CYTODYN

# Protocol Cover Page

**Protocol Title:** A Multicenter Study to Assess the Clinical Safety and Treatment Strategy of Using PRO 140 SC as Long-Acting Single-Agent Maintenance Therapy for 48 Weeks in Virologically Suppressed Subjects with CCR5-tropic HIV-1 infection.

**Protocol Number:** PRO 140_CD03

**Version:** 11.0

**Document Date:** 27-Nov-2019

**NCT Number:** NCT02859961

# A Multicenter Study to Assess the Clinical Safety and Treatment Strategy of Using PRO 140 SC as Long-Acting Single-Agent Maintenance Therapy for 48 Weeks in Virologically Suppressed Subjects with CCR5-tropic HIV-1 infection.

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| **Protocol Number:** | **PRO 140_CD03** |
| **Version:** | **11.0** |
| **Date:** | **27-Nov-2019** |


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|---|---|
| **Sponsor:** | **CytoDyn, Inc.**<br>1111 Main Street, Suite 660<br>Vancouver, Washington 98660<br>(360) 980-8524-Work<br>(360) 980-8549-Fax<br>www.cytodyn.com |


## Confidentiality Statement

# PROTOCOL APPROVAL PAGE

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|---|---|
| **Protocol Number:** | **PRO 140_CD03** |
| **Version:** | **11.0** |
| **Date:** | **27-Nov-2019** |

## 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.

[redacted]

**Prepared by:** [redacted]

**Reviewed by:** [redacted]

[redacted]

[redacted]

[redacted]

**Approved by:** [redacted]

# INVESTIGATOR'S SIGNATURE PAGE

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|---|---|
| **Protocol Number:** | **PRO 140_CD03** |
| **Version:** | **11.0** |
| **Date:** | **27-Nov-2019** |

## INVESTIGATOR'S SIGNATURE

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

Principal Investigator's Signature _____ Date _____

Print Name _____

Address _____

Site Number _____

## SPONSOR INFORMATION

### CytoDyn, Inc.

1111 Main Street, Suite 660
Vancouver, Washington 98660
(360) 980-8524-Work
(360) 980-8549-Fax
www.cytodyn.com

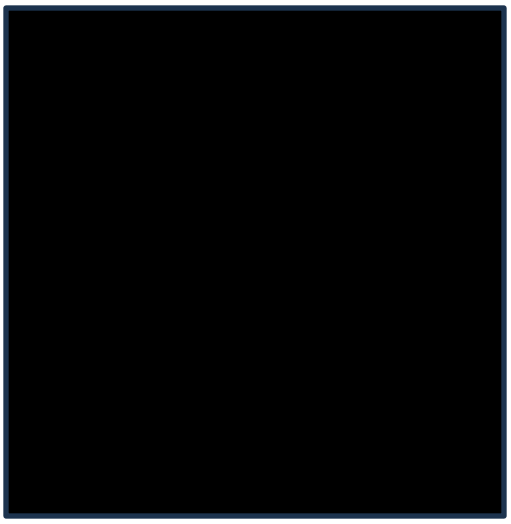
## CONTRACT RESEARCH ORGANIZATION INFORMATION

### Amarex Clinical Research, LLC (Amarex)

20201 Century Boulevard, Suite 450
Germantown, MD 20878 USA
www.amarexcro.com

**Program Director:**
Telephone number:
Fax number:
E-mail:

**Medical Monitor:**
Telephone number:
Fax number:
E-mail:



## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Name of Sponsor:**<br>CytoDyn, Inc. | |
| **Name of Study Product:**<br>PRO 140 (Humanized monoclonal antibody to CCR5) | |
| **Protocol Number:**<br>PRO 140 _CD03 | **Indication:**<br>Human Immunodeficiency Virus Type-1 (HIV-1) Infection |
| **Title of Study:**<br>A Multicenter Study to Assess the Clinical Safety and Treatment Strategy of Using PRO 140 SC as Long- Acting Single-Agent Maintenance Therapy for 48 Weeks in Virologically Suppressed Subjects with CCR5- tropic HIV-1 infection. | |
| **Study Center(s):** Up to 60 centers in the United States | |
| **Planned Number of Subjects:**<br>Approximately 500 | **Study Development Phase:**<br>Phase-2b/3 |
| **Indication for Use:** As single-agent maintenance therapy in virally suppressed, adult subjects with CCR5-tropic Human Immunodeficiency Virus Type-1 (HIV-1) infection who are on antiretroviral therapy. | |
| **Objectives:** The objective is to assess the clinical safety and treatment strategy of using PRO 140 SC 350mg or 525mg or 700mg as long-acting, single-agent maintenance therapy for the chronic suppression of CCR5- tropic HIV-1 infection. In addition, the prognostic factors of therapeutic success of PRO 140 monotherapy will be evaluated. | |
| **Outcome Measures:**<br>**Primary Safety Outcome Measures:**<br>The following metrics will be analyzed to assess the clinical safety of PRO 140 monotherapy regimen:<br>• Incidence of Treatment-Emergent Adverse Events (TEAE)<br>• Incidence of Treatment-Emergent Serious Adverse Events<br>• Incidence of Injection Site Reactions by Investigator evaluation<br>• Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale<br>• Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale)<br>• Changes and shifts in laboratory measurements over time<br>• Changes in vital signs and weight over time<br>• Changes and shift in Electrocardiogram (ECG) parameters over time<br>• Incidence of Physical Examination abnormalities over time | |

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| **Name of Sponsor:**<br>CytoDyn, Inc. | |
| **Name of Study Product:**<br>PRO 140 (Humanized monoclonal antibody to CCR5) | |
| **Protocol Number:**<br>PRO 140 _CD03 | **Indication:**<br>Human Immunodeficiency Virus Type-1 (HIV-1) Infection |

**Primary Efficacy Outcome Measures:**

- Proportion of participants experiencing virologic failure at the assigned dose

  *Note: (1) Virologic failure is defined as two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL. (2) Assigned dose refers to the dose allocated at the time of randomization/enrollment.*
- Time to virologic failure at the assigned dose
- Proportion of participants moved to rescue arm or higher dose group

  *Note: Rescue is defined as subjects who were unable to maintain viral suppression, or experienced virologic failure, and moved to a higher dose of PRO 140*
- Proportion of participants achieving viral re-suppression (HIV-1 RNA <50 copies/mL) during Treatment Phase after moving to rescue arm or higher dose group
- Time to achieving viral re-suppression (HIV-1 RNA <50 copies/mL) during Treatment Phase for subjects who moved to rescue arm or higher dose group
- Proportion of participants achieving viral re-suppression (HIV-1 RNA <50 copies/mL) after experiencing virologic failure (during the Treatment and Follow-up Phase)
- Time to achieving viral re-suppression (for virologic failure subjects) after re-initiation of oral combination antiretroviral regimen during the Follow-up Phase.
- Proportion of participants completing 24, 48 weeks of PRO 140 treatment with HIV-1 RNA <50 copies/mL
- Mean change in CD4 cell count, at each visit within the Treatment Phase
- To evaluate the prognostic factors of therapeutic success of PRO 140 monotherapy during the Treatment Phase.
  - CCR5 Receptor Occupancy
  - CCR5 Genotyping Status
  - gp120 genotyping
  - Baseline HIV-1 RNA Single Copy levels
  - Immune Activation Markers
  - PhenoSense® Entry Assay

**Secondary Exploratory Outcome Measures:**

- Measurement of treatment adherence to the PRO 140 monotherapy regimen; this will be assessed using number of missed PRO 140 administrations
- Loss of future drug options
  *The first occurrence of intermediate to high level resistance to any one or more of the standard*

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*antiretroviral drugs to which the patient's virus was considered to be sensitive at trial entry (i.e. excluding drug resistance present at baseline).*

- Proportion of participants overall and within each treatment group experiencing emerging resistance exhibited by fold increase in maraviroc and PRO 140 FC (Fold Change in $IC_{50}$ and $IC_{90}$ relative to wild-type virus) between baseline and the time of virologic failure, as a measure of post-baseline phenotypic resistance

  **Note:** *Virologic failure is defined as two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL.*

**Central Nervous System (CNS) sub-study:** In a subset of participants (n=20):

- Level of HIV-1 RNA in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits
- PRO 140 concentration in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits
- Relationship between PRO 140 concentration in plasma and CSF
- Relationship between PRO 140 concentration in CSF and HIV-1 RNA in CSF
- Relationship between plasma and CSF HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities)

**Genitourinary (GU) sub-study:** In a subset of participants (n=20):

- Level of HIV-1 RNA in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits.
- PRO 140 concentration in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits.
- Relationship between PRO 140 concentration in plasma and genital secretion
- Relationship between PRO 140 concentration and HIV-1 RNA in genital secretion,
- Relationship between plasma and genital secretion HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities)

**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 for all patients and within each group.
- Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale
- Frequency of Treatment–emergent serious adverse events

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| **Name of Sponsor:**<br>CytoDyn, Inc. | |
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**Trial Design:**

This study is a Phase 2b/3, multi-center, randomized, two-part, open-labeled study designed to evaluate the efficacy, safety, and tolerability of the strategy of shifting clinically stable patients receiving suppressive combination antiretroviral therapy to PRO 140 monotherapy and maintaining viral suppression for 48 weeks following study entry.

Consenting patients will be shifted from combination antiretroviral regimen to weekly PRO 140 monotherapy for 48 weeks during the Treatment Phase with the one week overlap of existing retroviral regimen and PRO 140 at the beginning of the study treatment and also one week overlap at the end of the treatment in subjects who do not experience virologic failure. The first ~150 eligible subjects were enrolled to receive PRO 140 350mg SC weekly injection in a single-arm study. Subsequently, next ~150 subjects were randomized 1:1 to PRO 140 350mg (Group A) or PRO 140 525mg (Group B). An additional ~200 subjects will be randomized 1:1 to PRO 140 525mg (Group B) or PRO 140 700mg (Group C).

- **For the first ~150 enrolled subjects:**
  - **Part 1:** 48-week, single-arm, open-label treatment phase
    - PRO 140 350mg SC weekly injection (Group A)
- **For the subsequent ~150 enrolled subjects:**
  - **Part 1:** 48-week, randomized, two-arm, open-label treatment phase
    - PRO 140 350mg SC weekly injection (Group A)
    - PRO 140 525mg SC weekly injection (Group B)
- **For the subsequent ~200 enrolled subjects:**
  - **Part 1:** 48-week, randomized, two-arm, open-label treatment phase
    - PRO 140 525mg SC weekly injection (Group B)
    - PRO 140 700mg SC weekly injection (Group C)

As noted below, subjects in Group A or Group B that experience virologic failure prior to week 48 in Part 1 have option of entering Part 2 wherein they receive higher dose of PRO 140 for remainder of treatment phase or may re-initiate prior ART regimen (or an alternative regimen selected by their treating physician) at the discretion of the subject and Investigator.

**Part 2 – Rescue Arm for Group A and Group B subjects**

- **Part 2 for Group A:** single arm, open-label treatment phase for Group A subjects electing to receive PRO 140 525mg SC after experiencing virologic failure on 350mg SC/weekly dose
- **Part 2 for Group B:** single arm, open-label treatment phase for Group B subjects electing to receive PRO 140 700mg SC after experiencing virologic failure on 525mg SC/weekly dose

| **Name of Sponsor:** CytoDyn, Inc. | |
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| **Protocol Number:** PRO 140 _CD03 | **Indication:** Human Immunodeficiency Virus Type-1 (HIV-1) Infection |

**Note:** All ongoing subjects assigned to Group A receiving PRO 140 350mg SC weekly or assigned to Group B receiving PRO 140 525mg SC weekly have the option of participating in Part 2 should virologic failure occur.

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

**Screening Phase (up to 6 weeks):**

This phase is designed to determine whether subjects are eligible to proceed to the Treatment Phase of the study. This phase consists of a series of 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.

Subjects will continue to take their existing antiretroviral regimen during the Screening Phase.

**Treatment Phase (48 weeks ± allowed windows):**

Treatment Phase begins with an evaluation of results of laboratory samples collected at the Screening Visit. Subjects who meet all eligibility criteria, as per data gathered from Screening Visit are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without further evaluation.

The first Treatment Visit (T1) will take place within 6 weeks of the Screening Visit, with weekly visits (± 3 days) thereafter.

Subjects will continue their existing antiretroviral regimen for up to one week after receiving initial dosing of PRO 140. The study treatment (PRO 140 350mg or 525mg SC or 700mg SC injections) will be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or home visit or self-administered by subjects, for the duration of 48 weeks in the Treatment Phase as shown in Table 0-1.

**Table 0-1: Part 1: Randomized, two-arm, open-label treatment phase [PRO 140 350mg or 525mg or 700mg]**

| Study Drug | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|
| **GROUP A** | | | | |
| PRO 140 350mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1 mL/inj.) for 48 weeks | SC injection |
| **GROUP B** | | | | |
| PRO 140 525mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1.5 mL/inj.) for 48 weeks | SC injection |
| **GROUP C** | | | | |
| PRO 140 700mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 2 mL/inj.) for 48 weeks | SC injection |

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As shown in Table 0-2, Group A subjects that elect to participate in Part 2 of Treatment Phase after experiencing virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 200 copies/mL) during Part 1 of Treatment Phase will receive PRO 140 525mg SC weekly injection for remainder of 48-week Treatment Phase. Should subject experience subsequent virologic failure in Part 2 of Treatment Phase, subject will complete Virologic Failure (VF) Visit assessments and then enter the Follow-up Phase of the study.

