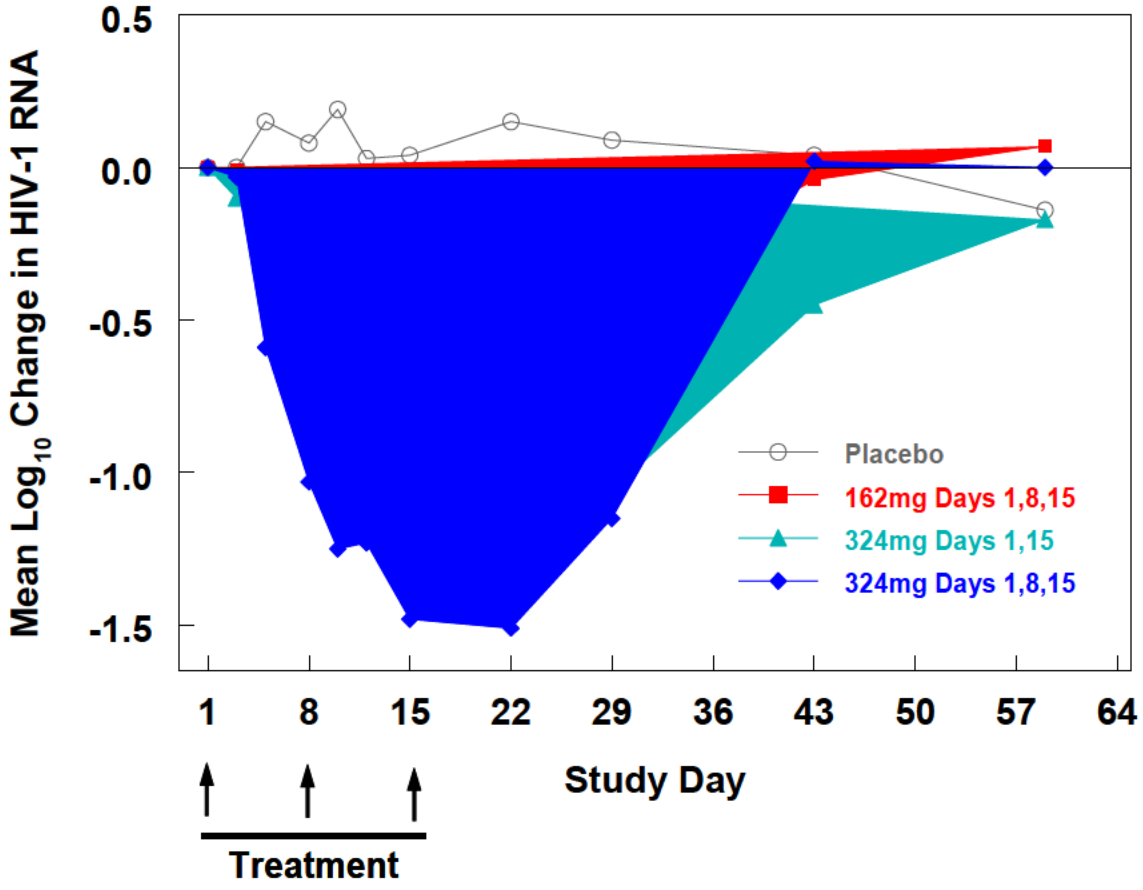


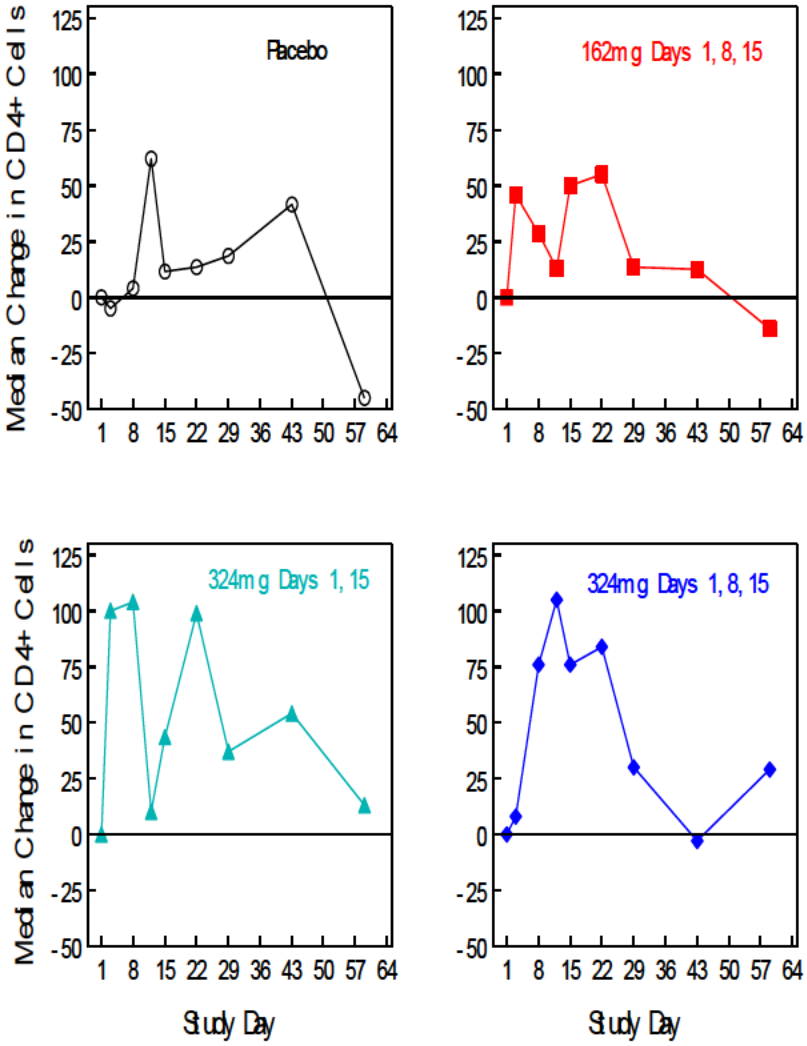
Figure 1-9: PRO 140 2101 Study: Mean change from baseline in HIV-1 RNA (Log10 copies/mL) over Time (ITT Subjects)



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 1-10). 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 1-10: 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.



1.5.2.7 PRO 140 _CD 01 Study

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

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

Forty (43) subjects (M/F: 40/3) with median age of 55 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-three out of 43 (54%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days.

Of the first 40 enrolled subjects enrolled under cohort 1 and cohort 2, three subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37 subjects were found to have exclusive CCR5-tropic virus. A letter of amendment was filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects enrolled in the study.

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

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

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

Safety data were analyzed for all 43 enrolled subjects. One (1) of 43 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-nine (29) of 43 subjects (67%) experienced one or more adverse events (AEs) after receiving at least one dose of PRO140. The most commonly occurring AEs were infections and infestation conditions which were reported by 14 of 43 (32.5%) subjects. The majority of the reported AEs (62/87; 71.2%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported AEs (70/87; 80.4%) were deemed mild in nature.

1.5.2.8 PRO 140 _CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 52 subjects, multi-center) evaluated the

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

In double-blind treatment period, virally non-suppressed subjects were randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days. The primary efficacy endpoint 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 received PRO 140 along with Optimized Background Therapy (OBT).

This clinical study is completed.

1.5.2.9 PRO 140 _CD02 _Open Label

PRO 140_CD02_Open Label (open label, single arm, 25 subjects, multicenter) seeks to evaluate the efficacy, clinical safety, and tolerability parameters of PRO140 in combination with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks. The patient population for this trial are treatment-experienced HIV-infected patients with CCR5-tropic virus and demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented genotypic or phenotypic resistance to ART drugs within three drug classes (or within two drug classes with limited treatment options).

This clinical study is currently ongoing.

1.5.2.10 PRO 140_CD02 Extension Study

The primary objective of this study is to provide PRO 140 on a continued basis to subjects who complete participation in PRO140_CD02 or PRO140_CD02_OpenLabel and would require continued access to PRO 140 to form a viable regimen, in the opinion of the treating physician. The patient population for this trial are treatment-experienced HIV infected patients with CCR5-tropic virus who demonstrate evidence of HIV-1 suppression after successfully completed 24 weeks of treatment in the PRO140_CD02 or PRO140_CD02_OpenLabel study.

1.5.2.11 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 PRO140 350mg SC weekly injection in a single-arm study. Subsequently, the next ~150 subjects were randomized 1:1 to PRO140 350mg (Group A) or PRO 140 525mg (Group B).

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

This clinical study is currently ongoing.

1.5.2.12 PRO 140_CD03 Extension Study

The objective of this study is to assess the long-term safety of using PRO 140 SC as single-agent maintenance therapy for the chronic suppression of CCR5-tropic HIV-1 infection. Study population includes treatment-experienced HIV-infected patients with CCR5-tropic virus who successfully complete 48 weeks of treatment with PRO140 SC monotherapy under CD03 study.

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 _CD 01	2b	43/40	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 _CD02	2b/3	50/52	Placebo or 350mg SC for 1 dose, followed by 350mg SC weekly dose for 24 weeks (total treatment duration 25 Weeks)	CHO	HIV-1 positive	This clinical study is completed
PRO140_CD02OpenLabel	2b/3	25/3	700mg SC + existing ART for 1 week followed by 700mg SC weekly OBT for 24 weeks	CHO	HIV-1 positive	This clinical study is currently ongoing
PRO 140 _CD02 Extension	2b/3	50/TBD	350mg SC weekly dose	CHO	HIV-1 positive	This clinical study is currently ongoing.

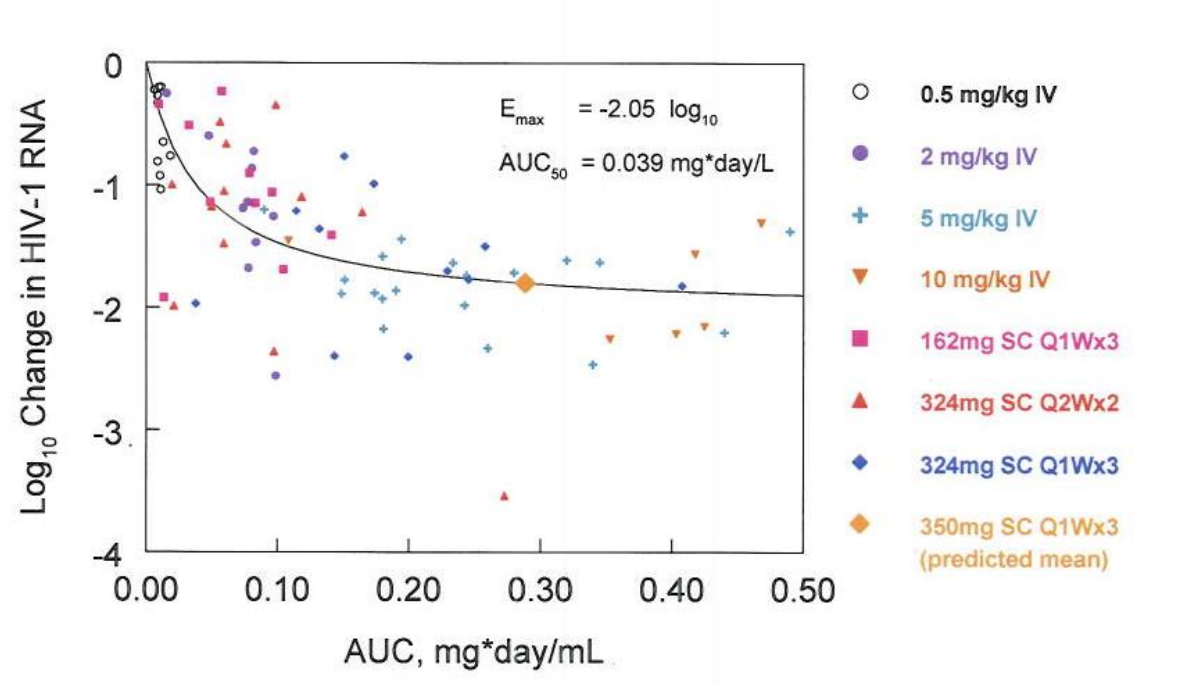
Protocol Number	Phase	No. of Subjects (Planned/Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
PRO 140 _CD 03	2b/3	500/TBD	350 mg, 525mg, or 700mg SC weekly dose for 48 Weeks of Monotherapy	CHO	HIV-1 positive	This clinical study is currently ongoing.
PRO 140 _CD 03 Extension	2b/3	300/TBD	350 mg SC weekly monotherapy dose	CHO	HIV-1 positive	This clinical study is currently ongoing.