**Table 0-2: Part 2:Rescue Arm for Group A subjects [PRO 140 525mg]**

| | | | | |
|---|---|---|---|---|
| PRO 140 525mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1.5 mL/inj.) for remainder of treatment phase | SC injection |

As shown in Table 0-3, Group B subjects that elect to participate in Part 2 of Treatment Phase after experiencing virologic failure during Part 1 of Treatment Phase will receive PRO 140 700mg SC weekly injection for remainder of 48-week Treatment Phase. Should subject experience subsequent virologic failure in Part 2 of Treatment Phase, subject will complete Virologic Failure (VF) Visit assessments and then enter the Follow-up Phase of the study.

**Table 0-3: Part 2:Rescue Arm for Group B subjects [PRO 140 700mg]**

| | | | | |
|---|---|---|---|---|
| PRO 140 700mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 2 mL/inj.) for remainder of treatment phase | SC injection |

Group A or Group B subjects that do not elect to participate in Part 2 of Treatment Phase and all Group C subjects who experience virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 200 copies/mL) at any time during the Treatment Phase will undergo the Virologic Failure (VF) Visit assessments and then exit the Treatment 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 48-week Treatment Phase.

All study subjects will re-initiate their previous antiretroviral regimen or an alternative regimen selected by their treating physician:

- One week prior to the end of 48-week Treatment Phase, or
- During the Treatment 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.

Efficacy assessments will include viral load measurement and CD4 cell counts at every alternate week during the first 16 weeks of Treatment Phase and once every four weeks during the remaining 32 weeks of Treatment Phase. Safety assessments will consist of determining and recording all AEs and SAEs; laboratory evaluation of hematology, blood chemistry, and urine analysis; periodic measurement of vital signs; and the performance

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of physical examinations, as detailed in the schedule of procedures and assessments of the protocol.

**Follow-up Phase:**

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

- Group A or Group B subjects not participating in Part 2 and Group C subjects who experience virologic failure during the Treatment Phase will be assessed every 4 weeks until the viral suppression is achieved (i.e., plasma HIV-1 RNA levels decline to < 50 copies/mL). Additionally, virologic failure subjects will return to clinic for long-term follow-up at 6 months and at one year from the time of the Virologic Failure (VF) Visit.
- Subjects who do not experience virologic failure and complete Treatment Visit 48 (T48), will be assessed every 2 weeks for total of 4 weeks.

**Duration of Treatment:**

- **Screening Phase:** up to 6 weeks
- **Treatment Phase:** 48 weeks ± allowed windows (up to 48 treatments every week (±3 days)).
- **Follow-up Phase:**
  - Virologic Failure: Until viral suppression is achieved. Additionally, subjects who experience virologic failure will return to clinic for long-term follow-up at 6 months and at one year from the time of the Virologic Failure Visit.
  - Non-Virologic Failure (NVF): 4 weeks

**Total Study Duration:**

58 weeks [Does not include additional long-term 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. Males and females, age ≥18 years
2. Receiving combination antiretroviral therapy for last 24 weeks
3. No change in antiretroviral regimen within last 4 weeks prior to Screening Visit and in-between Screening Visit and First Treatment Visit.
4. Subject has two or more potential alternative approved antiretroviral drug options to consider.
5. Documented Exclusive CCR5-tropic virus at Screening Visit as determined by Trofile™ DNA Assay
6. Plasma HIV-1 RNA < 50 copies/mL at Screening Visit as determined by Human Immunodeficiency Virus 1 (HIV-1) Quantitative, RNA (Taqman® Real-Time PCR)
7. No documented detectable viral loads (HIV-1 RNA > 50 copies/mL) within the last 24 weeks prior to

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Screening Visit

*A patient who has had one VL "blip" to < 200 copies/mL in the 24 weeks prior to screening may be included, provided that the plasma HIV-1 RNA level that immediately preceded the blip and VL test that immediately followed the blip was < 50 copies/mL.*

8. CD4 cell count of > 200 cells/$mm^3$ since initiation of anti-retroviral therapy
9. CD4 cell count of > 350 cells/$mm^3$ in preceding 24 weeks and at Screening Visit
10. Laboratory values at Screening of:
    a. Absolute neutrophil count (ANC) ≥ 750/$mm^3$
    b. Hemoglobin (Hb) ≥ 10.5 gm/dL (male) or ≥ 9.5 gm/dL (female)
    c. Platelets ≥ 75,000 /$mm^3$
    d. Serum alanine transaminase (SGPT/ALT) < 5 x upper limit of normal (ULN)
    e. Serum aspartate transaminase (SGOT/AST) < 5 x ULN
    f. Bilirubin (total) < 2.5 x ULN unless Gilbert's disease is present or subject is receiving atazanavir in the absence of other evidence of significant liver disease
    g. Creatinine ≤ 1.5 x ULN
11. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
12. Both male and female patients and their partners of childbearing potential must agree to use 2 medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative serum pregnancy test at Screening visit and negative urine pregnancy test prior to receiving the first dose of study drug.
13. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

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

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

1. CXCR4-tropic virus or dual/mixed tropic (R5X4) virus determined by the Trofile™ DNA Assay at the

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Screening Visit

2. Hepatitis B infection as manifest by the presence of Hepatitis B surface antigen (HBsAg)
3. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)
4. Laboratory test values ≥ grade 4 DAIDS laboratory abnormality.
5. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
6. Unexplained fever or clinically significant illness within 1 week prior to the first study dose
7. Any vaccination within 2 weeks prior to the first study dose.
8. Subjects who have failed on a maraviroc containing regimen.
9. Subjects weighing < 35kg
10. History of anaphylaxis to any oral or parenteral drugs
11. History of Bleeding Disorder or patients on anti-coagulant therapy (except aspirin)
    **Note**: Subjects with well-controlled bleeding disorder while on stable anti-coagulant therapy dose with documented stable INRs can be enrolled as per discretion of the Investigator.
12. Participation in an experimental drug trial(s) within 30 days of the Screening Visit
13. Any known allergy or antibodies to the study drug or excipients
14. Treatment with any of the following:
    a. Radiation or cytotoxic chemotherapy with 30 days prior to the screening visit
    b. Immunosuppressants within 60 days prior to the screening visit
    c. Immunomodulating agents (e.g., interleukins, interferons), hydroxyurea, or foscarnet within 60 days prior to the screening visit
    d. Oral or parenteral corticosteroids within 30 days prior to the Screening Visit. Subjects on chronic steroid therapy > 5 mg/day will be excluded with the following exception:
        - Subjects on inhaled, nasal, or topical steroids will not be excluded
15. 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:**

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Approximately 500 subjects will be enrolled or randomized, in this study. A total of 100 subjects will be randomized to receive PRO 140 700 mg. The sample size is selected on the basis of clinical judgment.

**Analysis Populations:**

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

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.

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:**

The interim analysis will be directed and conducted by an independent DMC (iDMC), which will include a statistician who is not otherwise involved in the trial and two clinicians. The iDMC will monitor the safety of the trial from the beginning and at approximately six month intervals based on enrollment thereafter. The main purpose of this IA is to ensure the safety of the subjects in the trial and to recommend whether the trial should be stopped early to protect the safety of the participants.

The iDMC will closely monitor the following:

- Virologic failure and viral re-suppression (after oral combination therapy is re-instituted).
- Long-term safety follow-up data for one year after completion of treatment phase
- In addition to other safety parameters, all baseline/post-treatment tropism, resistance, prognostic factors such as, HIV-1 RNA single copy assay, immune activation markers etc. and any potential cardiovascular events (that may occur from inflammatory bursts post-drug withdrawal).

A detailed interim analysis plan will be prepared and presented to the DMC prior to the conduct of the interim analysis.

**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:

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

**Primary Outcome Analysis**

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

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| **Protocol Number:**<br>PRO 140 _CD03 | **Indication:**<br>Human Immunodeficiency Virus Type-1 (HIV-1) Infection |
| The primary outcome measures for this study are to assess the clinical safety of PRO 140 monotherapy regimen, proportion of participants experiencing virologic failure, and to evaluate the prognostic factors of therapeutic success of PRO 140 monotherapy during the Treatment Phase. | |

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## LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AIDS | Acquired Immune Deficiency Syndrome |
| ALT | Alanine Transaminase |
| ANC | Absolute Neutrophil Count |
| ART | Anti Retroviral Therapy |
| AST | Aspartate Transaminase |
| ATC | Anatomic Therapeutic Classification |
| AUC | Area Under Curve |
| °C | Celsius |
| cART | Combination Antiretroviral Therapy |
| CBC | Complete Blood Count |
| CCR5 | C-C chemokine receptor type 5 |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CHO | Chinese Hamster Ovary |
| cm | Centimeter |
| CRF | Case Report Form |
| $C_{max}$ | Maximal Concentration |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| DAIDS | Division of AIDS |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic Acid |
| DO | Doctor of Osteopathic Medicine |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| Emax | Maximum drug effect |
| et al | et aliae; Latin for "and others" |
| °F | Fahrenheit |
| FDA | U.S. Food and Drug Administration |
| FDP | Fixed Dose Procedure |
| FU | Follow-Up |
| GCP | Good Clinical Practice |
| HAART | Highly Active Antiretroviral Therapy |
| Hb | Hemoglobin |

| Abbreviation | Term |
|---|---|
| HBsAg | Hepatitis B Surface Antigen |
| HCT | Hematocrit |
| HEENT | Head, Ears, Eyes, Nose, and Throat |
| HIPAA | Health Insurance Portability Accountability Act |
| HIV | Human Immunodeficiency Virus |
| IA | Interim Analysis |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| i.e. | id est; Latin for "that is" |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ISR | Injection Site Reactions |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LAR | Legally Acceptable Representative |
| LDH | Lactate dehydrogenase |
| LPN | Licensed Practical Nurse |
| LVN | Licensed Vocational Nurse |
| mAb | Monoclonal Antibody |
| MD | Doctor of Medicine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mL | Milliliter |
| mm | Millimeter |
| MW | Molecular Weight |
| NCS | Not Clinically Significant |
| NP | Nurse Practitioner |
| NTF | Non-Treatment Failure |
| OBT | Optimized Background Therapy |
| PA | Physician Assistant |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PP | Per Protocol |

| Abbreviation | Term |
|---|---|
| PT | Prothrombin Time |
| QC | Quality Control |
| RBC | Red Blood Cells |
| RN | Registered Nurse |
| RNA | Ribonucleic acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| SV | Screening Visit |
| TEAE | Treatment Emergent Adverse Events |
| TF | Treatment Failure |
| USA | United States of America |
| VAS | Visual Analogue Scale |
| WBC | White Blood Cells |

# 1 INTRODUCTION

## 1.1 STATEMENT OF INTENT

The design, conduct and reporting of this trial shall be conducted in compliance with 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 & CO4., 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.

Also, there is an interest in the development of infrequently administered therapy both as a treatment and a prevention strategy. The Long-Acting Antiretroviral Treatment Enabling (LATTE) study tested a combination of two oral antiretroviral drugs, the non-nucleoside reverse transcriptase inhibitor rilpivirine and the new integrase inhibitor GSK1265744 (Spreen WR, 2013). Furthermore, a long-acting injectable medication can be an effective approach to circumvent the need for daily medication 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 weekly or bi-weekly. 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 study of PRO 140 monotherapy as maintenance therapy for subjects previously fully suppressed on combination antiretroviral regimen. PRO 140 is a promising new antiretroviral agent that does not show any cross-resistance with drugs from other classes. The purpose of this study is to assess the clinical safety and treatment strategy of using PRO 140 SC as long-acting, single-agent maintenance therapy for the chronic suppression of CCR5-tropic HIV-1 infection.

### 1.3 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

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

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

## 1.4 SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES

### 1.4.1 Pre-Clinical Studies with PRO 140

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

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

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

### 1.4.2 Clinical Studies with PRO 140

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

#### 1.4.2.1 PRO 140 1101 Study

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

#### 1.4.2.2 PRO 140 1102 Study

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

#### 1.4.2.3 PRO 140 1103 Study

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

#### 1.4.2.4 PRO 140 1302 Study

This initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only 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 all treatment groups.

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

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

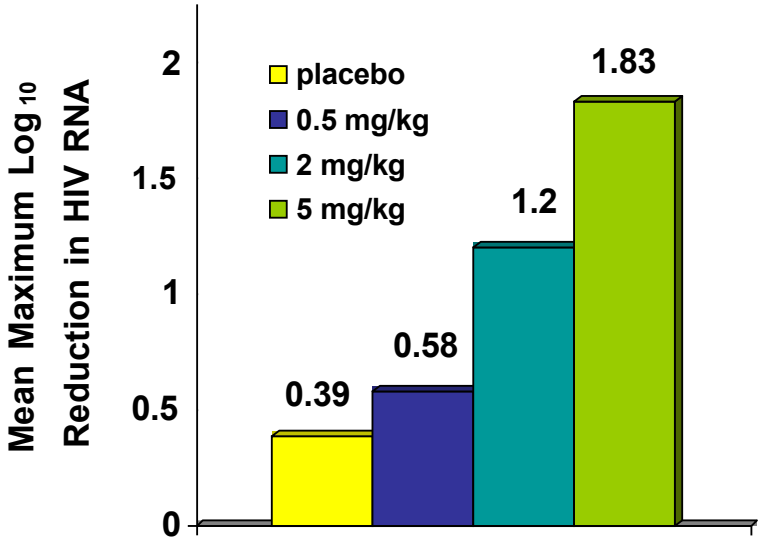
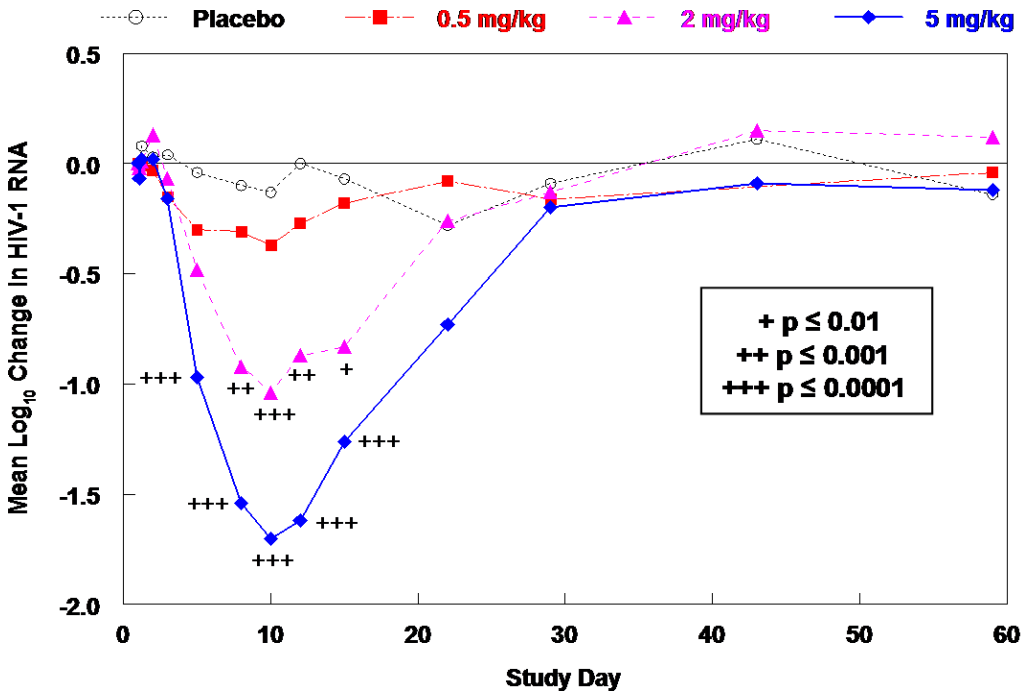



**Figure 1-2: PRO 140 1302 Study: Mean $log_{10}$ reductions in HIV RNA over time**

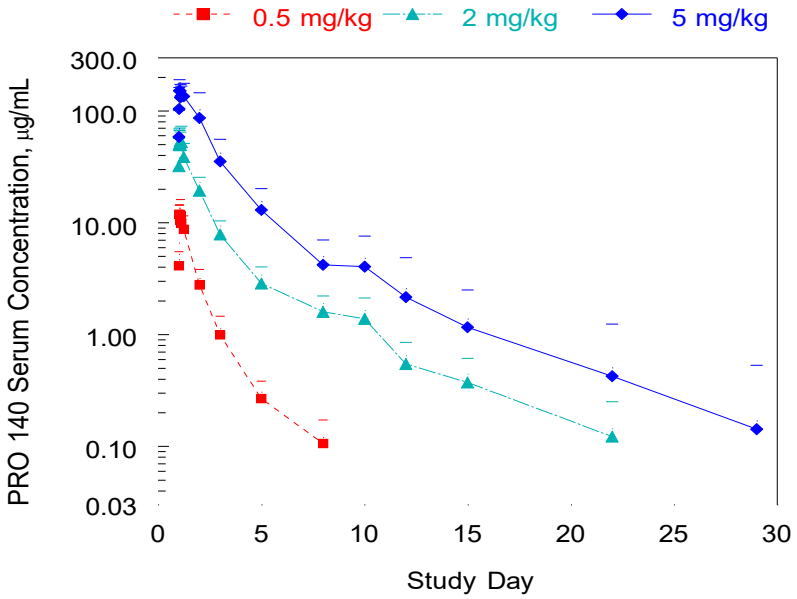



There was no change in R5 virus susceptibility to PRO 140 following treatment. All subjects had R5-only virus at screening in the first-generation Trofile assay. R5-only tropism results were observed in all subjects at all other timepoints, with two exceptions: One of nine (11%) of

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 S. M., 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 1-3 illustrates the mean serum concentrations of PRO 140 after IV injection. Serum levels increased with increasing dose. The mean Area Under Curve (AUC) from time zero to infinity ($AUC_\infty$) 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 S. M., 2008). The PK and receptor occupancy data were broadly consistent with the duration of antiviral effects.

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




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

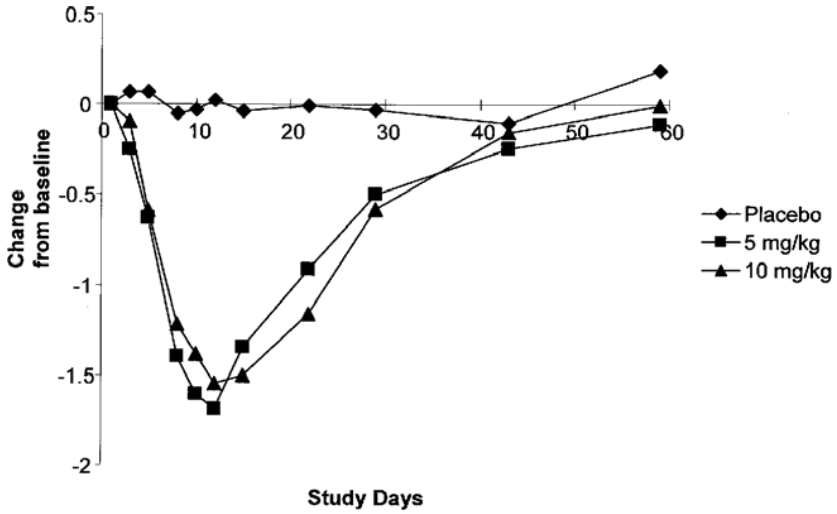
Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose- limiting toxicity was observed. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant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

#### 1.4.2.5 PRO 140 2301 Study

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

All PRO 140-treated subjects had more than 10-fold reduction in viral loads (mean max log10 reductions were 1.83 for treatment groups and 0.32 for placebo) (Figure 1-4). Both the 5 mg/kg and 10 mg/kg doses have shown favorable tolerability and no dose-limiting toxicity has been observed. High levels of receptor occupancy (> 85% reduction in the number of cells detected) were observed for 29 days after treatment with both 5 and 10 mg/kg doses.

**Figure 1-4: PRO 140 2301 Study: Mean change from baseline in HIV-1 RNA (Log10 copies/mL) over Time (ITT Subjects)**



### 1.4.2.6 PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only 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 1-5 and Figure 1-6). The 324mg weekly dose resulted in a mean 1.65 $\log_{10}$ reduction in viral load, and highly significant reductions were observed for the other dose groups as well (Figure 1-5). There was no viral rebound between 324mg doses, and the antiviral effects persisted for one week after the final dose Figure 1-6. The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection (Thompson, 2009).

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

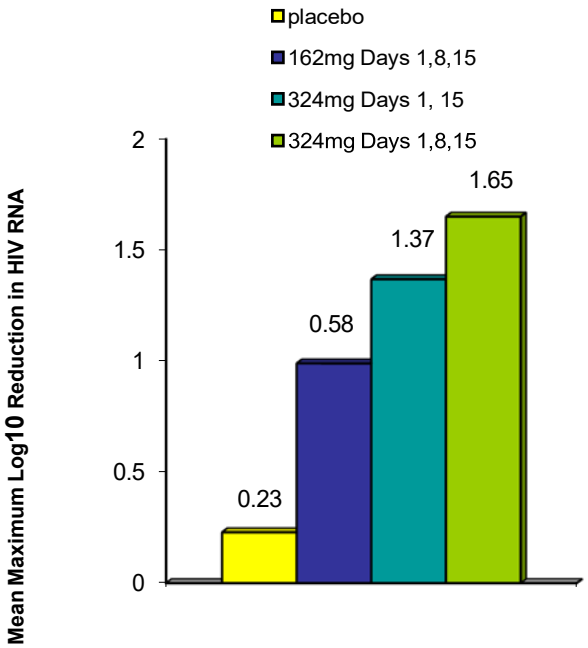
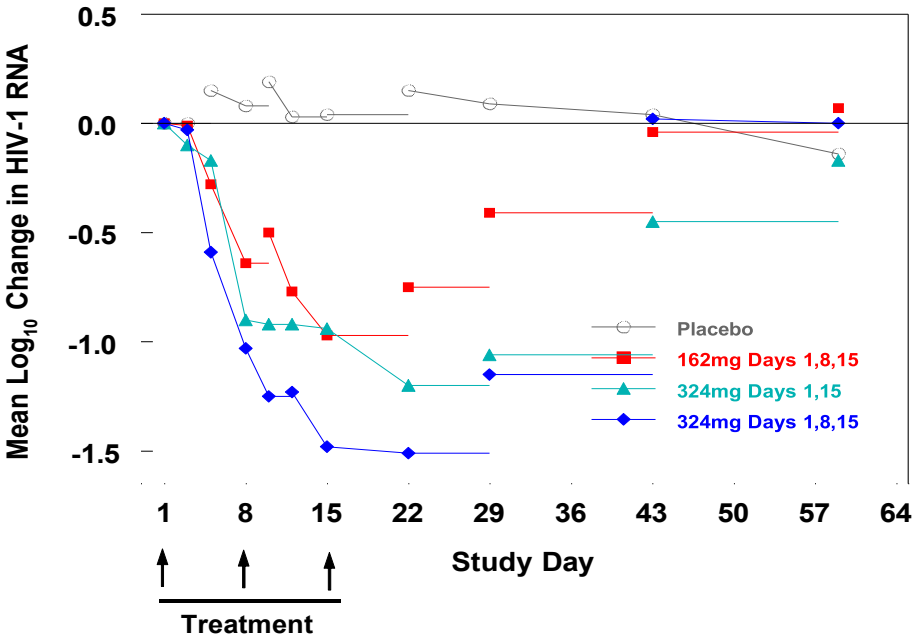


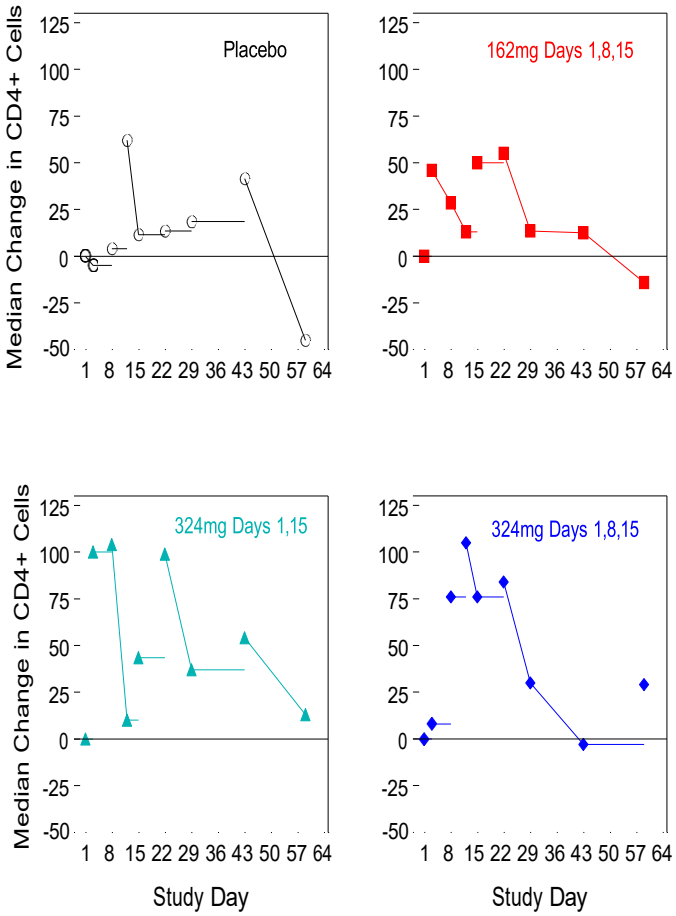
**Figure 1-6: PRO 140 2101 Study: Mean change from baseline in HIV-1 RNA ($Log_{10}$ copies/mL) over Time (ITT Subjects)**




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

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

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




### 1.4.2.7 PRO 140 _CD01 Study

PRO 140_CD01 study (open-label, 43 subjects, multi-center) (12-cohort 1, 28-cohort 2, 3-cohort 3) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution of antiretroviral therapy in HIV-1 infected patients (with exclusive CCR5- tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty (43) subjects (M/F: 40/3) with median age of 55 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 $IC_{50}$ and $IC_{90}$ 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.

#### 1.4.2.8 PRO 140 _CD01-Extension Study

PRO 140_CD01-Extension study (open-label, 17 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 160 weeks) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy for up to 160 weeks.

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

Sixteen (16) eligible subjects (M/F: 14/2) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled in an extension study. One patient discontinued at week 37 (with viral load of <40 copies/mL) due to relocation. Two subjects were

withdrawn due to non-treatment related SAEs at week 140 and 149, respectively. One subject was withdrawn due to re-starting their ART at week 99. Two subjects withdrew consent at week 81 and 139, respectively. Five (5) subjects experienced virologic failure (VF) (two consecutive viral load of ≥400 copies/mL). The mean time to virologic failure was 329 days (106-691).

Five (5) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than three years of treatment (176 - 198 weeks). Overall, 12 subjects completed at least one year of treatment and 9 subjects completed at least two years of treatment in this study

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

This clinical study is currently ongoing.