1.6 RATIONALE FOR DOSE SELECTION

The dose of 350 mg administered SC was chosen in light of a previous analysis suggesting that such a dose would be likely to provide maximal viral load suppression.

In studies with antiviral agents that block viral entry through the CCR5 receptor, there is a general consensus that in order to achieve robust antiviral effects and minimize the potential for drug resistance in combination therapy, the dose of drug should result in exposures that fall on the plateau of a Maximum Drug Effect (Emax) plot.

Figure 1-11: 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 1-11 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]. As a consequence, a significant percentage of SC PRO 140 can be expected to encounter and bind CCR5-expressing cells and exert antiviral effects without ever reaching the bloodstream. For this reason, the serum AUC observed for SC administration may provide a conservative measure of drug exposure relative to that observed with IV administration.

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 We expect that this target will be achieved by most or all of the dosing regimens to be studied in PRO 140 2103.

Finally, the mean nadir reduction in viral load achieved with 3 weekly 324 mg SC doses (1.65 log10) was similar to the mean nadir reductions observed with single 5 or 10 mg/kg IV doses (1.8 log10 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.

Due to the majority of subjects receiving 350 mg weekly SC dosing in monotherapy setting experiencing virologic failure in the CD03 study, a dose increase was proposed. 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).

Subjects enrolled under a previous Protocol version have the option to continue receiving the 350 mg dose or increase to the 700 mg dose.

1.7 RISKS / BENEFITS ASSESSMENT

1.7.1 RISKS/DISCOMFORT TO SUBJECTS AND PRECAUTIONS TO MINIMIZE RISK

1.7.1.1 Risks associated with Temporary Discontinuation of current Antiretroviral Treatment Regimen

The study treatment (PRO 140 monotherapy) may not be effective in maintaining the viral suppression for all subjects. In such cases, temporary discontinuation of antiretroviral therapy could lead to a rebound in viral load and might be associated with an increase risk of developing drug resistance, opportunistic infections and clinical progression of the disease.

Study participants will be regularly monitored for viral rebound following initiation of PRO 140 monotherapy and will re-initiate their previous antiretroviral regimen if plasma HIV-1 RNA levels rise up to or above 400 copies/ml on two consecutive blood draws at least 3 days apart.

1.7.1.2 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 administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

1.7.1.3 Immune Response

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

1.7.1.4 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).

1.7.1.5 Venipuncture for blood sampling and Subcutaneous injection for Study Drug Administration

Venipuncture for blood sample collection and subcutaneous injection for study drug administration 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.

1.7.1.6 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).

1.7.1.7 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.

1.7.1.8 Theoretical risk for increased severity of West Nile virus infection

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

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

1.7.2 Intended Benefit for Subjects

This is a proof of concept study for the purpose of selecting a dose and regimen for further clinical testing. The most significant limitation with highly active antiretroviral therapy (HAART) has been the necessity and challenge of continued daily adherence to the medications. This study provides opportunity to the subjects to have once weekly SC treatment with PRO 140. Subjects participating in the present monotherapy study will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

2 STUDY OBJECTIVES

The primary objective is to assess the long-term efficacy of PRO 140 monotherapy for the maintenance of viral suppression in patients who have completed 12 weeks of treatment under Protocol PRO 140_CD 01 without experiencing virologic failure.

The secondary objective of the trial is to assess the long-term clinical safety and tolerability parameters of continued PRO 140 use in patients who have completed 12 weeks of treatment under Protocol PRO 140_CD 01 without experiencing virologic failure.

The primary efficacy endpoint for this study is time to virologic failure after initiating PRO 140 monotherapy. Virologic failure is defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days.

The secondary efficacy endpoints will be proportion of participants with virologic failure after initiating PRO 140 monotherapy, mean change in viral load (HIV-1 RNA levels), mean change in CD4 cell count, and change in Quality of Life (QoL) up to TE107 within the treatment extension phase.

Safety assessments include evaluation of 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 Grade 3 or 4 adverse events and frequency of Treatment-emergent serious adverse events.

3 STUDY DESIGN

3.1 STUDY CENTER(S)

Site(s) participating in PRO 140 _CD 01 Protocol

3.2 STUDY POPULATION

This study will recruit subjects with HIV-1 infection who did not experience virologic failure while in the treatment phase of the PRO 140_CD 01 study.

3.3 ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

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

1. Subjects who have completed 12 weeks of treatment in PRO 140_CD 01 study without experiencing virologic failure.
2. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods (birth control pills, barriers, or abstinence) throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative urine pregnancy test prior to receiving the first dose of study drug.
3. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

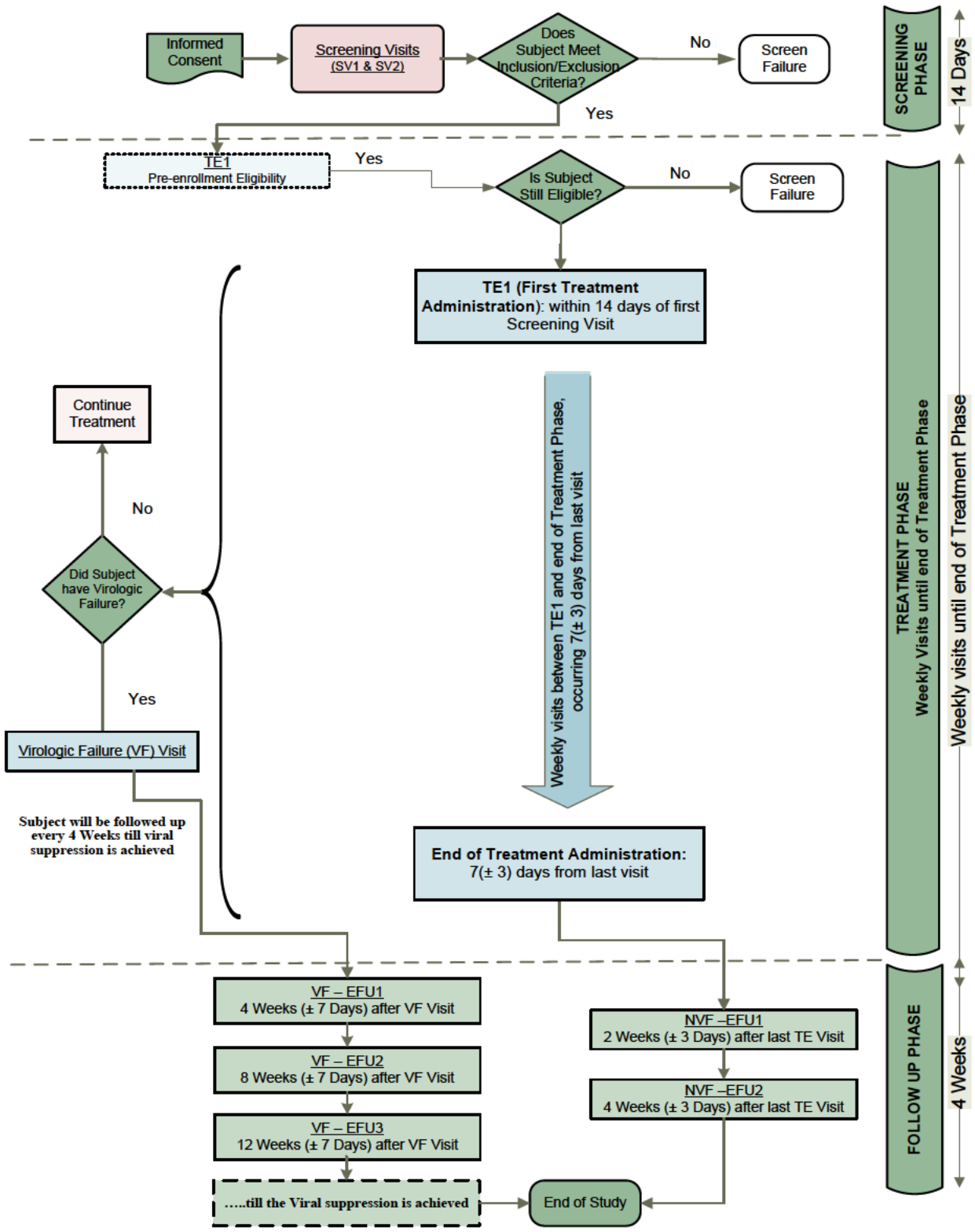
3.3.2 Exclusion Criteria

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

1. Not currently enrolled in PRO 140_CD 01 Treatment Substitution Study
2. Any acquired immune deficiency syndrome (AIDS)-defining illness according to the 1993 Centers for Disease Control and Prevention (CDC) AIDS surveillance definition
3. Laboratory test values ≥ grade 4 DAIDS laboratory abnormality.
4. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
5. Unexplained temperature >38.5^{O}C (101.3^{O}F) for seven consecutive days within 14 days prior to the first study dose

6. Diagnosed with either substance dependence or substance abuse or any history of a concomitant condition (e.g., medical, psychological, or psychiatric) that in the opinion of the primary care provider and/or site investigator would interfere with the subject's successful completion of the study requirements
7. 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

This research study is divided into three study phases:

(1) **Screening Phase:** This phase lasts up to 14 days and consists of two Screening Visits (SV1 and SV2) which are 7 (±3) days apart.

SV1 begins with signing of Informed Consent and corresponds to T12 of the PRO 140_CD 01 protocol. SV2 corresponds with T13 of the PRO 140_CD 01 protocol.

Assessments from both T12 and T13 will be used to determine final eligibility for PRO 140_CD 01-Extension protocol. First treatment will be administered within 14 days of SV1.

(2) **Treatment Extension Phase (weekly ± allowed windows):** Subjects will receive weekly treatments (window period of ±3 days).

Any time during the Treatment Extension Phase, if virologic failure occurs, subject will stop the study treatment and re-start their previous antiretroviral regimen.

(3) **Follow-Up Phase**: The duration of follow-up depends on the status of viral load suppression.

- Subjects who experience virologic failure will be followed up every 4 weeks until the viral load suppression is achieved (i.e., plasma HIV-1 RNA levels to return back to <50 copies/mL)
- Subjects who do not experience virologic failure at the end of Treatment Extension Period, will be followed up every 2 week for total of 4 weeks.

➢ ***Note****: Virologic failure subjects will have a long term safety follow up visit once a year within 2 years of completing the last VF-FU visit.*

Procedures to be performed during each of these study phases are described below and provided as a Schedule of Assessments in Table 4-1, Table 4-2, Table 4-3, Table 4-4, Table 4-5, Table 4-6, Table 4-7, Table 4-8, and Table 4-9.

Table 4-1: Schedule of Assessments – Screening and Treatment Extension Phase (1 of 8)

Procedure/Assessments	Screening Visit 1 (coincide with T12 under the PRO 140 CD 01 protocol)	Screening Visit 2 (coincide with T13 under the PRO 140 CD 01 protocol)	Treatment Extension Visit 1 (Week-1)	Treatment Extension Visit 2 (Week-2)	Treatment Extension Visit 3 (Week-3)	Treatment Extension Visit 4 (Week-4)	Treatment Extension Visit 5 (Week-5)	Treatment Extension Visit 6 (Week-6)	Treatment Extension Visit 7 (Week-7)	Treatment Extension Visit 8 (Week-8)	Treatment Extension Visit 9 (Week-9)	Treatment Extension Visit 10 (Week-10)	Treatment Extension Visit 11 (Week-11)	Treatment Extension Visit 12 (Week-12)	Treatment Extension Visit 13 (Week-13)	In case of Virologic Failure
Visit	SV1	SV2	TE1	TE2	TE3	TE4	TE5	TE6	TE 7	TE8	TE9	TE10	TE11	TE12	TE13	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Informed Consent[1]	X															
Eligibility Evaluation[2]	X	X														
Pre-enrollment Eligibility[3]			X													
Medical History[4]			-													
Physical Examination	X	-X-[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X	X
Neurological Assessment[6]	-X-					X				X				X		X
Quality of Life Assessment[7]	-X-					X				X				X		X
Vital Signs[8]	-X-	-X-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[9]																X
Biochemistry[10]																X
Serum Pregnancy Test[11]	X															
Urine Pregnancy Test[11]		X														
Plasma HIV-1 RNA level	-X-	-X-		X		X		X		X		X		X		X
TruCount T assay[12]	-X-	-X-		X		X		X		X		X		X		X
PK sample for PRO 140[13]	-X-					X				X				X		X
Serum concentration for ART drugs[14]	-X-					X				X				X		
HIV Genotyping Assay																X
Trofile® RNA and PhenoSense Assay																X

Procedure/Assessments	Screening Visit 1 (coincide with T12 under the PRO 140 CD 01 protocol)	Screening Visit 2 (coincide with T13 under the PRO 140 CD 01 protocol)	Treatment Extension Visit 1 (Week-1)	Treatment Extension Visit 2 (Week-2)	Treatment Extension Visit 3 (Week-3)	Treatment Extension Visit 4 (Week-4)	Treatment Extension Visit 5 (Week-5)	Treatment Extension Visit 6 (Week-6)	Treatment Extension Visit 7 (Week-7)	Treatment Extension Visit 8 (Week-8)	Treatment Extension Visit 9 (Week-9)	Treatment Extension Visit 10 (Week-10)	Treatment Extension Visit 11 (Week-11)	Treatment Extension Visit 12 (Week-12)	Treatment Extension Visit 13 (Week-13)	In case of Virologic Failure
Visit	SV1	SV2	TE1	TE2	TE3	TE4	TE5	TE6	TE 7	TE8	TE9	TE10	TE11	TE12	TE13	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Anti-idiotypic antibodies to PRO 140	-X-					X				X				X		X
Blood sample collection for Exploratory/Confirmatory analysis[15]		X														X
PRO 140 Administration	-X-	-X-	X	X	X	X	X	X	X	X	X	X	X	X	X	
PRO 140 Administration by subject[16]					X		X		X		X		X		X	
Subject drug dispensing/accountability[17]				X		X		X		X		X		X		
Re-initiate Antiretroviral Regimen[18]																X
Injection Site Reaction Assessment[19]	-X-	-X-	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[20]	-X-	-X-	X	X	X	X	X	X	X	X	X	X	X	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

Table 4-2: Schedule of Assessments – Screening and Treatment Extension Phase (2 of 8)

Procedure/Assessments	Treatment Extension Visit 14 (Week-14)	Treatment Extension Visit 15 (Week-15)	Treatment Extension Visit 16 (Week-16)	Treatment Extension Visit 17 (Week-17)	Treatment Extension Visit 18 (Week-18)	Treatment Extension Visit 19 (Week-19)	Treatment Extension Visit 20 (Week-20)	Treatment Extension Visit 21 (Week-21)	Treatment Extension Visit 22 (Week-22)	Treatment Extension Visit 23 (Week-23)	Treatment Extension Visit 24 (Week-24)	Treatment Extension Visit 25 (Week-25)	In case of Virologic Failure
Visit	TE14	TE15	TE16	TE17	TE18	TE19	TE20	TE21	TE22	TE23	TE24	TE25	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Informed Consent[1]													
Eligibility Evaluation[2]													
Pre-enrollment Eligibility[3]													
Medical History[4]													
Physical Examination	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Neurological Assessment[6]			X				X				X		X
Quality of Life Assessment[7]			X				X				X		X
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[9]													X
Biochemistry[10]													X
Serum Pregnancy Test[11]													
Urine Pregnancy Test[11]													
Plasma HIV-1 RNA level	X		X		X		X		X		X		X
TruCount T assay[12]	X		X		X		X		X		X		X
PK sample for PRO 140[13]			X				X				X		X
Serum concentration for ART drugs[14]			X				X				X		
HIV Genotyping Assay													X
Trofile® RNA and PhenoSense Entry Assay													X
Anti-idiotypic antibodies to PRO 140			X				X				X		X

Procedure/Assessments	Treatment Extension Visit 14 (Week-14)	Treatment Extension Visit 15 (Week-15)	Treatment Extension Visit 16 (Week-16)	Treatment Extension Visit 17 (Week-17)	Treatment Extension Visit 18 (Week-18)	Treatment Extension Visit 19 (Week-19)	Treatment Extension Visit 20 (Week-20)	Treatment Extension Visit 21 (Week-21)	Treatment Extension Visit 22 (Week-22)	Treatment Extension Visit 23 (Week-23)	Treatment Extension Visit 24 (Week-24)	Treatment Extension Visit 25 (Week-25)	In case of Virologic Failure
Visit	TE14	TE15	TE16	TE17	TE18	TE19	TE20	TE21	TE22	TE23	TE24	TE25	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Blood sample collection for Exploratory/Confirmatory analysis[15]													X
PRO 140 Administration	X	X	X	X	X	X	X	X	X	X	X	X	
PRO 140 Administration by subjects[16]		X		X		X		X		X		X	
Subject drug dispensing/accountability[17]	X		X		X		X		X		X		
Re-initiate Antiretroviral Regimen[18]													X
Injection Site Reaction Assessment[19]	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[20]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	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

Table 4-3: Schedule of Assessments – Screening and Treatment Extension Phase (3 of 8)

Procedure/Assessments	Treatment Extension Visit 26 (Week-26)	Treatment Extension Visit 27 (Week-27)	Treatment Extension Visit 28 (Week-28)	Treatment Extension Visit 29 (Week-29)	Treatment Extension Visit 30 (Week-30)	Treatment Extension Visit 31 (Week-31)	Treatment Extension Visit 32 (Week-32)	Treatment Extension Visit 33 (Week-33)	Treatment Extension Visit 34 (Week-34)	Treatment Extension Visit 35 (Week-35)	Treatment Extension Visit 36 (Week-36)	Treatment Extension Visit 37 (Week-37)	In case of Virologic Failure
Visit	TE26	TE27	TE28	TE29	TE30	TE31	TE32	TE33	TE34	TE35	TE36	TE37	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Informed Consent[1]													
Eligibility Evaluation[2]													
Pre-enrollment Eligibility[3]													
Medical History[4]													
Physical Examination	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Neurological Assessment[6]			X				X				X		X
Quality of Life Assessment[7]			X				X				X		X
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[9]													X
Biochemistry[10]													X
Serum Pregnancy Test[11]													
Urine Pregnancy Test[11]													
Plasma HIV-1 RNA level	X		X		X		X		X		X	X	X
TruCount T assay[12]	X		X		X		X		X		X	X	X
PK sample for PRO 140[13]			X				X				X		X
Serum concentration for ART drugs[14]			X				X				X		
HIV Genotyping Assay													X
Trofile® RNA and PhenoSense Entry Assay													X
Anti-idiotypic antibodies to PRO 140			X				X				X		X

Procedure/Assessments	Treatment Extension Visit 26 (Week-26)	Treatment Extension Visit 27 (Week-27)	Treatment Extension Visit 28 (Week-28)	Treatment Extension Visit 29 (Week-29)	Treatment Extension Visit 30 (Week-30)	Treatment Extension Visit 31 (Week-31)	Treatment Extension Visit 32 (Week-32)	Treatment Extension Visit 33 (Week-33)	Treatment Extension Visit 34 (Week-34)	Treatment Extension Visit 35 (Week-35)	Treatment Extension Visit 36 (Week-36)	Treatment Extension Visit 37 (Week-37)	In case of Virologic Failure
Visit	TE26	TE27	TE28	TE29	TE30	TE31	TE32	TE33	TE34	TE35	TE36	TE37	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Blood sample collection for Exploratory/Confirmatory analysis[15]													X
PRO 140 Administration	X	X	X	X	X	X	X	X	X	X	X	X	
PRO 140 Administration by subjects[16]		X		X		X		X		X		X	
Subject drug dispensing/accountability[17]	X		X		X		X		X		X		
Re-initiate Antiretroviral Regimen[18]													X
Injection Site Reaction Assessment[19]	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[20]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	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

Table 4-4: Schedule of Assessments – Screening and Treatment Extension Phase (4 of 8)

Procedure/Assessments	Treatment Extension Visit 38 (Week-38)	Treatment Extension Visit 39 (Week-39)	Treatment Extension Visit 40 (Week-40)	Treatment Extension Visit 41 (Week-41)	Treatment Extension Visit 42 (Week-42)	Treatment Extension Visit 43 (Week-43)	Treatment Extension Visit 44 (Week-44)	Treatment Extension Visit 45 (Week-45)	Treatment Extension Visit 46 (Week-46)	Treatment Extension Visit 47 (Week-47)	Treatment Extension Visit 48 (Week-48)	Treatment Extension Visit 49 (Week-49)	In case of Virologic Failure
Visit	TE38	TE39	TE40	TE41	TE42	TE43	TE44	TE45	TE46	TE47	TE48	TE49	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Informed Consent[1]													
Eligibility Evaluation[2]													
Pre-enrollment Eligibility[3]													
Medical History[4]													
Physical Examination	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Neurological Assessment[6]			X				X				X		X
Quality of Life Assessment[7]			X				X				X		X
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[9]													X
Biochemistry[10]													X
Serum Pregnancy Test[11]													
Urine Pregnancy Test[11]													
Plasma HIV-1 RNA level	X		X		X		X		X		X		X
TruCount T assay[12]	X		X		X		X		X		X		X
PK sample for PRO 140[13]			X				X				X		X
Serum concentration for ART drugs[14]			X				X				X		
HIV Genotyping Assay													X
Trofile® RNA and PhenoSense Entry Assay													X
Anti-idiotypic antibodies to PRO 140			X				X				X		X

Procedure/Assessments	Treatment Extension Visit 38 (Week-38)	Treatment Extension Visit 39 (Week-39)	Treatment Extension Visit 40 (Week-40)	Treatment Extension Visit 41 (Week-41)	Treatment Extension Visit 42 (Week-42)	Treatment Extension Visit 43 (Week-43)	Treatment Extension Visit 44 (Week-44)	Treatment Extension Visit 45 (Week-45)	Treatment Extension Visit 46 (Week-46)	Treatment Extension Visit 47 (Week-47)	Treatment Extension Visit 48 (Week-48)	Treatment Extension Visit 49 (Week-49)	In case of Virologic Failure
Visit	TE38	TE39	TE40	TE41	TE42	TE43	TE44	TE45	TE46	TE47	TE48	TE49	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Blood sample collection for Exploratory/Confirmatory analysis[15]													X
PRO 140 Administration	X	X	X	X	X	X	X	X	X	X	X	X	
PRO 140 Administration by subjects[16]		X		X		X		X		X		X	
Subject drug dispensing/accountability[17]	X		X		X		X		X		X		
Re-initiate Antiretroviral Regimen[18]													X
Injection Site Reaction Assessment[19]	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[20]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	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