#### 1.4.2.9 PRO 140 _CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 30 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 in combination with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks in patients infected with HIV-1. The study population includes 30 treatment-experienced HIV- infected adult patients with CCR5-tropic virus who demonstrates evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented history of genotypic or phenotypic resistance to at least one ART drug within 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 will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days. The primary efficacy endpoint is proportion of participants with ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

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

This clinical study is completed.

**Table 1-1: Clinical Studies with PRO 140**

| Protocol Number | Phase | No. of Subjects (Planned/ Analyzed) | Doses | Cell line used to make PRO-140 | Subject Population | Comments |
|---|---|---|---|---|---|---|
| PRO 140 1101 | 1 | 20/20 | Single 0.1, 0.5, 2.0, or 5.0 mg/kg | Sp2/0 myeloma | Healthy | Generally well tolerated; non-immunogenic; dose-dependent coating of CCR5; significant coating of CCR5 over placebo at 0.5, 2, and 5 mg/kg |
| PRO 140 1102 | 1 | 20/20 | Either two or three doses totaling 200 or 350 mg respectively | CHO | Healthy | Generally well tolerated; drug derived from CHO cells well tolerated also; SC administration by Autoject® 2 better tolerated than manual injection |
| PRO 140 1103 | 1 | 15/14 | Two doses, each of 350 mg | CHO | Healthy | More AEs associated with arm injection; trend of lower exposure in arm injections; thigh and abdominal administration preferred |
| PRO 140 1302 | 1b | 40/39 | Single 0.5, 2.0, or 5.0 mg/kg | Sp2/0 myeloma | HIV-1 positive | Generally well tolerated; antiviral suppression maintained for approx. 10 days with higher doses; favorable tolerability and potent, dose-dependent antiviral activity provide proof-of-concept |
| PRO 140 2301 | 2a | 30/31 | Single 5.0 or 10.0 mg/kg | CHO | HIV-1 positive | Generally well tolerated with no dose-limiting toxicities; potent antiviral suppression maintained for approx. 20 days when administered IV at 5 or 10 mg/kg. No dose-limiting toxicities at 10 mg/kg. |
| PRO 140 2101 | 2a | 40/44 | Three doses of 162 or 324 mg each | CHO | HIV-1 positive | Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; antiviral activity was statistically significant; two-fold exposure at higher dose; single dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity. |
| PRO 140 _CD01 | 2b | 43/43 | 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. |

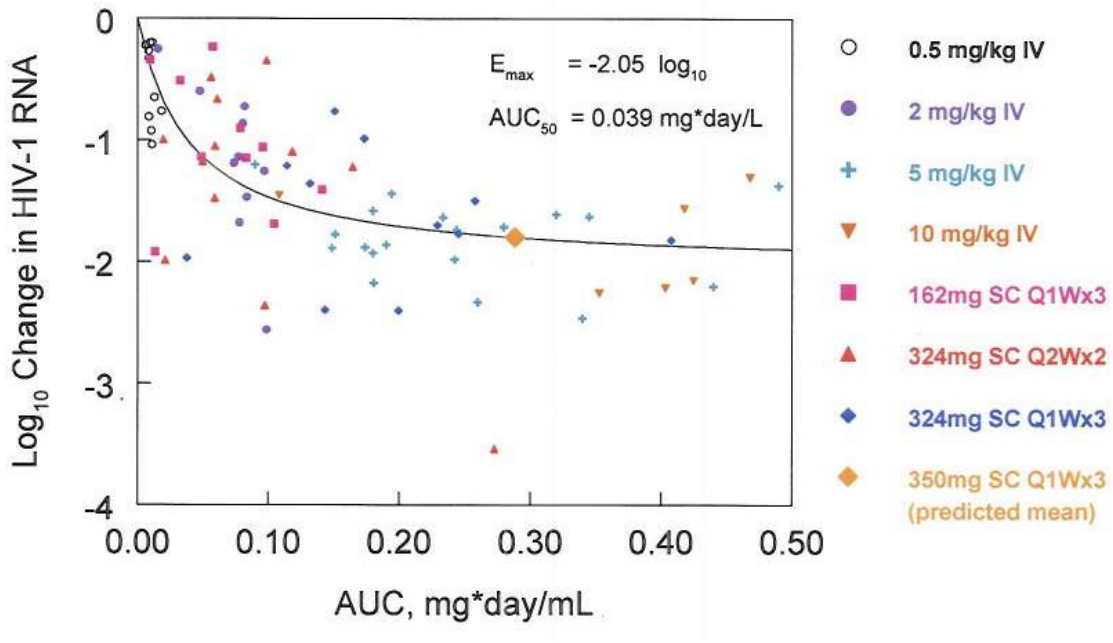
| | | | | | | |
|---|---|---|---|---|---|---|
| PRO 140 _CD01-Extension | 2b | 17/17 | 350 mg SC weekly dose for 160 weeks of Monotherapy (total treatment duration 161 weeks) | CHO | HIV-1 positive | This clinical study is currently ongoing |
| PRO 140 _CD02 | 2b/3 | 50/52 | Placebo or 350mg SC for 1 dose, followed by 350mg SC weekly dose for 24 weeks (total treatment duration 25 weeks) | CHO | HIV-1 positive | This clinical study is completed |

## 1.5 RATIONALE FOR DOSE SELECTION

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

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

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




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

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

It is important to note that when larger proteins (MW > 10,000) are administered SC, they initially traffic through the lymphatic system. Uptake into the bloodstream occurs after the proteins reach the thoracic duct (Nishikawa M, 2005). In addition, based on pharmacodynamic data from our prior SC and IV studies, maximum virologic suppression is expected to be achieved with trough concentrations that equal or exceed approximately 5 μg/mL.

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

Majority of subjects receiving 350 mg weekly SC dosing in monotherapy setting experienced virologic failure in CD01-Extension study. Review of PRO 140 clinical data to date with 350mg SC weekly dosing, suggests no evidence of emergence of viral isolates with reduced susceptibility to PRO 140, no altered viral tropism or anti-PRO 140 antibodies formation suggesting the most likely cause of viral rebound is inadequate dosing to fully cover CCR5 receptor populations. Based on pharmacologic modeling studies, we anticipate that the 525mg and 700mg dose will result in a lower fraction of study participants with trough levels below that which will 'uncoat' a significant number of CD4 cells (i.e., less than a certain multiple of the IC50 or IC90 for PRO 140).

## 1.6 RISKS / BENEFITS ASSESSMENT

### 1.6.1 Risks/Discomfort to Subjects and Precautions to Minimize Risk

#### 1.6.1.1 Risks associated with using monotherapy treatment

Study treatment (PRO 140 350mg or 525mg or 700mg SC injection) may not be effective in achieving a reduction in viral load for all subjects. Such cases could lead to an increased risk of developing drug resistance, opportunistic infections and clinical progression of the disease. As patients will not be receiving concomitant antiretroviral drugs of other antiviral classes, should PRO 140 therapy fail, selection of viral variants with reduced susceptibility to these agents would be unlikely (and was not observed in the PRO 140_CD 01 or PRO 140_CD 01-Extension studies).

#### 1.6.1.2 Allergic Reaction

PRO 140 belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions (fatigue, diarrhea, fever, vomiting, headache, nausea, pain at the site of injection, low blood pressure, rash, itching, and chills) or flu-like

reactions such as fever, chills, and aches. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of PRO 140, infusion of proteins always carries with it the theoretical risk for anaphylactic shock. Accordingly, whenever PRO 140 is initially administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

#### 1.6.1.3 Immune Response

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

#### 1.6.1.4 Pregnancy

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

#### 1.6.1.5 Venipuncture 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.

#### 1.6.1.6 Risks related to resumption of viral replication in anatomically privileged compartments

It is possible that penetration of PRO 140 into certain key anatomic compartments such as the central nervous system (CNS) or the male genital tract will be insufficient to control viral replication in those locations. Loss of control of viral replication in the CNS could result in the development or exacerbation of HIV-1 Associated Neurocognitive Disorders (HAND) and that a lack of control of HIV-1 replication in the male genital tract could be associated with an increased risk of HIV-1 transmission following unprotected sexual encounters.

#### 1.6.1.7 Risks to the Study Personnel and the Environment

The principal risk in the clinical setting is in the handling of needles that may be contaminated with HIV, or other human pathogens. Adherence to universal precautions for working with infectious agents will reduce the risk of exposure to these individuals. All bio-hazardous waste

will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site Standard Operating Procedures (SOPs).

#### 1.6.1.8 Unknown Risks

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

#### 1.6.1.9 Theoretical risk for increased severity of West Nile virus infection

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

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

### 1.6.2 Intended Benefit for Subjects

This study provides an opportunity for subjects to receive once weekly SC treatment with PRO 140. Subjects participating in the present monotherapy study for 48 weeks will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

## 2 STUDY OBJECTIVES

The objective of this study is to assess the clinical safety and treatment strategy of using PRO 140 SC as long-acting, single-agent maintenance therapy for the chronic suppression of CCR5- tropic HIV-1 infection. In addition, the prognostic factors of therapeutic success of PRO 140 monotherapy will be evaluated.

The primary outcome measures will be to assess the clinical safety of PRO 140 monotherapy regimen, proportion of participants experiencing virologic failure for all subjects and within each treatment group, and to evaluate the prognostic factors of therapeutic success of PRO 140 monotherapy during the Treatment Phase. In addition, time to virologic failure for all subjects and within each treatment group, proportion of participants achieving viral re-suppression (HIV- 1 RNA < 50 copies/mL) after experiencing virologic failure for all subjects and within each treatment group, time to achieving viral re-suppression (HIV-1 RNA < 50 copies/mL) after experiencing virologic failure for all subjects and within each treatment group, proportion of virologic failure subjects achieving viral re-suppression with re-initiation of previous baseline antiretroviral regimen for all subjects and within each treatment group, proportion of participants with viral suppression (HIV-1 RNA < 50 copies/mL) at week 48 for all subjects and within each treatment group, and mean change in CD4 cell count, at each visit within the Treatment Phase for all subjects and within each treatment group.

The secondary outcome measures will be measurement of treatment adherence to the PRO 140 monotherapy regimen, loss of future drug options [The first occurrence of intermediate to high level resistance to any one or more of the standard antiretroviral drugs to which the patient's virus was considered to be sensitive at trial entry (i.e. excluding drug resistance present at baseline)] and proportion of participants overall and within each treatment group experiencing emerging resistance exhibited by fold increase in maraviroc and PRO 140 FC (Fold Change in $IC_{50}$ and $IC_{90}$ relative to wild-type virus) between baseline and the time of virologic failure, as a measure of post-baseline phenotypic resistance.

**Note:** *Virologic failure is defined as two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL.*

In a subset of participants (n=20) from Central Nervous System (CNS) study: Level of HIV-1 RNA in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits, PRO 140 concentration in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits, relationship between PRO 140 concentration in plasma and CSF, relationship between PRO 140 concentration in CSF and HIV-1 RNA in CSF, and relationship between plasma and CSF HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities) will be evaluated.

In a subset of participants (n=20) from Genitourinary (GU) sub-study: Level of HIV-1 RNA in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits, PRO 140 concentration in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits, relationship between PRO 140 concentration in plasma and genital secretion, relationship between PRO 140 concentration and HIV-1 RNA in genital secretion, and relationship between plasma and genital secretion HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities) will be evaluated.

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 for all subjects and within each treatment group, frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale and frequency of treatment-emergent serious adverse events.

# 3 STUDY DESIGN

This study is a Phase 2b/3, multi-center, randomized, two-part, open-label study designed to evaluate the efficacy, safety, and tolerability of the strategy of shifting clinically stable patients receiving suppressive combination antiretroviral therapy to PRO 140 monotherapy and maintaining viral suppression for 48 weeks following study entry.

Consenting patients will be shifted from combination antiretroviral regimen to weekly PRO 140 monotherapy for 48 weeks during Part 1 of Treatment Phase with the one week overlap of existing retroviral regimen and PRO 140 at the beginning of the study treatment and also one week overlap at the end of the treatment in subjects who do not experience virologic failure. The first ~150 eligible subjects were enrolled to receive PRO 140 350mg SC weekly injection in a single-arm study. Subsequently, next ~150 subjects were randomized 1:1 to PRO 140 350mg (Group A) or PRO 140 525mg (Group B). An additional ~200 subjects will be randomized 1:1 to PRO 140 525mg (Group B) or PRO 140 700mg (Group C).

As shown, subjects in Group A or Group B that experience virologic failure prior to week 48 in Part 1 have option of entering Part 2 wherein they receive higher dose of PRO 140 for remainder of treatment phase or may re-initiate prior ART regimen (or an alternative regimen selected by their treating physician) at the discretion of the subject and Investigator.

- **For the first ~150 enrolled subjects:**
  - **Part 1:** 48-week, single-arm, open-label treatment phase
    - PRO 140 350mg SC weekly injection (Group A)
- **For the subsequent ~150 enrolled subjects:**
  - **Part 1:** 48-week, randomized, two-arm, open-label treatment phase
    - PRO 140 350mg SC weekly injection (Group A)
    - PRO 140 525mg SC weekly injection (Group B)
- **For the subsequent ~200 enrolled subjects:**
  - **Part 1:** 48-week, randomized, two-arm, open-label treatment phase
    - PRO 140 525mg SC weekly injection (Group B)
    - PRO 140 700mg SC weekly injection (Group C)

**Part 2 – Rescue Arm for Group A and Group B subjects**

- **Part 2 for Group A:** single arm, open-label treatment phase for Group A subjects electing to receive PRO 140 525mg SC after experiencing virologic failure on 350mg SC/weekly dose
- **Part 2 for Group B:** single arm, open-label treatment phase for Group B subjects electing to receive PRO 140 700mg SC after experiencing virologic failure on 525mg SC/weekly dose

**Note:** All ongoing subjects assigned to Group A receiving PRO 140 350mg SC weekly or assigned to Group B receiving PRO 140 525mg SC weekly have the option of participating in Part 2 should virologic failure occur.