Table 4-5: Schedule of Assessments – Screening and Treatment Extension Phase (5 of 8)

Procedure/Assessments	Treatment Extension Visit 50 (Week-50)	Treatment Extension Visit 51 (Week-52)	Treatment Extension Visit 52 (Week-52)	Treatment Extension Visit 53 (Week-53)	Treatment Extension Visit 54 (Week-54)	Treatment Extension Visit 55 (Week-55)	Treatment Extension Visit 56 (Week-56)	Treatment Extension Visit 57 (Week-57)	Treatment Extension Visit 58 (Week-58)	Treatment Extension Visit 59 (Week-59)	In case of Virologic Failure
Visit	TE50	TE51	TE52	TE53	TE54	TE55	TE56	TE57	TE58	TE59	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Informed Consent[1]											
Eligibility Evaluation[2]											
Pre-enrollment Eligibility[3]											
Medical History[4]											
Physical Examination	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Neurological Assessment[6]			X				X				X
Quality of Life Assessment[7]			X				X				X
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[9]											X
Biochemistry[10]											X
Serum Pregnancy Test[11]											
Urine Pregnancy Test[11]											
Plasma HIV-1 RNA level	X		X		X		X		X		X
TruCount T assay[12]	X		X		X		X		X		X
PK sample for PRO 140[13]			X				X				X
Serum concentration for ART drugs[14]			X				X				
HIV Genotyping Assay											X
Trofile® RNA and PhenoSense Entry Assay											X
Anti-idiotypic antibodies to PRO 140			X				X				X

Procedure/Assessments	Treatment Extension Visit 50 (Week-50)	Treatment Extension Visit 51 (Week-52)	Treatment Extension Visit 52 (Week-52)	Treatment Extension Visit 53 (Week-53)	Treatment Extension Visit 54 (Week-54)	Treatment Extension Visit 55 (Week-55)	Treatment Extension Visit 56 (Week-56)	Treatment Extension Visit 57 (Week-57)	Treatment Extension Visit 58 (Week-58)	Treatment Extension Visit 59 (Week-59)	In case of Virologic Failure
Visit	TE50	TE51	TE52	TE53	TE54	TE55	TE56	TE57	TE58	TE59	VF
Window Period	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	±3 days since last treatment	
Blood sample collection for Exploratory/Confirmatory analysis[15]											X
PRO 140 Administration	X	X	X	X	X	X	X	X	X	X	
PRO 140 Administration by subjects[16]		X		X		X		X		X	
Subject drug dispensing/accountability[17]	X		X		X		X		X		
Re-initiate Antiretroviral Regimen[18]											X
Injection Site Reaction Assessment[19]	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[20]	X	X	X	X	X	X	X	X	X	X	
Adverse Events	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 (red bold)**:** Activities performed under Extension study protocol
-X- : Activities performed under PRO 140_CD 01 protocol

[1] Informed consent must be obtained at the Screening Visit 1 (SV1) coincides with the T12 clinic visit under the PRO 140_CD 01 protocol.

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

[3] Based on results of lab samples collected at the Screening Visit 1 under Extension protocol / T12 clinic visit under the PRO 140_CD 01 protocol

[4] Medical history collected at the time of screening for PRO 140_CD 01 protocol will be carried forward. Medical history will not be collected for the PRO 140_CD 01-Extension protocol.

[5] Symptom-directed physical examination

[6] Performed by Principal Investigator or designated study personnel. 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.

[7] Performed by Principal Investigator or Study Coordinator

[8] Blood pressure, heart rate, respiration rate, temperature assessed before and 15 minutes after study treatment administered at clinic

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

[10] 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)

[11] ONLY performed on women of childbearing potential.

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

[13] PK samples for PRO 140 may be collected at during Treatment Extension Phase and at virologic failure

[14] To assess subject compliance in abstaining from previous ART regimen after SV1 visit;

[15] Blood sample collection prior to first treatment administration at SV2 and at the time of early breakthrough/virologic failure will be used for exploratory or confirmatory purposes.

[16] ONLY for subjects trained to perform self-administration of study treatment on weeks when clinic visit optional, i.e., no lab samples are required

[17] Study treatment for self-administration will be provided to subjects during treatment visits at clinic; used vials from prior self-administration must be collected and accounted for (see Section 4.2.2)

[18] All study subjects will re-initiate their previous antiretroviral regimen: (1) One week prior to the end of 161-week Treatment Extension Phase, or (2) Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in the protocol.

[19] As assessed by Investigator when study treatment administered at the clinic.

[20] 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 for subject's randomized to PRO 140

Table 4-6: Schedule of Assessments – Screening and Treatment Extension Phase (6 of 8)

Procedure/Assessments	Treatment Extension Visit 60 - 63	Treatment Extension Visit 64-67	Treatment Extension Visit 68-71	Treatment Extension Visit 72-75	Treatment Extension Visit 76-79	Treatment Extension Visit80-83	Treatment Extension Visit 84-87	Treatment Extension Visit 88-91	Treatment Extension Visit 92-95	Treatment Extension Visit 96-99	Treatment Extension Visit100-103	Treatment Extension Visit104-107	In case of Virologic Failure
Visit	TE60-63	TE64-67	TE68-71	TE72-75	TE76-79	TE80-83	TE84-87	TE88-91	TE92-95	TE96-99	TE100-103	TE104-107	VF
Window Period	±3 days since last treatment												
Symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination													X
Neurological Assessment[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[22]	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Blood Count (CBC)[23]													X
Biochemistry[24]													X
Plasma HIV-1 RNA level[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
TruCount T assay[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample for PRO 140[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum concentration for ART drugs[21]	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-idiotypic antibodies to PRO 140[21]	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Genotyping Assay													X
Trofile® DNA/RNA and PhenoSense Entry Assay													X
Blood sample collection for Exploratory/Confirmatory analysis[25]													X
CCR5 Receptor Occupancy[32]	X												
PRO 140 Administration[26]	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure/Assessments	Treatment Extension Visit 60 - 63	Treatment Extension Visit 64-67	Treatment Extension Visit 68-71	Treatment Extension Visit 72-75	Treatment Extension Visit 76-79	Treatment Extension Visit80-83	Treatment Extension Visit 84-87	Treatment Extension Visit 88-91	Treatment Extension Visit 92-95	Treatment Extension Visit 96-99	Treatment Extension Visit100-103	Treatment Extension Visit104-107	In case of Virologic Failure
Visit	TE60-63	TE64-67	TE68-71	TE72-75	TE76-79	TE80-83	TE84-87	TE88-91	TE92-95	TE96-99	TE100-103	TE104-107	VF
Window Period	±3 days since last treatment												
Subject drug dispensing/accountability[28]	X	X	X	X	X	X	X	X	X	X	X	X	
Antiretroviral Regimen[29]													X
Injection Site Reaction Assessment[30]	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[31]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	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

[21] Performed when subject comes to clinic by Principal Investigator or designated study personnel. ***NOTE:*** *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..*

[22] Blood pressure, heart rate, respiration rate, temperature assessed before and 15 minutes after study treatment administered at clinic

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

[24] 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)

[25] Sample collected on adhoc basis, as per discretion of Sponsor/Investigator during the treatment phase.

[26] ONLY for subjects trained to perform self-administration of study treatment on weeks when clinic visit optional, i.e., no lab samples are required

[27] Study treatment should be administered at clinic.

[28] Study treatment for self-administration will be provided to subjects during treatment visits at clinic; used vials from prior self-administration must be collected and accounted for (see Section 4.2.2).

[29] All study subjects will re-initiate their previous antiretroviral regimen: (1) One week prior to the end of 161-week Treatment Extension Phase, or (2) Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in the protocol.

[30] As assessed by Investigator when study treatment administered at the clinic.

[31] 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 for subjects randomized to PRO 140.

[32] Refer to Section 7.10.12.

Table 4-7: Schedule of Assessments – Screening and Treatment Extension Phase (7 of 8)

Procedure/Assessments	Subsequent Weekly TE Visits (TE108 onwards)	Treatment Extension Visit	Treatment Extension Visit	In case of Virologic Failure
Visit[33]		TE160	TE161	VF
Window Period	±3 days since last treatment			
Symptom-directed physical examination	X[33]	X		
Physical Examination			X	X
Neurological Assessment[32]	X[33]	X		X
Quality of Life Assessment[32]		X		X
Vital Signs[36]	X[33]	X	X	X
Complete Blood Count (CBC)[37]			X	X
Biochemistry[38]			X	X
Plasma HIV-1 RNA level	X[33]	X	X	X
TruCount T assay	X[33]	X	X	X
PK sample for PRO 140	X[33]	X		X
Serum concentration for ART drugs[39]	X[33]	X		
Anti-idiotypic antibodies to PRO 140	X[33]	X		X
HIV Genotyping Assay				X
Trofile® DNA/RNA and PhenoSense Entry Assay			X	X
Blood sample collection for Exploratory/Confirmatory analysis[39]			X	X
PRO 140 Administration	X[40]	X[41]	X[41]	
Subject drug dispensing/accountability[42]	X	X		
Antiretroviral Regimen[43]		X	X	X
Injection Site Reaction Assessment[44]	X[33]	X	X	
Injection Site Pain Assessment (VAS)[45]	X[33]	X	X	
Adverse Events[34]	X	X	X	X
Concomitant Medications	X	X	X	X

[33] In-clinic assessment(s) should be performed at least once every 4 weeks from TE108 onwards.

[34] Subjects should be instructed to report any new AEs that occur between clinic visits to site promptly

[35] Performed by Principal Investigator (or designee) when subject comes to clinic. NOTE: 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.

[36] Blood pressure, heart rate, respiration rate, temperature assessed before and 15 minutes after study treatment administered at clinic

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

[38] 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)

[39] Sample may be collected on ad hoc basis, as per discretion of Sponsor/Investigator during the Treatment Extension Phase

[40] ONLY for subjects trained to perform self-administration of study treatment on weeks when clinic visit optional, i.e., no lab samples are required

[41] Study treatment for self-administration will be provided to subjects during treatment visits at clinic; used vials from prior self-administration must be collected and accounted for (see Section 4.2.2).

[42] Study treatment should be administered at clinic.

[43] All study subjects will re-initiate their previous antiretroviral regimen: (1) One week prior to the end of Treatment Extension Phase, or (2) Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in the protocol.

[44] As assessed by Investigator when study treatment administered at the clinic.

[45] 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 for subjects randomized to PRO 140.