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

## 3.1 STUDY CENTER(S)

Approximately up to 60 centers in the United States will enroll patients in this study.

## 3.2 STUDY POPULATION

Study population consists of virally suppressed HIV-1 patients with CCR5-tropic virus who are on antiretroviral therapy.

## 3.3 ELIGIBILITY CRITERIA

### 3.3.1 Inclusion Criteria

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

1. Males and females, age ≥18 years
2. Receiving combination antiretroviral therapy for last 24 weeks
3. No change in antiretroviral regimen within last 4 weeks prior to Screening Visit and in-between Screening Visit and First Treatment Visit
4. Subject has 2 or more potential alternative approved antiretroviral drug options to consider
5. Documented Exclusive CCR5-tropic virus at Screening Visit as determined by Trofile® DNA Assay
6. Plasma HIV-1 RNA < 50 copies/mL at Screening Visit as determined by Human Immuno-deficiency Virus 1 (HIV-1) Quantitative, RNA ( Taqman® Real-Time PCR)
7. No documented detectable viral loads (HIV-1 RNA > 50 copies/mL) within the last 24 weeks prior to Screening Visit

   *A patient who has had one VL "blip" to < 200 copies/mL in the 24 weeks prior to screening may be included, provided that the plasma HIV-1 RNA level that immediately preceded the blip and VL test that immediately followed the blip was < 50 copies/mL.*
8. CD4 cell count of > 200 cells/$mm^3$ since initiation of anti-retroviral therapy
9. CD4 cell count of > 350 cells/$mm^3$ in preceding 24 weeks and at Screening Visit
10. Laboratory values at Screening of:
    a. Absolute neutrophil count (ANC) ≥ 750/$mm^3$
    b. Hemoglobin (Hb) ≥ 10.5 gm/dL (male) or ≥ 9.5 gm/dL (female)

c. Platelets ≥ 75,000 /mm$^3$

d. Serum alanine transaminase (SGPT/ALT) < 5 x upper limit of normal (ULN)

e. Serum aspartate transaminase (SGOT/AST) < 5 x ULN

f. Bilirubin (total) < 2.5 x ULN unless Gilbert's disease is present or subject is receiving atazanavir in the absence of other evidence of significant liver disease

g. Creatinine ≤ 1.5 x ULN

11. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator
12. Both male and female patients and their partners of childbearing potential must agree to use 2 medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative serum pregnancy test at Screening visit and negative urine pregnancy test prior to receiving the first dose of study drug
13. Willing and able to participate in all aspects of the study, including use of SC medication, completion of subjective evaluations, attendance at scheduled clinic visits, and compliance with all protocol requirements as evidenced by providing written informed consent.

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

### 3.3.2 Exclusion Criteria

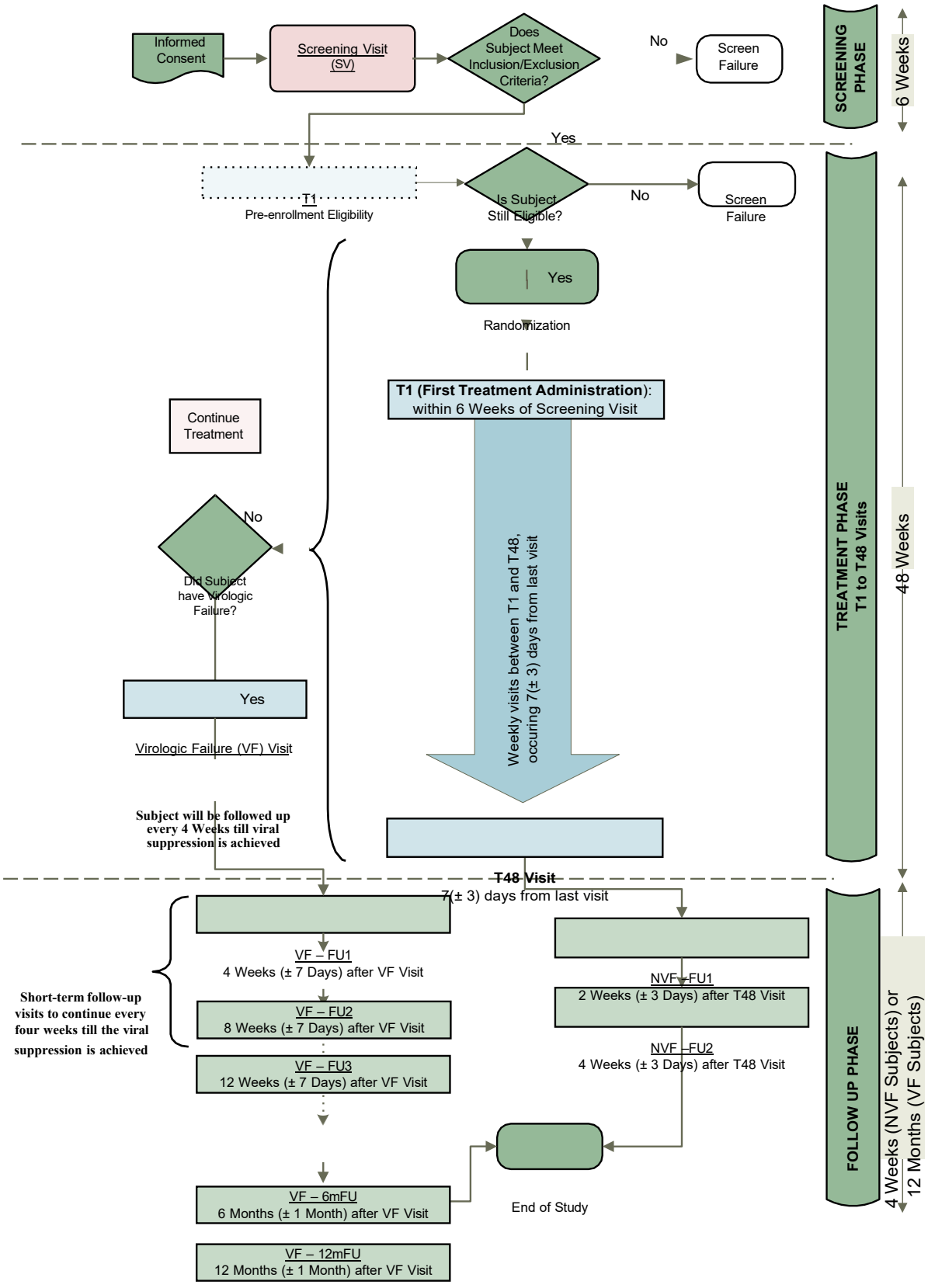
Potential subjects meeting any of the following criteria will be excluded from enrollment:

1. CXCR4-tropic virus or Dual/Mixed tropic (R5X4) virus as determined by Trofile® DNA Assay at Screening Visit
2. Hepatitis B infection as manifested by the presence of Hepatitis B surface antigen (HBsAg)
3. Any active infection or malignancy requiring acute therapy (with the exception of local cutaneous Kaposi's sarcoma)
4. Laboratory test values of ≥ grade 4 DAIDS laboratory abnormality
5. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study

6. Unexplained fever or clinically significant illness within 1 week prior to the first study dose
7. Any vaccination within 2 weeks prior to the first study dose.
8. Subjects who have failed on a maraviroc containing regimen.
9. Subjects weighing < 35kg
10. History of anaphylaxis to any oral or parenteral drugs
11. History of Bleeding Disorder or patients on anti-coagulant therapy (except aspirin)

    **Note**: Subjects with well-controlled bleeding disorder while on stable anti-coagulant therapy dose with documented stable INRs can be enrolled as per discretion of the Investigator.
12. Participation in an experimental drug trial(s) within 30 days of the Screening Visit
13. Any known allergy or antibodies to the study drug or excipients
14. Treatment with any of the following:
    a. Radiation or cytotoxic chemotherapy with 30 days prior to the screening visit
    b. Immunosuppressants within 60 days prior to the screening visit
    c. Immunomodulating agents (e.g., interleukins, interferons), hydroxyurea, or foscarnet within 60 days prior to the screening visit
    d. Oral or parenteral corticosteroids within 30 days prior to the Screening Visit. Subjects on chronic steroid therapy > 5 mg/day will be excluded with the following exception:
        - Subjects on inhaled, nasal, or topical steroids will not be excluded
15. 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

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

**(1)** **Screening Phase** (Screening to T1 Visit) begins with signing of Informed Consent and lasts up to 6 weeks. Subject will enter the Treatment Phase as soon as HIV-1 viral tropism results are available for review by Investigator.

**Treatment Phase** (T1 to T48 Visit) begins with Treatment Phase begins with an evaluation of results of laboratory samples collected at the Screening Visit. The first treatment (T1) visit will be administered within 42 days of the Screening Visit, with weekly visits (± 3 days) thereafter. The first 300 eligible subjects were randomized 1:1 to receive either PRO 140 350mg weekly (Group A) or PRO 140 525mg weekly (Group B). Once the enrollment of 300 subjects was completed, additional subjects will be randomized 1:1 to PRO 140 525mg (Group B) or PRO 140 700mg (Group C).

All subjects will continue taking their existing ART during the Screening Phase and for first week of the Treatment Phase. After Week 1 of the Treatment Phase, subjects will stop their existing ART regimen and receive assigned dose of PRO 140 SC monotherapy.

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

Subjects who experience virologic failure at any point during Part 1 of Treatment Phase will undergo the Virologic Failure (VF) Visit assessments and then exit the Treatment Phase to enter the Follow-up Phase of the study. unless subjects in Group A opt to enter Part 2 of Treatment Phase and receive PRO 140 525mg SC weekly injections or subjects in Group B opt to enter Part 2 of Treatment Phase and receive PRO 140 700mg SC weekly injections for remainder of 48-week Treatment Phase.

Subjects who do not experience virologic failure will enter the Follow-up Phase of the study at the end of 48-week Treatment Phase.

**(2)** **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 viral suppression is achieved (i.e., plasma HIV-1 RNA levels to return to < 50 copies/mL). Additionally, virologic failure subjects will return to clinic at 6 months and at one year from the time of the Virologic Failure (VF) Visit.
- Subjects who do not experience virologic failure at the end of 48-week Treatment Phase, will be followed up every 2 week for total of 4 weeks.

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

## Table 4-1: Schedule of Assessments – Screening and Treatment Phase (T1 – T16)

| Procedure/Assessments | | Treatment Phase (T1 – T16) | | | | | | | | | | | | | | | | | In case of Treatment Failure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | SV | T1 (Pre-Rx) | T1 (Post-Rx) | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | T13 | T14 | T15 | T16 | VF |
| Window Period | | Within 6 weeks of SV | | ±3 days since last treatment | | | | | | | | | | | | | | | |
| Informed Consent[1] | X | | | | | | | | | | | | | | | | | | |
| Eligibility Evaluation[2] | X | | | | | | | | | | | | | | | | | | |
| Pre-enrollment Eligibility | | X | | | | | | | | | | | | | | | | | |
| Subject Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical History[3] | X | X | | | | | | | | | | | | | | | | | |
| Physical Examination | X | X[4] | | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X[4] | X |
| Neurological Assessment[5] | | X | | | | | | | | | | | | | | | | X | X |
| Vital Signs[6] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body Weight & Height | X | | | | | | | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | | | | | | | X |
| Complete Blood Count (CBC)[7] | X | | | | | | | | | | | | | X | | | | | X |
| Biochemistry[8] | X | | | | | | | | | | | | | X | | | | | X |
| Coagulation Indices | X | | | | | | | | | | | | | X | | | | | X |
| Serum Pregnancy Test[9] | X | | | | | | | | | | | | | | | | | | |
| Urinalysis[10] | X | | | | | | | | | | | | | X | | | | | X |
| Urine Pregnancy Test[9] | | X | | | | | | | | | | | | | | | | | |
| HBsAg | X | | | | | | | | | | | | | | | | | | |
| Plasma HIV-1 RNA level | X | X | | X | | X | | X | | X | | X | | X | | X | | X | X |
| TruCount T assay[11] | X | X | | X | | X | | X | | X | | X | | X | | X | | X | X |
| Trofile® DNA Assay | X | | | | | | | | | | | X | | | | | | | X[28] |
| Trofile® RNA Assay | | | | | | | | | | | | | | | | | | | X[28] |
| HIV-1 Drug Resistance Assay [12] | X | X | | | | | | | | | | | | | | | | | X |
| Serum concentration of ART drugs[13] | | | | | | X | | | | X | | | | X | | | | X | |
| Randomization (via CTMS)[29] | | | | | | | | | | | | | | | | | | | |
| PRO 140 Administration[30]<br>– Group A (350mg SC)<br>– Group B (525mg SC)<br>– Group C (700mg SC) | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

| Procedure/Assessments | | Treatment Phase (T1 – T16) | | | | | | | | | | | | | | | | | In case of Treatment Failure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | SV | T1 (Pre-Rx) | T1 (Post-Rx) | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | T13 | T14 | T15 | T16 | VF |
| Window Period | | Within 6 weeks of SV | | ±3 days since last treatment | | | | | | | | | | | | | | | |
| Combination ART Regimen [14] | X | X | | | | | | | | | | | | | | | | | X |
| Injection Site Reaction Assessment [15] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Injection Site Pain Assessment (VAS)[16] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| PK sample for PRO 140[17] | | X | | | | X | | | | X | | | | X | | | | X | X |
| Anti-idiotypic antibodies to PRO 140[17] | | X | | | | X | | | | X | | | | X | | | | X | X |
| Measurement of treatment adherence[18] | | | | | | X | | | | X | | | | X | | | | X | X |
| Adverse Events | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Potential Biomarkers** | | | | | | | | | | | | | | | | | | | |
| gp120 genotypes[19] | | X | | | | | | | | | | | | | | | | | |
| HIV-1 RNA Single Copy Assay[20] | | X | | | | | | | | X | | | | X | | | | | |
| Immune Activation Markers[21] | | X | | | | | | | | | | | | | | | | | X |
| PhenoSense® Entry Assay[22] | | X | | | | | | | | | | X | | | | | | | X |
| CCR5 expression levels[23] | | X | | | | | | | | | | | | | | | | | |
| Quest Diagnostics Tropism Assay[24] | X | X[25] | | | | | | | | | | | | | | | | | X |
| **CNS sub-study (n=20)** | | | | | | | | | | | | | | | | | | | |
| CSF sample collection[26] | | X | | | | X | | | | | | | | | | | | | X |
| **GU sub-study (n=20)** | | | | | | | | | | | | | | | | | | | |
| Genital Secretion sample collection[27] | | X | | | | X | | | | | | | | | | | | X | X |
| CCR5 Receptor Occupancy[31] | | X | | X | | X | | X | | X | | X | | X | | X | | X | X |
| CCR5 Genotyping[32] | X | | | | | | | | | | | X | | | | | | | X |

**Foot Notes:**

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

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

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

[4] Symptom-directed physical examination at clinic visits.