Table 4-8: Schedule of Assessments – Screening and Treatment Extension Phase (8 of 8)

Procedure/Assessments	Subsequent Weekly TE Visits (TE160 onwards)	Treatment Extension Visit	In case of Virologic Failure
Visit[32]		EOT	VF
Window Period	±3 days since last treatment		
Symptom-directed physical examination	X[32]		
Physical Examination		X	X
Neurological Assessment[34]	X[32]		X
Vital Signs[35]	X[32]	X	X
Complete Blood Count (CBC)[36]	X[45]	X	X
Biochemistry[37]	X[45]	X	X
Plasma HIV-1 RNA level	X[32]	X	X
TruCount T assay	X[32]	X	X
PK sample for PRO 140	X[32]	X	X
Serum concentration for ART drugs[38]	X[32]	X	
Anti-idiotypic antibodies to PRO 140	X[32]	X	X
HIV Genotyping Assay			X
Trofile® DNA/RNA and PhenoSense® Entry Assay		X	X
Blood sample collection for Exploratory/Confirmatory analysis[38]		X	X
PRO 140 Administration	X[39]	X[40]	
Subject drug dispensing/accountability[41]	X	X	
Antiretroviral Regimen[42]		X	X
Injection Site Reaction Assessment[43]	X[32]	X	
Injection Site Pain Assessment (VAS)[44]	X[32]	X	
Adverse Events[33]	X	X	X
Concomitant Medications	X	X	X

[32] In-clinic assessment(s) should be performed at least once every 4 weeks from TE108 onwards.

[33] Subjects should be instructed to report any new AEs that occur between clinic visits to site promptly

[34] Performed by Principal Investigator (or designee) when subject comes to clinic. NOTE: 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.

[35] Blood pressure, heart rate, respiration rate, temperature assessed before and 15 minutes after study treatment administered at clinic

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

[37] 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)

[38] Sample may be collected on ad hoc basis, as per discretion of Sponsor/Investigator during the Treatment Phase

[39] Subjects will attend clinic visits, and receive PRO 140 treatment in clinic, on weeks when lab samples are required (at least once every 4 weeks). Subjects trained to perform self-administration of study treatment may do so outside of the clinic (at home) on weeks when no lab samples are required.

[40] Study treatment should be administered at clinic.

[41] PRO 140 for subsequent self-administration visits will be provided to subjects during treatment visits at clinic; used vials from prior self-administration must be collected and accounted for (see Section 4.2.2).

[42] All study subjects will re-initiate their previous antiretroviral regimen: (1) One week prior to the end of Treatment Extension Phase, or (2) Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in the protocol.

[43] As assessed by Investigator when study treatment administered at the clinic.

[44] 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 for subjects randomized to PRO 140.

[45] Should be performed at least once every 12 weeks from TE160 onwards.

Table 4-9: Schedule of Assessments –Follow-Up (FU) Phase

(a) Subjects who do NOT experience virologic failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2
	NVF-EFU1	NVF-EFU2
Window Period	2 weeks (±3 days) after TE161	4 weeks (±3 days) after TE161
Physical Examination	X[1]	X[1]
Vital Signs	X	X
Plasma HIV-1 RNA level	X	X
TruCount T assay	X	X
Previously used Antiretroviral Regimen	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 virologic failure

- Short term follow up visits

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2	Follow-Up Visit -3[1]
	VF-EFU1	VF-EFU2	VF-EFU3
Window Period	4 weeks (±7 days) after VF	8 weeks (±7 days) after VF	12 weeks (±7 days) after VF
Physical Examination	X[2]	X[2]	X[2]
Vital Signs	X	X	X
Plasma HIV-1 RNA level	X	X	X
TruCount T assay	X	X	X
Previously used Antiretroviral Regimen	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 every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels to return back to <50 copies/mL). Subject will undergo additional follow-up visits every 4 weeks beyond VF-EFU3 visit, if viral suppression is not achieved at the end of VF-EFU3 visit.

[2] Symptom-directed physical examination

(c) Subjects who experience virologic failure

- Long term follow up visits

Procedure/Assessments	Long-Term Follow-Up Visit -1	Long-Term Follow-Up Visit -2
	VF-12mFU	VF-24mFU
Window Period	12 months (±1 month) after VF visit	24 months (±1 month) after VF visit
Assessment of cART changes[1]	X	X
Plasma HIV-1 RNA level	X	X
TruCount T assay	X	X
Trofile® DNA or RNA Assay[3]	X*	X*
PhenoSense® Entry Assay[4]	X*	X*
HIV-1 Drug Resistance Assay[5]	X*	X*

[1] Any changes to the combination antiretroviral regimen since the viral re-suppression is achieved.
[2] Monogram Biosciences Trofile® DNA or RNA (or both) assay will be performed depending on last known HIV-1 RNA levels.
[3] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (X4 inhibitor drug), Maraviroc and PRO 140 (R5 inhibitor drugs).
[4] Monogram Biosciences GenoSure Archive® Assay or PhenoSense® GT (and PhenoSense® Integrase and GeneSeq Integrase testing, if applicable), will be performed depending on last known HIV-RNA levels.

*As per discretion if the investigator

4.1 SCREENING PHASE

4.1.1 Screening Visits 1 & 2

The subject will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures.

The unique identification number (screening number) that was assigned for PRO 140_CD 01 study will continue to be used for this extension study.

Once the ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility. Assessments that are in addition to those performed at T12 or T13 of the PRO 140_CD 01 protocol are noted below:

- Detailed medical history – SV1 (see section 7.4),
- Demographic information (see section 7.3),
- Collection of Blood Specimens (see section 7.10) for
    - 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 (SV1)
    - Blood sample collection for Exploratory/Confirmatory analysis (SV2)
- Urine pregnancy test at second Screening Visit, for female subjects of childbearing potential (see section 7.10.5)

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

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

Eligible subjects that are not enrolled within 14 days of Screening Visit 1 must enter the Follow-up Phase of PRO 140_CD 01 Treatment Substitution protocol.

4.2 TREATMENT EXTENSION PHASE

Treatment Extension 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 failures, exit the study without further evaluation and enter the Follow-up Phase of the PRO 140_CD 01 Treatment Substitution protocol.

Eligible subjects will receive PRO 140 weekly SC treatments, given every week (± 3 days) or until virologic failure, whichever occurs first.

PRO 140 will be administered as a 350 mg subcutaneous injection weekly. 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 subjects trained to perform self-administration of study treatment (see section 6.4).

Note: Patients enrolled under a previous Protocol (V.1.0-9.0) have the option of increasing their dose to receive 700mg weekly for the remainder of the Treatment Extension Phase.

All study subjects will re-initiate their previous antiretroviral regimen:

- One week prior to the end of Treatment Extension Phase, or
- Anytime during the Treatment Extension Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in section 5.2.1 of the protocol.

Note:

- In case of increase in plasma HIV-1 RNA levels above 200 copies/mL, subjects will return to clinic for another blood draw in-between the Treatment Visits for repeat plasma HIV-1 RNA levels, as per the discretion of the Investigator.
- Subjects who experience virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days) at any time during the Treatment Extension Phase will undergo the Virologic Failure (VF) Visit assessments and enter the Follow-up Phase of the study.
- Subjects who meet any criteria (other than virologic failure) for discontinuation of study treatment as specified in section 5.2.1 of the protocol, will undergo TE161 Visit assessments and enter the Follow-up Phase of the study.
- Subjects who do not experience virologic failure will enter the Follow-up Phase of the study at the end of 161-week Treatment Extension Phase.

Visits during the Treatment Extension Phase will commence on TE1, i.e. the date of first treatment, with weekly visits (± 3 days) thereafter.

4.2.1 Treatment Visit-1 (TE1)

The following assessments will be performed at the first treatment visit.

Pre-Treatment

- Confirmation of eligibility criteria by reviewing test results and other criteria assessments performed at the Screening Visits (see section 7.2)
- Change in concomitant medications (see section 7.5)
- Vital signs (see section 7.9),
- Any changes in medical history since Screening Visit (see section 7.4),
- Symptom-directed physical examination (see section 7.6),
- Neurological assessment (see section 7.7)
- Quality of life assessment (see section 7.8)
- Subject-perceived Injection Site Pain Assessment (see section 7.13)
  - **Note:** *Subject-perceived injection site pain will be assessed using the Pain Visual Analog Scale (VAS)* ***prior*** *to study treatment administration assessing average pain since last treatment.*

Administration of PRO 140

PRO 140 350 mg is administered as subcutaneous injection in the abdomen weekly. A total of 350 mg (175 mg/mL) is delivered as two 1 mL injections on opposite sides of the abdomen. Subjects who were enrolled under a previous Protocol version and are still receiving the 350 mg dose, have the option of increasing their dose to 700mg for the remainder of the Treatment Extension Phase. PRO 140 700 mg is delivered as two 2 mL injections on opposite sides of the abdomen.

Note: Alternatively, the 700 mg dose may be delivered as four 1mL doses (two SC injections on opposite sides of abdomen) for those that experience discomfort with the 2mL injections (i.e. subjects with low body fat percentages).

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 subjects trained to perform self-administration of study treatment.

Post-Treatment

- Injection Site Reaction Assessment (see section 7.12)
  - **Note:** *To assess injection site reactions, the investigator will use the DAIDS AE grading table (refer to section 17.3).*
  - **Note:** *Performed when treatment visit occurs at clinic*
- Assessment of Adverse Events (AE) (see section 9)
- Vital Signs (see section 7.9) will be assessed within 15 minutes of study treatment administration.

4.2.2 Treatment Visit-2 (TE2) to Visit-59 (TE59) – Bi-weekly Visits

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 7.6),
- Neurological Assessment (see section 7.7)
  - **Note:** *Performed by Principal Investigator (or designee) when subject comes to clinic; additional neurological assessment modalities may be used as per Investigator's discretion.*
- Quality of Life Assessment (see section 7.8)
  - **Note:** *Performed by Principal Investigator (or designee) when subject comes to clinic*
- Vital Signs (see section 7.9)
  - **Note:** *Vitals not obtained when subject self-administers study treatment outside clinic*
- Collection of Blood Specimens (see section 7.10) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - PK sample for PRO 140
  - Serum concentration of ART drugs
  - Anti-idiotypic antibodies to PRO 140
  - Blood sample for exploratory analysis

- **Note:** *Lab samples to be collected at the time of clinic visit*

- Study Treatment Administration (PRO 140)
  - **Note:** *Subjects trained to perform self-administration of study treatment may self-administer when clinic visit not required (no lab sample collection needed), at odd numbered treatment visits beyond TE2*
- Injection Site Reaction Assessment (see section 7.12)
  - **Note:** *To assess injection site reactions, the investigator will use the DAIDS AE grading table (see section 17.3).*
  - **Note:** *Assessment will be performed when subject administered study treatment at clinic visit*
- Subject-perceived Injection Site Pain Assessment (see section 7.13)
  - **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.*
  - **Note:** *Performed at the time of clinic visit.*

4.2.3 Treatment Visit-60 (TE60) onwards – Monthly Visits

Patients are required to have a clinic visit at least once every four weeks from TE60 onwards. Subjects will re-initiate previous antiretroviral regimen at end of treatment extension phase (one week prior to last PRO 140 treatment), if viral load remain suppressed.