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

[6] Vital signs (blood pressure, heart rate, respiration rate, and temperature) will be measured at clinic visit. Note: Only post-treatment vitals will be measured beyond T2.

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

[8] Serum Biochemistry

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

Renal function indicators: BUN, creatinine

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total)

[9] ONLY performed on women of childbearing potential.

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

[11] Includes: Absolute Lymphocytes, CD3 cell count, CD4 cell count, CD8 cell count, CD3%, CD4% and CD8%Monogram Biosciences GenoSure Archive Assay will be performed at Screening and prior to PRO 140 administration at T1 visit.

[12] Monogram Biosciences GenoSure Archive Assay performed at SV and T1; PhenoSense® GT (and PhenoSense Integrase and GeneSeq Integrase testing, if applicable), will be performed at the time of virologic failure.

[13] To assess subject compliance in abstaining from previous ART regimen after T2 visit

[14] Study subjects a will continue to take their existing antiretroviral regimen up to one week after receiving initial dosing of PRO 140. Subjects will re-initiate their previous antiretroviral regimen or an alternative regimen selected by their treating physician 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.

[15] Injection Site Reaction Assessment as assessed by Investigator (or designee) at the clinic visits and by visiting nurse or qualified medical professional during home visits. Injection Site Reaction Assessment will not be applicable if PRO 140 is self-administered by subjects at home.

[16] Subject-perceived injection site pain will be assessed using the Pain Visual Analog Scale (VAS) prior to study treatment administration which evaluates average pain since last treatment. Injection Site Pain Assessment will not be applicable if PRO 140 is self-administered by subjects at home.

[17] Blood sample collected at T1 ( prior to first dose of PRO 140), T4, T8, T12, T16 and VF visits

[18] Treatment adherence self-reported by subject at T4, T8, T12, T16 and VF visits when subject comes to clinic.

[19] Blood sample will be collected at T1 visit to assess the baseline gp120 genotypes from each enrolled subject to identify potential polymorphisms that may decrease PRO 140 susceptibility and may affect response to PRO 140

[20] Blood sample collected at T1 (prior to first dose of PRO 140), T8 and T12 visits. Blood sample will be collected at T8 and T12 visit only if last known viral load result is "Target Not Detected " or < 40 copies/mL.

[21] immune activation markers (CRP, IL-6, D-Dimer)

[22] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (X4 inhibitor drug), Maraviroc and PRO 140 (R5 inhibitor drugs). Sample collected for Trofile DNA/RNA at Screening will be used to test PhenoSense® Entry for eligible/enrolled subjects at Baseline.

[23] Flow cytometry and the 2D7 MAb will be used to measure CCR5 expression levels on peripheral blood mononuclear cells (PBMCs)

[24] Quest Diagnostics HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing or HIV-1 Proviral Tropism.

[25] If assessment **not** performed at SV.

[26] To evaluate PRO 140 concentration and HIV-1 RNA level in cerebrospinal fluid (CSF)

[27] To evaluate PRO 140 concentration and HIV-1 RNA level in genital secretions

[28] Monogram Biosciences Trofile® DNA or RNA assay (or both) will be performed at the Virologic Failure Visit depending on the last known HIV-1 RNA levels.

[29] Randomization will occur via CTMS

[30] Should VF occur, Group A or Group B subjects may transition to high dose IP and continue in 48-week treatment phase.

[31] To assess the number CCR5 receptors on patients' CD4 cell surface, and number and percentage of CCR5 receptors that are covered by PRO 140. Sites should not collect samples on Fridays, since InCellDx lab cannot receive samples on Saturdays.

[32] No new sample collection needed. The residual whole blood sample collected for tropism assessment at Screening or at post-treatment visits will be used for testing of CCR5 genotyping (homozygous or heterozygous status).

## Table 4-2: Schedule of Assessments –Treatment Phase (T17 – T48)

| Procedure/Assessments | Treatment Phase (T17 – T48) | | | | | | | | | | | In case of Treatment Failure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | T17 | T18-21 | T22-25 | T26-29 | T30-33 | T34-37 | T38-41 | T42-45 | T46 | T47 | T48 | VF |
| Window Period | ±3 days since last treatment | | | | | | | | | | | |
| Physical Examination | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X | X |
| Neurological Assessment[2] | | | | | | | | | | | X | X |
| Vital Signs[3] | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG | | | | | | | | | | | X | X |
| Complete Blood Count (CBC)[4] | | | X | | | X | | | | | X | X |
| Biochemistry[5] | | | X | | | X | | | | | X | X |
| Coagulation Indices | | | X | | | X | | | | | X | X |
| Urinalysis | | | X | | | X | | | | | X | X |
| Plasma HIV-1 RNA level[6] | X | X | X | X | X | X | X | X | | | X | X |
| TruCount T assay[7] | X | X | X | X | X | X | X | X | | | X | X |
| Trofile® DNA Assay | | | | | | | | | | | X | X[20] |
| Trofile® RNA Assay | | | | | | | | | | | | X[20] |
| HIV-1 Drug Resistance Assay [8] | | | | | | | | | | | X | X |
| PRO 140 Administration<br>– Group A (350mg SC)<br>– Group B (525mg SC)<br>– Group C (700mg SC) | X | X | X | X | X | X | X | X | X | X | X | |
| Combination ART Regimen [9] | | | | | | | | | | X | X | X |
| Injection Site Reaction Assessment [10] | X | X | X | X | X | X | X | X | X | X | X | |
| Injection Site Pain Assessment (VAS)[11] | X | X | X | X | X | X | X | X | X | X | X | |
| PK sample for PRO 140[12] | | X | | X | | X | | X | | | X | X |
| Anti-idiotypic antibodies to PRO 140[12] | | X | | X | | X | | X | | | X | X |
| Measurement of treatment adherence[13] | | 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 |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| **Potential Biomarkers** | | | | | | | | | | | | |
| Immune Activation Markers[14] | | | | | | | | | | | X | X |
| PhenoSense® Entry Assay[15] | | | | | | | | | | | X | X |
| Quest Diagnostics Tropism Assay[16] | | | | | | | | | | | | X |

| Procedure/Assessments | Treatment Phase (T17 – T48) | | | | | | | | | | | In case of Treatment Failure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | T17 | T18-21 | T22-25 | T26-29 | T30-33 | T34-37 | T38-41 | T42-45 | T46 | T47 | T48 | VF |
| Window Period | ±3 days since last treatment | | | | | | | | | | | |
| **CNS sub-study (n=20)** | | | | | | | | | | | | |
| CSF sample collection[17] | | | | | | | | | | | | X |
| **GU sub-study (n=20)** | | | | | | | | | | | | |
| Genital Secretion sample collection[18] | | | | | | | | | | | | X |
| CCR5 Receptor Occupancy[21] | X | X | X | X | X | X | X | X | X | X | X | X |
| CCR5 Genotyping [22] | | | | | | | | | | | X | X |

**Foot Notes:**

[1] Symptom-directed physical examination at clinic visits.

[2] 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.

[3] Post treatment vital signs (blood pressure, heart rate, respiration rate, and temperature) will be measured at clinic visit.

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

[5] 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)

[6] Blood sample for plasma HIV-1 RNA level collected at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41 and T42-45 visits when subject comes to clinic.

[7] Blood sample for TruCount T assay collected at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41 and T42-45 visits when subject comes to clinic. Assay includes: Absolute Lymphocytes, CD3 cell count, CD4 cell count, CD8 cell count, CD3%, CD4% and CD8%

[8] Monogram Biosciences GenoSure Archive Assay will be performed at T48 visit. PhenoSense® GT (and PhenoSense Integrase and GeneSeq Integrase testing, if applicable), will be performed at the time of virologic failure.

[9] Study subjects will re-initiate their previous antiretroviral regimen or an alternative regimen selected by their treating physician: (1) One week prior to the end of 48-week Treatment 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.

[10] Injection Site Reaction Assessment as assessed by Investigator (or designee) at the clinic visits and by visiting nurse or qualified medical professional during home visits. Injection Site Reaction Assessment will not be applicable if PRO 140 is self-administered by subjects at home.

[11] Subject-perceived injection site pain will be assessed using the Pain Visual Analog Scale (VAS) prior to study treatment administration which evaluates average pain since last treatment. Injection Site Pain Assessment will not be applicable if PRO 140 is self-administered by subjects at home.

[12] Blood sample collected at anytime between T18-21, T26-29, T34-37 and T42-45 visits followed by at T48 and VF visits.

[13] Treatment adherence self-reported by subject at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41 and T42-45 visits followed by at T48 and VF visits when subject comes to clinic

[14] immune activation markers (CRP, IL-6, D-Dimer)

[15] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (X4 inhibitor drug), Maraviroc and PRO 140 (R5 inhibitor drugs). Sample collected for Trofile DNA/RNA at Screening will be used to test PhenoSense® Entry for eligible/enrolled subjects at Baseline.

[16] Quest Diagnostics HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing or HIV-1 Proviral Tropism.

[17] To evaluate PRO 140 concentration and HIV-1 RNA level in cerebrospinal fluid (CSF)

[18] To evaluate PRO 140 concentration and HIV-1 RNA level in genital secretions

[19] Monogram Biosciences Trofile® DNA or RNA assay (or both) will be performed at the Virologic Failure Visit depending on the last known HIV-1 RNA levels

[20] Should VF occur, Group A or Group B subjects may transition to high dose IP and continue in 48-week Treatment Phase

[21] To assess the number CCR5 receptors on patients' CD4 cell surface, and number and percentage of CCR5 receptors that are covered by PRO 140. Sites should not collect samples on Fridays, since InCellDx lab cannot receive samples on Saturdays.

[22] No new sample collection needed. The residual whole blood sample collected for tropism assessment at Screening or at post-treatment visits will be used for testing of CCR5 genotyping (homozygous or heterozygous status).

**Table 4-3: 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-FU1 | NVF-FU2 |
| Window Period | 2 weeks (±3 days) after T48 | 4 weeks (±3 days) after T48 |
| Physical Examination | X[1] | X[1] |
| Vital Signs | X | X |
| Plasma HIV-1 RNA level | X | X |
| TruCount T assay | X | X |
| Anti-idiotypic Antibodies to PRO 140 | | X |
| Re-initiate combination Antiretroviral Therapy | X | X |
| Adverse Events | X | X |
| Concomitant Medications | X | 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-FU1 | VF-FU2 | VF-FU3 |
| Window Period | 4 weeks (±7 days) after VF visit | 8 weeks (±7 days) after VF visit | 12 weeks (±7 days) after VF visit |
| 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 |
| Anti-idiotypic Antibodies to PRO 140 | X | | |
| Re-initiate combination Antiretroviral Therapy | X | X | X |
| Adverse Events | X | X | X |
| Concomitant Medications | X | X | X |

[1] Subject will be followed up every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels decline to < 50 copies/mL). Subject will undergo additional follow-up visits every 4 weeks beyond VF-FU3 visit (up to a maximum of 6 months after re-initiation of combination antiviral therapy), if viral suppression is not achieved at the end of VF-FU3 visit.

[2] Symptom-directed physical examination

- Long-Term Follow-Up Visits

| Procedure/Assessments | Long-Term Follow-Up Visit -1 | Long-Term Follow-Up Visit -2 |
|---|---|---|
| | VF-6mFU | VF-12mFU |
| Window Period | 6 months (±1 month) after VF visit | 12 months (±1 month) after VF visit |
| Adverse Events[1] | X | X |
| Assessment of cART changes[2] | 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] Only SAEs and any AE that is considered possibly or probably or definitely related to the IP by the investigator will be captured during the long term follow up phase.

[2] Any changes to the combination antiretroviral regimen since the viral re-suppression is achieved.

[3] Monogram Biosciences Trofile® DNA or RNA (or both) assay will be performed depending on last known HIV-1 RNA levels.

[4] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (X4 inhibitor drug), Maraviroc and PRO 140 (R5 inhibitor drugs).