The following assessments will be performed at every clinic visit:

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.5),
- Symptom-directed physical examination (see section 7.6),
- Neurological Assessment (see section 7.7)
- Vital Signs (see section 7.9)
  - **Note:** *Vitals not obtained when subject self-administers study treatment outside clinic*
- Study Treatment Administration (PRO 140)
  - **Note:** *Subjects trained to perform self-administration of study treatment may self-administer when clinic visit not required (no lab sample collection needed)*

- Injection Site Reaction Assessment (see section 7.12)
  - **Note:** *To assess injection site reactions, the investigator will use the DAIDS AE grading table (see section 17.3).*
  - **Note:** *Assessment will be performed when subject administered study treatment at clinic visit*
- Subject-perceived Injection Site Pain Assessment (see section 7.13)
  - **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.*
  - **Note:** *Performed at the time of clinic visit.*
- Collection of Blood Specimens (see section 7.10) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - Routine CBC
  - Biochemistry
  - PK sample for PRO 140
  - Serum concentration of ART drugs
  - Anti-idiotypic antibodies to PRO 140
  - Blood sample for exploratory analysis
  - **Note:** *Trofile® RNA or Trofile® DNA and PhenoSense Entry Assay will be performed at the last treatment visit (EOT)*
  - CCR5 Receptor Occupancy
  - **Note:** *Blood will be taken prior to PRO 140 injection (trough sample) and 24-48 hours (peak sample) after the PRO 140 injection to check for CCR5 occupancy, and correlative analysis will be performed with PRO 140 PK concentration and HIV-1 RNA levels. This assessment will be performed up to 5 times at different treatment visits.*

4.2.4 Virologic Failure (VF) Visit

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

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.5),
- Complete Physical Examination (see section 7.6),
- Vital Signs (see section 7.9),
- Neurological Assessment (see section 7.7),
- Collection of Blood Specimens (see section 7.10) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - HIV Genotyping Assay
  - Trofile® RNA or Trofile® DNA and PhenoSense Entry Assay
  - Anti-idiotypic antibodies to PRO 140
  - Routine CBC
  - Biochemistry
  - PK sample for PRO 140
  - Blood sample collection for Exploratory/Confirmatory analysis
- Re-initiate previous Antiretroviral Regimen

4.3 FOLLOW-UP PHASE

The duration of follow-up depends on the status of viral load suppression.

- Subjects who experience virologic failure will be followed up every 4 weeks until the viral load suppression is achieved (i.e., plasma HIV-1 RNA levels to return to <50 copies/mL)
- Subjects who do not experience virologic failure at the end of Treatment Extension Period, will be followed up every 2 weeks for total of 4 weeks.
- ***Note**: Virologic failure subjects will have a long term safety follow up visit once a year within 2 years of completing the last VF-FU visit.*

4.3.1 Follow-Up Visits

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

- Assess for any Adverse Events and changes in Concomitant medications (see section 9 and 7.5),
- Symptom-directed physical examination (see section 7.6) *at NVF-EFU and short term VF-EFU visits*,
- Vital Signs (see section 7.9),
- Collection of Blood Specimens (see section 7.10) for
    - Plasma HIV-1 RNA level
    - TruCount T Assay
    - Anti-idiotypic antibodies to PRO 140 *(NVF-EFU2 and VF-EFU1 visits)*
    - Trofile® DNA or RNA Assay *(VF-12mFU and VF-24mFU visits)*
    - PhenoSense® Entry Assay *(VF-12mFU and VF-24mFU visits)*
    - HIV-1 Drug Resistance Assay *(VF-12mFU and VF-24mFU visits)*

5 SUBJECT COMPLETION AND WITHDRAWAL

5.1 SUBJECT COMPLETION

- A subject who completes the Treatment Extension Phase (without virologic failure) and 4-week Non-Virologic Failure Follow-Up Phase will be considered as having completed the study.
- A subject who experiences virologic failure during the Treatment Extension Phase, undergoes the VF Visit assessments and is followed up until viral suppression is achieved, will be considered as having completed the study.

5.2 SUBJECT WITHDRAWAL

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

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

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

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

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

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

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

- A subject is treated with a prohibited medication.
- Major protocol violation

5.2.1 Discontinuation of Study Treatment

Discontinuation of study treatment and resumption of previous antiretroviral therapy is recommended if:

- Subject experiences virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days)
- Develops retroviral rebound syndrome or AIDS-defining conditions as specified in Appendix I (Section 17.1).
- Shows signs or symptoms of clinically significant immunosuppression
- Subject or the subject's clinician wishes to restart ART.
- 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, Inc. is dedicated to minimizing missing data in this study. It is therefore suggested that all patients, regardless of whether they continue to receive study treatment, continue within the study.

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

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

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

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

5.3 SCREEN FAILURES

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

6 STUDY TREATMENT

6.1 INVESTIGATIONAL PRODUCT DESCRIPTION

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

Kits will be labeled with a unique identification number. Each kit used during Study Treatment will contain vials of PRO 140 for SC injection. Based on the dose administered to the subjects, 1 mL (350 mg dose) or 2 mL (700 mg dose) PRO 140 solution will be drawn from a vial and loaded into the syringe. A total of 350 mg or 700 mg of PRO 140 (from stock concentration 175mg/mL) is delivered as two injections administered subcutaneously on opposite sides of the abdomen or as one of the alternative methods listed in Section 6.4 below. One study injection kit will be assigned per subject per treatment visit (with exception for 350 mg dose with 2.4 mL fill volume in which one kit can be used for two doses).

Table 6-1: PRO140 Dose Administration: Kit Information

PRO 140 Kits Containing 1.4 mL per Vial				
PRO 140 Dose	# of Vials Used per Dose	Total Injection Volume (mL)	Volume (mL) Administered per Injection*	Volume (mL) Discarded per Vial
350 mg	2	2	1	0.4
700 mg	4	4	2	0.4
PRO 140 Kits Containing 2.4 mL per Vial				
PRO 140 Dose	# of Vials Used per Dose	Total Injection Volume (mL)	Volume (mL) Administered per Injection	Volume (mL) Discarded per Vial
350 mg*	1	2	1	0.4
700 mg**	2	4	2	0.4

PRO 140 175 mg/mL will be provided in 3 mL vials containing ~ 2.4 mL of PRO 140 in a sterile buffered solution of 5mM Histidine, 15 mM Glycine, 95 mM Sodium Chloride, 0.3% (w/v) Sorbitol, 0.005% (w/v) Polysorbate 20, at pH of 5.5.

Note: **Since each vial contains 2.4 mL of PRO140, only 1 vial is needed for the 350 mg dose. 2 mL injection will be drawn from ~~1~~2.4 mL solution in a vial. The second vial can be utilized to administer 350 mg dose at the subsequent visit. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

***Alternatively, when 2.4 mL vials are provided, 2 mL injection will be drawn from each vial and the remaining 0.4 mL medication will be discarded. Unused content of PRO 140 in a vial should remain in the vial and **not** be administered to any other subject.*

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

Table 6-2: Investigational Product - PRO 140

Study Drug	Dosage Form	Dose	PRO 140 concentration	Dosing Frequency and Amount	Route of Administration
PRO 140	Parenteral solution	350 mg	175 mg/mL	Two 1 mL inj. on opposite sides of abdomen Weekly SC doses of PRO 140 (2x1 mL)	SC injection
PRO 140	Parenteral solution	700 mg	175 mg/mL	Two 2 mL inj. on opposite sides of abdomen Weekly SC doses of PRO 140 (2x2 mL)	SC injection

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

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

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

Note: PRO 140 kits prepared for Protocol: PRO 140_CD 01 will be used for the extension protocol.

Below are representative samples of the PRO 140 (CHO), 175 mg/mL, 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: PRO 140 (CHO), 175 mg/mL Vial Label

Vial Label:

Protocol: PRO 140_CD 01 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 2.4 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	Protocol: PRO 140_CD 01 Kit No. xxx Subject No. _____ Single use 3 mL vial contains 2.4 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

Figure 6-2: PRO 140 (CHO), 175 mg/mL Syringe Label

Syringe Label:

Protocol: PRO 140_CD 01 Contents of Kit No. xxx This syringe contains 1 mL or 2 mL PRO 140 (175 mg/mL) solution for subcutaneous injection USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Note: *Subjects on 700 mg dose require a total of 4ml of study drug for single dose, given as two 2ml injections, or four 1 mL injections*

Figure 6-3: PRO 140 (CHO), 175 mg/mL Kit Label

Kit Label:

Protocol: PRO 140_CD 01 Kit No. xxx

Site No. _____ Subject No. _____
This kit contains 2 single-use vials
Each 3 mL vial contains 2.4 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 filled 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 or 2.0 mL of study drug for the 350 mg or 700mg dose, respectively

Equivalent volumes of study drug will be administered subcutaneously on opposite sides of the abdomen. However, based on subject preference or investigator discretion subjects receiving each of the doses can be administered using an alternate approach as follows:

350 mg Dose:

- One 2.0 mL injection on one side of the abdomen

700 mg Dose:

- Four 1.0 mL injections, on opposite sides of the abdomen, or other location

Note: *Patients with low body fat percentages may find subcutaneous injections uncomfortable especially in case of 2mL injection for the 700mg dosing. In such cases, PRO 140 700 mg can be injected as four 175mg/ml injections and/or subcutaneous injections can be placed at different areas other than abdomen as per discretion of the Investigator.*

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 more than 60 minutes.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as described in Section 17.3.

All doses of study drug will be prepared by the credentialed pharmacist 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 subject trained to self-administer study treatment.

Prior to self-administration, PI and/or study coordinator will train subjects on IP administration technique. Subject must demonstrate ability to perform injection in presence of PI/study coordinator before being allowed to administer subsequent weekly dose of study treatment outside clinic.

Site will dispense study treatment and injection administration supplies (i.e., syringes, needles, alcohol pads, gauze, band-aids, sharps container, frozen cooler pack, etc), and instruct subjects to return used IP vials/injection kit at next clinic visit.

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 to whom dispensed, the date of dispensing, the intended study participant, and the identification of the preparer.

Note: Site has option to maintain IP accountability via WebView IP Management system.

All used and unused study kits will be retained by the investigational site until drug accountability can be confirmed by study CRA during the monitoring visits. Similarly, accurate record of vials dispensed and returned to the investigational site should be kept for subjects performing self-administration.

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. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers and drug labels to the drug distributor as directed by the Sponsor. A copy of the completed drug disposition form will be sent to CytoDyn, Inc. or to its designee.

7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1 INFORMED CONSENT

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

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

7.2 ASSESSMENT OF ELIGIBILITY

During the Screening Phase and at TE1 Visit (prior to treatment administration), the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and

Exclusion criteria of this Protocol are described in Sections 3.3.1 and 3.3.2. If the subject is not suitable or eligible for the trial then the subject will be a screen failure.

7.3 DEMOGRAPHIC INFORMATION

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

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

7.4 MEDICAL HISTORY

Note: Medical history collected at the time of screening for PRO 140_CD 01 protocol will be carried forward. Medical history will not be collected for the PRO 140_CD 01-Extension protocol.

7.5 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.

7.5.1 Excluded Medications and Therapies

1. Use of concomitant antiretroviral therapy is NOT allowed during the Treatment Extension Phase of the study EXCEPT for one week overlap of oral retroviral regimen and PRO 140 at the end of the treatment in subjects who do not experience virologic failure. Subject is allowed to re-initiate their previous antiretroviral regimen during the Treatment Extension Phase, if virologic failure occurs or if subject meets any other criteria for discontinuation of study treatment as specified in section 5.2.1 of the protocol.

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.

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.

7.5.2 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.

7.6 PHYSICAL EXAMINATION

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

- Head, Ears, Eyes, Nose, Throat (HEENT)

- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal 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 or efficacy 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 first Screening Visit (SV1), End of Treatment (EOT) Visit, and at VF visit in case of virologic failure. Only symptom-directed physical examination will be performed at other Treatment Visits.

7.7 NEUROLOGICAL ASSESSMENT

Neurological assessment will be performed by the Principal Investigator (or designee) at Screening Visit 1 (SV1), TE4, TE40, at least once within TE80-83 and TE116-123, and at Virologic Failure (VF) Visit.

The screening tool is based on the three question survey used by Simioni et al. [Simioni S, 2010]. Additional assessment modalities can be used for further assessment as per Investigator's discretion. Refer to section 17.5 for further details.

7.8 QUALITY OF LIFE (QOL)

A quality of life assessment will be performed by the Principal Investigator or Study Coordinator at Screening Visit 1 (SV1), once every four weeks from TE4 through TE107, and at EOT. The instrument used for this assessment is the ACTG SF-21 (ACTG 601-602). Refer to section 17.6 for further details.