[5] 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.

## 4.1 SCREENING PHASE

### 4.1.1 Pre-Screening

Sites are encouraged to pre-screen subjects for study inclusion, evaluating HIV-1 DNA viral tropism prior to performing a full screening visit. Up to 15 clinical sites will be allowed to participate in this process.

The subject will sign and date the pre-screening informed consent form (ICF) prior to any study-related pre-screening procedures. A unique identification number (pre-screening number) will be assigned to each subject who has provided written pre-screening informed consent. The pre-screening number will incorporate a three-digit Study Center number (PS301, PS302, PS303….) and a two-digit numeric ID assigned in successive order of consenting to pre-screening procedures after signing the pre-screening ICF at each center, beginning with 001 at each site (e.g. PS301-01 or PS302-01).

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

- Review of prior medical records
- Blood sample collection for HIV-1 Co-receptor tropism analysis by Monogram Biosciences

A pre-screening log will be maintained to capture the following information:

- Pre-screening number
- Patient initials
- Date pre-screened
- Initial eligibility
- Date of re-consent (for the full consent form) or reason for ineligibility

### 4.1.2 Screening Visit

The subject (or Legally Acceptable Representative (LAR)) 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. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent.

**Note:** *Screening numbers are independent of pre-screening number, if pre-screening performed.*

The subject screening number will incorporate a three-digit Study Center number (301, 302,

303….) and a three-digit numeric ID assigned in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site (e.g. 301-001 or 302-001).

**Subject Screening # :** **XXX - YYY**

XXX=Study Center YYY=Subject Numeric ID

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

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

- Detailed medical history (see Section 7.4),
- Demographic information (see Section 7.3),
- Prior and current medications review (see Section 7.5),
- Physical examination (see Section 7.6),
- Electrocardiogram (ECG) (see Section 7.7),
- Body Weight & Height measurements (see Section 7.9)
- Vital Signs (see Section 7.9),
- Collection of Blood Specimens (see Section 7.10) for
    - Complete Blood Count
    - Biochemistry
    - Coagulation Indices [Prothrombin time (PT) and INR]
    - Hepatitis B surface antigen (HBsAg)
    - Plasma HIV-1 RNA level
    - TruCount T Assay
    - HIV-1 co-receptor tropism (Trofile® DNA Assay)
        - CCR5 Genotyping will be tested using residual whole blood sample from tropism sample collected at Screening
    - HIV-1 Drug Resistance Assay (GenoSure Archive Assay)

- HIV-1 PhenoSense® Entry (*Monogram BioSciences*)
- Serum pregnancy test, for female subjects of childbearing potential. Childbearing potential is defined as someone who is not surgically sterile or is not more than one year past complete cessation of menstrual cycles.
- Blood sample for evaluation of potential biomarkers
  - HIV-1 co-receptor tropism (Quest Diagnostics Proviral DNA® Assay)

- Collection of Urine Specimen for Urinalysis (see Section 7.10.15)

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 42 days of Screening Visit will have screening lab assessments repeated, with the exception of HIV-1 viral tropism, genotype and phenotype, to reconfirm eligibility.

### 4.2 TREATMENT PHASE

Treatment Phase begins with an evaluation of results of laboratory samples collected during the Screening Phase. Subjects who meet all eligibility criteria, as per data gathered from Screening Phase are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failure and exit the study without further evaluation.

All subjects will continue their existing antiretroviral regimen for one week after receiving initial assigned dosing of PRO 140. Subjects will receive up to 48 weekly PRO 140 injections in the Treatment Phase, given once per week (± 3 days) or until virologic failure, whichever occurs first. The study treatment (PRO 140 350mg or 525mg or 700mg SC injections) will be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or home visit or self-administered by subjects, for the duration of 48 weeks in the Treatment Phase.

As shown in Table 4-4, eligible subjects will be randomized 1:1 to two treatment arms for 48 weeks.

**Table 4-4: Part 1: Randomized, Two-Arm, Open-Label Treatment Phase**

| Study Drug | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|
| **GROUP A** | | | | |
| PRO 140 350mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1 mL/inj.) for 48 weeks | SC injection |
| **GROUP B** | | | | |
| PRO 140 525mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1.5 mL/inj.) for 48 weeks | SC injection |
| **GROUP C** | | | | |
| PRO 140 700mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 2 mL/inj.) for 48 weeks | SC injection |

As shown in Table 4-5, Group A subjects experiencing virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 200 copies/mL) in Part 1 of Treatment Phase will have option of reinitiating ART regimen or begin PRO 140 525mg SC weekly injections for remainder of 48-week Treatment Phase.

**Table 4-5: Part 2: Single-Arm, Open-label Treatment Phase [Group A]**

| Study Drug | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|
| PRO 140 525mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 1.5 mL/inj.) up to Week 48 | SC injection |

As shown in Table 4-6, Group B subjects that elect to participate in Part 2 of Treatment Phase after experiencing virologic failure during Part 1 of Treatment Phase will receive PRO 140 700mg SC weekly injection for remainder of 48-week Treatment Phase. Should subject experience subsequent virologic failure in Part 2 of Treatment Phase, subject will complete Virologic Failure (VF) Visit assessments and then enter the Follow-up Phase of the study.

**Table 4-6: Part 2: Single-Arm, Open-label Treatment Phase [Group B]**

| Study Drug | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|
| PRO 140 700mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 X 2 mL/inj.) up to Week 48 | SC injection |

Group A or Group B subjects that do not elect to participate in Part 2 of Treatment Phase and all Group C subjects who experience virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 200 copies/mL) at any time during the Treatment Phase will undergo the Virologic

Failure (VF) Visit assessments and then exit the Treatment 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 48-week Treatment Phase.

All study subjects will re-initiate their previous antiretroviral regimen or an alternative regimen selected by their treating physician:

- One week prior to the end of 48-week Treatment Phase, or
- Anytime during the Treatment Phase, if virologic failure occurs or have met any other criteria for discontinuation of study treatment as specified in Section 5.2.1 of the protocol. Subjects will be allowed to continue PRO 140 monotherapy while waiting for new ART regimen to be constructed by the Investigator.

**Note:**

- Subjects may return to clinic for an additional blood draw in-between the clinic visits for plasma HIV-1 RNA levels, per the discretion of the Investigator.
- Virologic failure is defined as two consecutive levels of ≥ 200 copies/mL.
  - Subjects in Group A that experience virologic failure have option of re-initiating ART regimen or participating in Part 2 of Treatment Phase and receive higher dose of PRO 140 (525mg SC) weekly injection for remainder of 48-week Treatment Phase or until subsequent virologic failure event after viral re-suppression on higher dose.
  - Subjects in Group B that experience virologic failure have option of re-initiating ART regimen or participating in Part 2 of Treatment Phase and receive higher dose of PRO 140 (700mg SC) weekly injection for remainder of 48-week Treatment Phase or until subsequent virologic failure event after viral re-suppression on higher dose.
- 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 T48 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 48-week Treatment Phase.

Visits during the Treatment Phase will commence on T1, i.e. the date of first treatment, with weekly visits (± 3 days) thereafter. The first Treatment Visit (T1) will take place as soon as HIV-

1 viral tropism, genotype and phenotype resistance results are available for review by Investigator, within 6 weeks of the Screening Visit.

### 4.2.1 Treatment Phase: Treatment Visit-1 (T1)

The following assessments will be performed at T1 visit, unless otherwise specified:

**Pre-Treatment**

- Confirmation of eligibility criteria by reviewing test results and other criteria assessments performed at Screening Visit (see Section 7.2 )
- Neurological Assessment (see Section 7.8)
- Symptom-directed physical examination (see Section 7.6)
- Change in concomitant medications (see Section 7.5)
- Any changes in medical history since Screening Visit (see Section 7.4)
- Vital Signs (see Section 7.9)
  - **Note:** *Vitals will be taken twice: pre- and post-treatment. Post-Treatment Vital Signs will be assessed within 15 minutes following study treatment administration*.
- Collection of Blood Specimens (see Section 7.10) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay
  - CCR5 Receptor Occupancy (IncellDx Lab)
  - HIV Drug Resistance Assay
  - PK sample for PRO 140
  - Anti-idiotypic antibodies to PRO 140
  - Blood sample for evaluation of potential biomarkers [*occurs at T1*]
    - gp120 genotypes
    - Plasma *HIV-1 RNA S*ingle Copy Assay
    - Immune Activation Markers
    - PhenoSense® Entry Assay [*performed at T1 using the blood sample collected for Tropism at Screening for subjects who are found eligible to be enrolled in the study*]
    - CCR5 expression levels

- Quest Diagnostics Proviral DNA® Tropism Assay [*if not performed at SV*]

- Cerebrospinal fluid *(CSF) sample* collection for Central Nervous System (CNS) sub-study (see Section 7.10.16)
  - **Note:** *CSF sample should be collected at T1 (prior to first dose of PRO 140), visit for subjects participating in CNS sub-study.*
- Genital secretion sample collection for Genitourinary (GU) sub-study (see Section 7.10.17)
  - **Note:** *Genital secretion sample should be collected at T1 (prior to first dose of PRO 140) visit for subjects participating in GU sub-study.*
- Urine Pregnancy Test (see Section 7.10.8)

**Administration of PRO 140**

PRO 140 is administered as subcutaneous injection in the abdomen weekly. A total of 350mg or 525 mg or 700mg (175 mg/mL) is delivered as two injections on opposite sides of the abdomen. The 350mg dose will be delivered as two injections of 1 mL each, 525mg dose will be delivered as two injections of 1.5 mL each or one injection of 3.0 mL, and 700mg dose will be delivered as two injections of 2 mL each.

**Note:** All treatment injections must be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or home visit or self-administered by subjects, for the duration of 48 weeks in the Treatment Phase.

**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).*
- Assessment of Adverse Events (AE) (see Section 9)
- Vital Signs (see Section 7.9) will be assessed within 15 minutes of study treatment administration.

**Note:** Subjects will continue their existing antiretroviral regimen for one week after receiving initial dosing of PRO 140.

### 4.2.2 Treatment Phase: Treatment Visit-2 (T2) to Treatment Visit-16 (T16)

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 7.8) [*occurs at T16*]
- Vital Signs (see Section 7.9)
  - **Note:** *Post-treatment vital signs will be assessed within 15 minutes following study treatment administration*
- Collection of Blood Specimens (see Section 7.10) for
  - Complete Blood Count at T12 visit
  - Biochemistry at T12 visit
  - Coagulation Indices [Prothrombin time (PT) and INR] at T12 visit
  - CCR5 Receptor Occupancy (IncellDx Lab)
  - Plasma HIV-1 RNA level
  - TruCount T Assay
    - **Note:** *Blood sample for plasma HIV-1 RNA level, TruCount T Assay, and CCR5 Receptor Occupancy should be collected at T2, T4, T6, T8, T10, T12, T14 and T16 visits when subject comes to clinic.*
  - Plasma HIV-1 RNA Single Copy Assay
    - **Note:** *Blood sample for plasma HIV-1 RNA Single Copy Assay should be collected at T8 and T12 visits when subject comes to clinic.*
  - Trofile DNA Assay and PhenoSense Entry Assay at T10 visit
  - PK sample for PRO 140
  - Anti-idiotypic antibodies to PRO 140
    - **Note:** *PK and ADA blood sample should be collected at T1 (prior to first dose), T4, T8, T12 and T16 visits.*
- Collection of Urine Specimen for Urinalysis (see Section 7.10.15) at T12 visit
- Measurement of treatment adherence (see Section 7.14) at T4, T8, T12 and T16 visits
- Study Treatment Administration (PRO 140)

  **Note:** All treatment injections must be administered by a qualified medical professional

(MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or home visit or self-administered by subjects, for the duration of 48 weeks in the Treatment Phase.

- 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).*
- 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.*
- Cerebrospinal fluid (CSF) sample collection for Central Nervous System (CNS) sub-study (see Section 7.10.16)
  - **Note:** *CSF sample should be collected at T4 visit for subjects participating in CNS sub-study.*
- Genital secretion sample collection for Genitourinary (GU) sub-study (see Section 7.10.17)
  - **Note:** *Genital secretion sample should be collected at T4 and T16 visits for subjects participating in GU sub-study.*

### 4.2.3 Treatment Phase: Treatment Visit-17 (T17) to Treatment Visit-48 (T48)

The following assessments will be performed at each visit during the remaining 32 weeks of the Treatment Phase, 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),
  - **Note:** *Complete physical examination at T48*
- Neurological Assessment (see Section 7.8) [*occurs at T48*]
- Vital Signs (see Section 7.9)
  - **Note:** *Post-treatment vital signs will be assessed within 15 minutes following study treatment administration*
- Electrocardiogram (ECG) (see Section 7.7) [*occurs at T48*]

- Collection of Blood Specimens (see Section 7.10) for
    - Complete Blood Count at least once every 12 weeks at T22-25, T34-37 and at T48 visits
    - Biochemistry at least once every 12 weeks at T22-25, T34-37 and at T48 visits Coagulation Indices [Prothrombin time (PT) and INR] at least once every 12 weeks at T22-25, T34-37 and at T48 visits
    - CCR5 Receptor Occupancy (IncellDx Lab)
    - Plasma HIV-1 RNA level
    - TruCount T Assay
        - **Note:** *Blood sample for plasma HIV-1 RNA level and TruCount T Assay should be collected at T17 and at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41, T42-45 and T48 visits when subject comes to clinic.*
    - Trofile® DNA Assay [*occurs at T48*]
    - PK sample for PRO 140
    - Anti-idiotypic antibodies to PRO 140
        - **Note:** *PK and ADA blood sample should be collected at least once every four weeks between T18-21, T26-29, T34-37 and T42-45 visits, and at T48 visits.*
    - HIV-1 Drug Resistance Assay – GenoSure Archive [*occurs at T48*]
    - Blood sample for evaluation of potential biomarkers [*occurs at T48*]
        - Immune Activation Markers
        - PhenoSense® Entry Assay

- Collection of Urine Specimen for Urinalysis (see Section 7.10.15) at least once every 12 weeks at T22-25, T34-37 and at T48 visits.