7.9 VITAL SIGNS

The following vital signs will be collected:

- Height (at Screening Visit 1 only)

- Weight
- BMI (derived from the height and weight measurements; at Screening Visit 1 only)
- Seated blood pressure (taken after the subject has been seated for at least 5 minutes)
- Heart Rate
- Respiration Rate
- Temperature

Note: *Within Treatment Phase, post-treatment vital signs will be assessed within 15 minutes following study treatment administration..*

Note: *Vitals will not be collected when subjects perform self-administration.*

7.10 CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected according to the time points in the schedule of assessments for analysis of the following parameters:

7.10.1 Routine CBC

- Frequency of testing: Every 12 weeks from TE160 onwards, and at the end of Treatment Extension Phase OR at the time of virologic failure
- Includes hemoglobin, hematocrit (HCT), red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count (%), absolute neutrophils count and platelets count.

7.10.2 Biochemistry

- Frequency of testing: Every 12 weeks from TE160 onwards, and at the end of Treatment Extension Phase OR at the time of virologic failure
- 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)

7.10.3 PK sample for PRO 140

- Frequency of testing: At first Screening Visit, at Treatment Visits 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. Beyond TE60, PK sample for PRO 140 assessment will be performed once every four weeks, and at Virologic Failure (VF) Visit.

7.10.4 Serum pregnancy test

- Frequency of testing: At first 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.

7.10.5 Urine pregnancy test

- Frequency of testing: At second Screening Visit 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.

7.10.6 Plasma HIV-1 RNA level and TruCount T Assay

- Frequency of testing: At Treatment Visits 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56 and 58. Beyond TE60, blood sample will be collected at least once every four weeks, at EOT, at VF, and at VF-EFU and NVF-EFU visits.
- To assess antiretroviral therapeutic response to PRO 140

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

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

7.10.7 Anti-idiotypic antibodies to PRO 140

- Frequency of sample collection*: At first Screening Visit, at Treatment Visits 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56. Beyond TE60, ADA sample for PRO 140 assessment will be performed once every four weeks. Sample also collected at VF, NVF-EFU2 and VF-EFU1 visits.

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

7.10.8 Trofile® RNA or Trofile® DNA and PhenoSense® Entry Assay (Trofile® with enhanced sensitivity)

- Frequency of testing: At EOT and at the time of virologic failure
- Trofile® RNA is a phenotypic viral RNA assay to assess any change in HIV-1 co-receptor tropism.
- Unlike the standard Trofile® RNA assay, which uses viral RNA found in the plasma of patients with viral loads ≥1000 copies/mL, Trofile® DNA uses viral DNA extracted from cells in a whole blood draw is a phenotypic viral RNA assay to assess any change in HIV-1 co-receptor tropism. PhenoSense® Entry is a phenotypic viral RNA assay to assess resistance of HIV-1 RNA virus to entry inhibitors

7.10.9 HIV Genotyping Assay

- Frequency of testing: At the time of virologic failure
- To identify reverse transcriptase (RT), protease (Pr) and gp120 gene mutations associated with current or evolving drug resistance.

7.10.10 Serum Concentration of ART drugs

- Frequency of testing: At Treatment Extension Visits 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, and at least once every four weeks for the rest of the treatment phase starting at Treatment Visit 60.
- To confirm that enrolled subjects are abstaining from taking their previous ART regimen during the monotherapy treatment phase.

7.10.11 Blood sample collection for Exploratory/Confirmatory analysis

- Frequency of testing: At second Screening Visit, at interim treatment visits, EOT and at the time of virologic failure
- CytoDyn is currently investigating the possibility of developing a more accurate test for detection of co-receptor tropism in patients with undetectable viral loads and in case of early breakthrough/virologic failure during the treatment phase of the study, in addition to assessing viral load reduction efficacy with alternate plasma HIV-1 RNA assays.

7.10.12CCR5 Receptor Occupancy

CCR5 Receptor Occupancy

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

All laboratory reports will be reviewed by the Investigator.

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

7.11 PRO 140 ADMINISTRATION

Refer to Section 6.4 for details.

7.12 INJECTION SITE REACTION ASSESSMENT

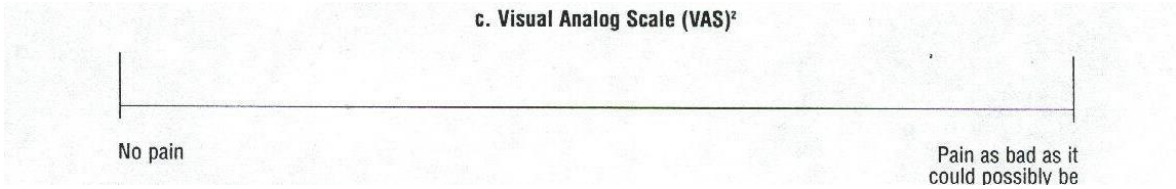
At each visit during the Treatment Extension Phase, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded by the Investigator starting after the first injection is given. Injection site reaction assessments will not be completed when subjects perform self-administration. Refer to sections 9.1.8 and 17.3 for more details.

7.13 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).

Beginning at Screening Visit 1, 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



7.14 COVID-19 GUIDANCE

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

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

- Any changes in the study visit schedule or missed visit should be entered as protocol deviation in the EDC and reason should be documented as missed study visit or visit performed out of window period due to COVID-19.
- If subject is early withdrawn from the study due to COVID-19, the reason should be clearly documented in the End of Study (EOS) section in EDC as “study discontinuation due to COVID-19”.
- Monitoring activities will be performed remotely until Centers for Disease Control (CDC) recommendations allow travel to resume.

8 STATISTICAL CONSIDERATIONS

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

8.1 TREATMENT GROUPS

This is a single active arm study. All eligible subjects in the study will receive PRO 140 as a 350 mg subcutaneous injection weekly and have the option of increasing their dose to receive 700mg subcutaneous injections weekly.

8.2 DESCRIPTION OF STUDY ENDPOINTS

8.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint for this study is time to virologic failure after initiating PRO 140 monotherapy.

Virologic failure is defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days.

8.2.2 Secondary Efficacy Endpoints

- Proportion of participants with virologic failure after initiating PRO 140 monotherapy.
- Mean change in viral load (HIV-1 RNA levels)
- Mean change in CD4 cell count
- Change in quality of life metrics (up to TE107)

8.2.3 Safety Endpoints

Safety measurements will include:

- 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 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

Sample size determination is not applicable as only those subjects who are currently enrolled in PRO 140_CD 01 Treatment Substitution Study are allowed to participate in this extension study.

8.4 RANDOMIZATION AND BLINDING

This study is an open label study with one treatment arm with no randomization and blinding requirements.

8.5 INTERIM ANALYSIS

There is no planned interim analysis (IA) for efficacy. IA for safety will be conducted after all enrolled subjects complete extended treatment with PRO 140 or until study treatment is discontinued, whichever comes first.

8.5.1 Analysis Population

Subjects who have been treated and completed the treatment extension phase (or until treatment is discontinued) will be included in the analysis. All available data from these subjects will be included in the analysis.

8.5.2 Procedures

a. Cut-off dates for review of eCRFs, data cleaning, database lock and analysis will be established based on an estimated target date of all enrolled subjects completing pre-defined treatment period.

b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.

c. The database will be locked for IA.

d. The statistician will generate planned data and information for the DMC, as described below.

8.5.3 Data and Information Provided to DMC

The DMC will receive: AEs, SAEs, labs, ECGs, vital signs, and all other safety related variables identified per the DMC Charter. No inferential statistics will be conducted for this interim analysis.

8.5.4 Type I Error Rate Adjustment

No type I error adjustment will be made due to this safety analysis for this proof of concept 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 have at least one dose of PRO 140 and have at least one post-treatment efficacy assessment for viral load.

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. The PP population will be the primary analysis population for the analysis of primary and secondary endpoints.

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 9.3 or later.

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

8.6.3 Prognostic Factors/Covariates

There are no pre-planned covariates analyses of the data from this proof of concept 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 analysis of the primary and secondary endpoints.

8.6.5 Multiplicity

This is a proof of concept study and there is no need for adjustment of Type I error rate.

8.7 DATA SUMMARY

8.7.1 Subject Disposition

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

8.7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Gender, Time since HIV diagnosis, Viral load at 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 PP population.

The primary efficacy endpoint for this study is time to virologic failure after initiating PRO 140 monotherapy.

Virologic failure is defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/ml separated by at least 3 days.

The time to virologic failure for the subjects treated with PRO 140 monotherapy will be compared to a historical data (i.e., time to HIV-1 RNA viral load > 500 copies/mL of 29 days). The statistical comparison will be conducted using Wilcoxon rank sum test and the median time to virologic failure for this study will be compared to 30 days.

8.7.4.2 Secondary Analysis

- Proportion of participants with virologic failure after initiating PRO 140 monotherapy.
- Mean change in viral load (HIV-1 RNA levels)
- Mean change in CD4 cell count
- Change in quality of life metrics (up to TE107)

All data from the secondary endpoints will be summarized according to the variable type for the PP population:

- 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

8.7.4.3 Supportive Analysis

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the ITT 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 endpoints.

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

8.7.5.1 Adverse Events

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

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

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

8.7.5.2 Tolerability Assessment

All data from tolerability assessments of repeated subcutaneous administration of PRO 140 as assessed by 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.

8.7.5.8 Quality of Life Assessment

All quality of life assessment findings will be listed and 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 NVF-EFU2 for subject who do not experience virologic failure or until viral suppression is achieved for subjects who experience virologic failure). All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the eCRFs. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.2), the impact the event had on study treatment (see Section 9.1.2), the CTCAE 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 extension phase of the protocol, or if the outcome of the event was "death".

9.1.3 CTCAE Grade (Severity) Assessment

The investigator will carefully evaluate the comments of each subject and the response to treatment in order to judge the true nature and severity of the AE. The question of the relationship of AEs to study drug should be determined by the investigator after thorough consideration of all available facts. To assess severity, the investigator will use the DAIDS AE grading table (for adverse events as well as any injection site reactions refer to Section 17.2 and Section 17.3).

If a severity rating is not defined in the DAIDS AE grading table for a particular AE, severity will be rated according to the guidelines outlined in CTCAE v4.03. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 9-1: CTCAE v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v4.03: June 14, 2010

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 17.2 (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 17.3.

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

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

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

For grade 4 events permanently discontinue therapy.

9.2 SERIOUS ADVERSE EVENTS (SAE)

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the AE)

- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

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

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

9.3 REPORTING OF SERIOUS ADVERSE EVENTS

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

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

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

the safety information and determines that the information qualifies for reporting. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)).

9.3.1 SAE Follow-Up

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

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

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

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

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

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 MONITORING REQUIREMENTS

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

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

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

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

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 of the change, with two exceptions:

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

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

11.4 REPORTING PROTOCOL DEVIATIONS

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

12 DATA MONITORING COMMITTEE (DMC)

The study will be monitored by an independent DMC (DMC) to ensure patient safety and to assess efficacy. The CRO is responsible for the overall management of DMC, including development of its charter and membership selection. The DMC will be managed in conformance with the FDA guidelines for DMC independence, management, and oversight.

DMC will conduct scheduled independent reviews of the data in order to ensure that an ongoing acceptable safety profile is being achieved.

DMC will conduct an independent review after all enrolled subjects complete extended treatment with PRO 140 or until study treatment is discontinued, whichever comes first.

The DMC will consist of at least three independent members (including clinicians with expertise in HIV disease, a psychiatrist and at least one biostatistician) and will review all safety signals including number of virologic rebounds, unexpected AEs, all related AEs, all SAEs, and all deaths during the Treatment and Follow-Up Phases.

The DMC will make the following recommendations at the end of safety evaluation:

- Continue the study as planned;
- Modify the study and continue;
- Terminate the study;
- Gather more data to address a specific safety issue and reconvene;
- Other (e.g., request changes to the protocol and propose sanctions).

The Sponsor retains the responsibility to contact FDA and the final decision regarding the recommendation to continue or to terminate the study.

A further description of the DMC reporting requirements, meeting frequency, and the study stopping/continuation criteria can be found in the DMC charter.

13 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.

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

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

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

13.2 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.

13.3 SUBJECT INFORMED CONSENT REQUIREMENTS

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

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

14 DATA HANDLING AND RECORD KEEPING

14.1 RECORDING AND COLLECTION OF DATA

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

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

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

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

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

screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

14.2 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.

14.3 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.

15 PUBLICATION PLAN

All information supplied by CytoDyn, Inc. 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, Inc. shall not be disclosed to others without the written consent of CytoDyn, Inc. and shall not be used except in the performance of this study.

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

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

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17 APPENDIX

17.1 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

17.2 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/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf

17.3 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	

17.4 APPENDIX IV: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03

For complete detailed information please refer to the link below

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

17.5 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, additional neurological assessment modalities may be used as per Investigator's discretion.

17.6 APPENDIX V1: QUALITY OF LIFE ASSESSMENT – ACTG SF-21

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OVERALL HEALTH STATUS ASSESSMENT
NIAID AIDS CLINICAL TRIALS GROUP
Page 1 of 2

Patient Number ☐☐ ☐☐☐☐☐☐ ☐ Date of Patient Visit ☐☐☐ ☐☐ ☐☐☐☐
mmm dd yyyy
Protocol Number ☐☐☐☐☐☐ Institution Code ☐☐☐☐☐☐
Form Week ☐☐☐ * Seq No. ☐ **Step No. ☐ Key Operator Code ☐☐☐

* Enter a "1" if this is the first of this form for this date. Designate subsequent forms on the same date with a 2, 3, etc.
**Enter the subject's current study step number. Enter '1' if the study does not have multiple steps.

FOR OFFICE USE ONLY - TEAR OFF SHEET
MODULE A

INSTRUCTIONS TO THE STUDY NURSE:
Have the patient answer each question at each visit. If the patient does not answer a question at this visit, use "-1" to indicate "Not Done." OVERALL HEALTH STATUS ASSESSMENT - MODULE A should be given to the patient prior to the clinical exam and preferably in a quiet secluded area (e.g., exam room or other office). The patient must be able to read at the sixth-grade level at a minimum to complete the questionnaire without additional assistance.

It is important to be familiar with the content and format of the questionnaire before giving it to study participants. At the first visit, please begin by telling the participant:

> "We would like you to answer some questions about how you are. Your answers will help us understand the effects of the study medication. We appreciate your filling out this questionnaire."

You should then briefly go over the format of the questions and how to complete them. Have the participant complete the questionnaire before clinical evaluations.

The questionnaire is very brief and should take no more than 5 minutes to complete. Before giving the patient the questionnaire, please fill out the header(s) and DETACH THIS PAGE.

Collect the completed questionnaire before the clinical exam. Before going on, review the questionnaire for omissions. If the participant missed any of the questions, point this out and have him/her complete the omissions.

PLEASE COMPLETE THE FOLLOWING ITEMS AFTER PATIENT COMPLETES THE QUESTIONNAIRE OR AFTER YOU ASCERTAIN THAT THIS IS NOT POSSIBLE:

1. How was the questionnaire completed? .....1-Self administered by the study participant ☐
   2-Face-to-face interview that you conducted
   3-Phone interview
   4-Not completed
   9-Other, specify

   If Other, specify [30]: _____

   a. If you answered "4-Not completed," please indicate the reason why : ☐
      1-Patient refused initially
      2-Patient missed clinic visit
      3-There was not enough time
      9-Other reason, specify

      If Other, specify [30]: _____

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OVERALL HEALTH STATUS ASSESSMENT

NIAID AIDS CLINICAL TRIALS GROUP

Patient Number ☐☐ ☐☐☐☐ ☐ Date of Patient Visit ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

Protocol Number ☐☐☐☐☐ Institution Code ☐☐☐☐☐

Form Week ☐☐☐ * Seq. No. ☐ ** Step No. ☐ Key Operator Code ☐☐☐

MODULE A

INSTRUCTIONS TO CLINICIAN: Have the patient answer each question at each visit.
If the patient does not answer the questions at a visit, use "-1" to indicate "Not Done."

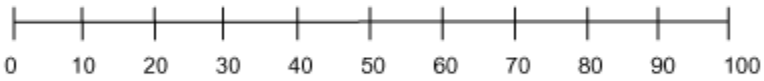
INSTRUCTIONS TO PATIENT: Please answer the following questions at every visit.

(Check One)

1. In general, would you say your health is:
   Place a "✓" in one box.

Excellent.....	1	☐
Very Good	2	☐
Good	3	☐
Fair	4	☐
Poor.....	5	☐

2. On the line below, 0 is death and 100 is perfect health:



DEATH OR WORST POSSIBLE HEALTH (as bad or worse than being dead)

PERFECT OR BEST POSSIBLE HEALTH (without HIV infection)

a. Using the line as a guide, how would you rate your current state of health?

Write down any number between 0 and 100: _____

Language: English [E]

Parens: [Y]

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Date Form Keyed (DO NOT KEY): _____ / _____ / _____

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MULTIDIMENSIONAL HEALTH STATUS ASSESSMENT

NIAID AIDS CLINICAL TRIALS GROUP

Patient Number ☐☐ ☐☐☐☐☐ Date of Patient Visit ☐☐☐ ☐☐ ☐☐☐☐ (mmm dd yyyy)

Protocol Number ☐☐☐☐☐☐ Institution Code ☐☐☐☐☐☐

Form Week ☐☐☐ Seq No. ☐ Step No. ☐ Key Operator Code ☐☐☐

FOR OFFICE USE ONLY - TEAR OFF SHEET
MODULE B

INSTRUCTIONS TO THE STUDY NURSE:

The following should always be used in conjunction with MODULE A, OVERALL HEALTH STATUS ASSESSMENT. MODULE B asks the patient about many aspects of his/her health and health care. It should be given to the patient prior to the clinical exam and preferably in a quiet secluded area (e.g., exam room or other office). The patient must be able to read at the sixth-grade level at a minimum to complete the questionnaire without additional assistance.

It is important to be familiar with the content and format of the questionnaire before giving it to study participants. At the first visit, please begin by telling the participant:

> "We would like you to answer some questions about how you are feeling and the kinds of things you are able to do. Your answers will help us understand the effects of the medication you are taking. We appreciate your filling out this questionnaire."

You should then briefly go over the format of the questions and how to complete them. Have the participant complete the questionnaire before vital signs, history, and physical are completed.

The questionnaire is very brief and should take no more than 10 minutes to complete. Before giving the patient the questionnaire, please fill out the header(s) and DETACH THIS PAGE.

Each question is in the same general format and contains several items. Note that the patient is always asked to make a "✓" next to the appropriate category. All questions refer to the PAST 4 WEEKS.

Collect the completed questionnaire before the clinical exam. Before going on, review the questionnaire for omissions. If the participant missed any of the questions, point this out and have him/her complete the omissions.

PLEASE COMPLETE THE FOLLOWING ITEMS AFTER PATIENT COMPLETES THE QUESTIONNAIRE OR AFTER YOU ASCERTAIN THAT THIS IS NOT POSSIBLE:

1. How was the questionnaire completed? .....1-Self administered by the study participant ☐
   2-Face-to-face interview that you conducted
   3-Phone interview
   4-Not completed
   9-Other, specify

   If Other, specify [30]: _____

   a. If you answered "4-Not completed," please indicate the reason why : ☐
      1-Patient refused initially
      2-Patient missed clinic visit
      3-There was not enough time
      9-Other reason, specify

      If Other, specify [30]: _____

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MULTIDIMENSIONAL HEALTH STATUS ASSESSMENT

NIAID AIDS CLINICAL TRIALS GROUP

Patient Number | Date of Patient Visit (mmm dd yy)

Protocol Number 0 0 0 | Institution Code

Form Week | Key Operator Code

INSTRUCTIONS: Please answer the following questions by placing a "✓" in the appropriate box.

1. During the past 4 weeks, has your health kept you from working at a job, doing work around the house, or going to school?

(Check one)

- Yes, for all of the time ..... 1 ☐
- Yes, for some of the time ..... 2 ☐
- No ..... 3 ☐

2. During the past 4 weeks, how much bodily pain have you had?

(Check one)

- None ..... 1 ☐
- Very Mild ..... 2 ☐
- Mild ..... 3 ☐
- Moderate ..... 4 ☐
- Severe ..... 5 ☐
- Very severe ..... 6 ☐

3. During the past 4 weeks, how much has your physical health or emotional problems interfered with your normal social activities?

(Check one)

- Not at all ..... 1 ☐
- A little bit ..... 2 ☐
- Moderately ..... 3 ☐
- Quite a bit ..... 4 ☐
- Extremely..... 5 ☐

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MULTIDIMENSIONAL HEALTH STATUS ASSESSMENT

Patient Number ☐☐☐☐☐☐☐ Seq. # ☐ Step # ☐ Date ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

4. During the past 4 weeks, have you been unable to do certain kinds or amounts of work, housework, or schoolwork because of your health?

(Check one)

- Yes, for all of the time ..... 1 ☐
- Yes, for some of the time ..... 2 ☐
- No ..... 3 ☐

5. During the past 4 weeks, how much did pain interfere with your normal work (including housework)?

(Check one)

- Not at all ..... 1 ☐
- A little bit ..... 2 ☐
- Moderately ..... 3 ☐
- Quite a bit ..... 4 ☐
- Extremely..... 5 ☐

6. How much, if at all, does your health now limit you in the following activities?

Please check one box for each question.	**YES Limited A Lot**	**YES Limited A Little**	**NO Not Limited At All**
a. The kind or amounts of vigorous activities you can do, like lifting heavy objects, running or participating in strenuous sports.	☐ 1	☐ 2	☐ 3
b. The kind or amounts of moderate activities you can do, like moving a table or carrying groceries.	☐ 1	☐ 2	☐ 3
c. Walking uphill or climbing a few flights of stairs.	☐ 1	☐ 2	☐ 3
d. Eating, dressing, bathing, or using the toilet.	☐ 1	☐ 2	☐ 3

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MULTIDIMENSIONAL HEALTH STATUS ASSESSMENT

Patient Number ☐☐☐☐☐☐☐ Seq. # ☐ Step # ☐ Date ☐☐☐ mmm ☐☐ dd ☐☐☐☐ yyyy

7. For **each** of the following questions, please check the box for the **one** answer that comes **closest** to the way you have been feeling **during the past 4 weeks**.
How much of the time during the past 4 weeks...

Please check one box for each question.	**All of the Time**	**Most of the Time**	**A Good Bit of Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Has your health limited your social activities, like visiting with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b. Did you have trouble keeping your attention on any activity for long?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c. Did you have difficulty reasoning and solving problems?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e. Have you felt down-hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g. Did you have enough energy to do the things you wanted to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h. Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
I. Have trouble remembering things?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Please check the box that best describes whether each of the following statements is true or false for you.

Please check one box for each question.	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. My health is excellent.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I have been feeling bad lately.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Language: English ☐ E

04-24-95/05-07-96/03-05-97

Date Form Keyed: (DO NOT KEY) ___/___/___