- Measurement of treatment adherence (see Section 7.14)
    - **Note:** *At least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41 and T42-45 visits followed by at T48 and VF visits when subject comes to clinic.*

- Study Treatment Administration (PRO 140)

  **Note:** All treatment injections must be administered by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or

home visit or self-administered by subjects, for the duration of 48 weeks in the Treatment Phase.

- 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).*
- 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.*
- Re-initiate previous antiretroviral regimen or an alternative regimen selected by the treating physician at Week-47, if viral load remain suppressed.

### 4.3 VIROLOGIC FAILURE (VF) VISIT

Virologic failure is defined as two consecutive levels of ≥ 200 copies/mL.

Subjects in Group A or Group B that experience virologic failure have option of re-initiating ART regimen or participating in Part 2 of Treatment Phase and receive higher dose of PRO 140 weekly injection for remainder of 48-week Treatment Phase or until subsequent virologic failure event after viral re-suppression on higher dose.

The following assessments will be performed for all subjects who experience virologic failure during the Treatment Phase, prior to entering Follow-up 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 Section7.8),
- Electrocardiogram (ECG) (see Section 7.7)
- Subject-perceived Injection Site Pain Assessment (see Section 7.13),
- Collection of Blood Specimens (see Section 7.10) for
  - Plasma HIV-1 RNA level
  - TruCount T Assay

- Complete Blood Count
- Biochemistry
- Coagulation Indices
- HIV Drug Resistance Assay (PhenoSense GT/Integrase)
- HIV Trofile® RNA Assay
- CCR5 Receptor Occupancy (IncellDx Lab)
- Anti-idiotypic antibodies to PRO 140
- PK sample for PRO 140
- Blood sample for evaluation of potential biomarkers [*occurs at T48*]
  - Immune Activation Markers
  - PhenoSense® Entry Assay
  - Quest Diagnostics HIV Co-receptor Tropism Assay

- CSF sample collection for CNS sub-study (see Section 7.10.16)
  - **Note:** *CSF sample should be collected at VF visit for subjects participating in CNS sub-study.*

- Genital secretion sample collection for GU sub-study (see Section 7.10.17)
  - **Note:** *Genital secretion sample should be collected at VF visit for subjects participating in GU sub-study.*

- Collection of Urine Specimen for Urinalysis (see Section 7.10.15)

- Measurement of treatment adherence (see Section 7.14)

- Re-initiate previous antiretroviral regimen or an alternative regimen selected by the treating physician

### 4.4 FOLLOW-UP PHASE

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

- Subjects who experience virologic failure within the Treatment Phase will be assessed every 4 weeks until viral suppression is achieved (i.e., plasma HIV-1 RNA levels decline to < 50 copies/mL). Additionally, virologic failure subjects will return to clinic for long- term follow-up at 6 months and at one year from the time of the Virologic Failure (VF) Visit.

- Subjects who do not experience virologic failure at the end of the Treatment Phase, will be assessed every 2 weeks for total of 4 weeks.

### 4.4.1 Follow-Up Visits

#### 4.4.1.1 Short-Term Follow-Up Visits

##### 4.4.1.1.1 Virologic Failure Subjects

Subjects who experience virologic failure during the Treatment Phase will be assessed every 4 weeks until the viral suppression is achieved (i.e., plasma HIV-1 RNA levels decline to < 50 copies/mL).

The following assessments will be performed at each follow-up visit (VF-FU1, VF-FU2, VF-FU3 etc.), 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),
- 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 (at Virologic Failure - FU1 and Non Virologic Failure - FU2)
- Continue previous antiretroviral regimen or an alternative regimen selected by treating physician

##### 4.4.1.1.2 Non Virologic Failure Subjects

Subjects who do not experience virologic failure at the end of the Treatment Phase, will be assessed every 2 weeks for total of 4 weeks.

The following assessments will be performed at each follow-up visit (NVF-FU1 and NVF-FU2 visits), 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),
- 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 (at Non Virologic Failure - FU2)
- Continue previous antiretroviral regimen or an alternative regimen selected by treating physician

#### 4.4.1.2 Long-Term Follow-Up Visits

Additionally, subjects who experience virologic failure will also return to clinic for the long-term follow-up at 6 months and at one year from the time of the Virologic Failure Visit.

The following assessments will be performed at VF-6mFU and VF-12mFU visit, unless otherwise specified:

- Assess for any Adverse Events and changes in combination antiretroviral therapy (see Section 9 and 7.5)
    - **Note**: *Only SAEs and any AE that is considered possibly or probably or definitely related to the study treatment by the Investigator will be captured during the long-term follow-up phase.*
- Collection of Blood Specimens (see Section 7.10) for
    - Plasma HIV-1 RNA level
    - TruCount T Assay
    - HIV Drug Resistance Assay (GenoSure Prime or PhenoSense GT/Integrase)
    - HIV Trofile® DNA or RNA Assay
    - HIV PhenoSense Entry® Assay

# 5 SUBJECT COMPLETION AND WITHDRAWAL

## 5.1 SUBJECT COMPLETION

- A subject who completes the 48-week Treatment Phase 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 48-week Treatment Phase, and undergoes the Virologic Failure (VF) Visit assessments and is followed up until viral suppression is achieved and complete Virologic Failure – 12 month Follow-Up (VF-12mFU) Visit, will be considered as having completed the study.

## 5.2 SUBJECT WITHDRAWAL

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

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

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

In addition, subjects WILL be withdrawn from the study, in consultation with the 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
- Recurring Grade 2 study drug injection related AE at two consecutive visits
- Occurrence of Grade 3 study drug injection related AE
- A subject becomes pregnant

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

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

- A subject is treated with a prohibited medication.

- Major protocol violation

### 5.2.1 Discontinuation of Study Treatment

Discontinuation of study treatment (PRO 140) and resumption of previous or alternative antiretroviral regimen is recommended if:

- Subject experiences virologic failure (defined as two consecutive HIV-1 RNA levels of ≥ 200 copies/mL).

  **Note**: *Subjects in Group A that experience virologic failure have option of re-initiating ART regimen or participating in Part 2 of Treatment Phase and receive higher dose of PRO 140 (525mg SC) weekly injection for remainder of 48-week Treatment Phase or until subsequent virologic failure event after viral re-suppression on higher dose.*

  *Subjects in Group B that experience virologic failure have option of re-initiating ART regimen or participating in Part 2 of Treatment Phase and receive higher dose of PRO 140 (700mg SC) weekly injection for remainder of 48-week Treatment Phase or until subsequent virologic failure event after viral re-suppression on higher dose.*

- Develops AIDS-defining conditions as specified in Appendix I (Section 17.1) under which subject is unable to continue treatment with study drug (PRO 140), or subject require treatment with prohibited concomitant medications.
- Shows signs or symptoms of clinically significant immunosuppression
- Subject or the subject's clinician wishes to 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 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 9.2.1, 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.

If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two screenings) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

# 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 the Treatment Phase will contain vials of PRO 140 for SC injection. One milliliter (1 mL), 1.5 mL, or 2 mL of PRO 140 solution will be drawn from a vial and loaded into the syringe. A total of 350 mg or 525 mg or 700 mg (175 mg/mL) of PRO 140 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).

| **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 |
| 525 mg | 3 | 3 | 1.5 | 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 |
| 525 mg | 2 | 3 | 1.5 | 0.9 |
| 700 mg | 2 | 4 | 2 | 0.4 |

*When 2 injections given per dose; 1 injection on opposite sides of the abdomen.

**Since each vial contains 2.4 mL of PRO 140, only 1 vial is needed for the 350 mg dose. The second vial can be utilized to administer 350 mg dose at the subsequent visit.

Each vial of the PRO 140 product contains ~1.4 or 2.4 mL antibody at 175mg/mL in a buffer containing 5 mM L-histidine, 15.0 mM glycine, 95 mM sodium chloride, 0.3% (w/v) sorbitol, 0.005% (w/v) polysorbate 20 (Tween 20®), and sterile water for injection, at pH of 5.5.

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

*Subjects in Group B may require three vials and subjects in Group C may require four vials for single dose. Unused content of PRO 140 in a vial should remain in the vial and* ***not*** *be administered to any other subject.*

*Alternatively, when 2.4 mL vials are provided, 1.5 or 2 mL injection will be drawn and the remaining will be discarded from each vial. Subjects in both group B and C will require two vials for a single dose. Unused content of PRO 140 in a vial should remain in the vial and* ***not*** *be administered to any other subject.*

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

**Table 6-1: Investigational Product - PRO 140**

| IP Dosage | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|
| PRO 140 350mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (1 mL/inj.) per week on opposite sides of abdomen for up to 48 weeks (T1 – T48) | SC injection |
| PRO 140 525 mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (1.5 mL/inj.) per week on opposite sides of abdomen for up to 48 weeks (T1 – T48) | SC injection |
| PRO 140 700 mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 mL/inj.) per week on opposite sides of abdomen for up to 48 weeks (T1 – T48) | 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 Sherpa Clinical Packaging, LLC.

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

Below are representative samples of the Investigational Product, FDP individual vial (Figure 6-1), syringe label (Figure 6-2), and kit 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) 175mg/mL - Vial Label**

| | |
|---|---|
| Protocol: PRO 140_CD03 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA | Protocol: PRO 140_CD03 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

| | |
|---|---|
| Protocol: PRO 140_CD03 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA | Protocol: PRO 140_CD03 Kit No. xxx<br>Subject No. _____<br>Single use 3 mL vial contains 2.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection<br>Store at 2ºC to 8ºC (36ºF to 46ºF)<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

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

| |
|---|
| Protocol: PRO 140_CD03 Contents of Kit No. xxx<br>This syringe contains 1 mL, 1.5 mL, or 2 mL PRO 140 (175 mg/mL) solution for subcutaneous injection<br>USE AS PER STUDY PROTOCOL<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

***Note:*** *Subjects in Group B will require a total of 3ml of study treatment for single dose, given as two 1.5ml injections, three 1.0 injections, or one 3 mL injection.*

*Subjects in Group C will require a total of 4ml of study treatment for single dose, given as two 2ml injections, or four 1 mL injections*

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

Protocol: PRO 140_CD03 Kit No. xxx

Site No. _____ Subject No. _____

**This kit contains 2 single-use vials**

Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection

Store at 2ºC to 8ºC (36ºF to 46ºF)

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

CytoDyn Inc., Vancouver, WA, USA

Protocol: PRO 140_CD03 Kit No. xxx

Site No. _____ Subject No. _____

**This kit contains 3 single-use vials**

Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection

Store at 2ºC to 8ºC (36ºF to 46ºF)

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

CytoDyn Inc., Vancouver, WA, USA

Protocol: PRO 140_CD03 Kit No. xxx

Site No. _____ Subject No. _____

**This kit contains 4 single-use vials**

Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection

Store at 2ºC to 8ºC (36ºF to 46ºF)

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

CytoDyn Inc., Vancouver, WA, USA

| |
|---|
| Protocol: PRO 140_CD03 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 2ºC to 8ºC (36ºF to 46ºF) |
| USE AS PER STUDY PROTOCOL |
| Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use |
| CytoDyn Inc., Vancouver, WA, USA |

***Note:*** *Subjects in Group B will receive two injections of 1.5mL each of study treatment and subjects in Group C will receive two injections of 2mL each of study treatment for single dose.*

*Patients with low body fat percentages may find subcutaneous injections uncomfortable esp. in case of 1.5 mL or 2mL injection for the 525 mg or 700mg dosing, respectively. In such cases, PRO 140 525 mg can be injected as three 175mg/ml injections, or 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.*

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

### 6.3 INVESTIGATIONAL PRODUCT STORAGE

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

The Investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed for 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, if receiving 350mg dose (or 1.5 mL, if receiving 525mg dose or 2 mL, if receiving 700mg dose) of study drug.

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:

**350mg Dose:**

- One 2 mL injection on one side of the abdomen.

**525mg Dose:**

- One 3 mL injection on one side of the abdomen.
- Three 1 mL injections, two on one side of the abdomen and one on the other side.

**700 mg Dose:**

- Four 1 mL injections, on opposite sides of the abdomen, or other location.

A 25-guage needle should be used to remove IP from vial and for administration to subjects, and drug should not be held in syringe for longer than 1 hour.

IP should be administered slowly over 15 seconds per mL.

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 administered as SC injection by a qualified medical professional (MD, DO, PA, LPN, LVN, NP, RN or CMA if permitted by state law) at clinic site or home visit or self-administered by subjects.

### 6.5 INVESTIGATIONAL PRODUCT RECEIPT AND ACCOUNTABILITY

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

### 6.6 INVESTIGATIONAL PRODUCT DISPOSITION

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

# 7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

## 7.1 INFORMED CONSENT

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

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

## 7.2 ASSESSMENT OF ELIGIBILITY

During the Screening Phase and at T1 Visit (prior to treatment administration), the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and Exclusion criteria of this Protocol are described in Sections 3.3.1 and 3.3.2. If the subject is not suitable or eligible for the trial then the subject will be a screen failure.

### 7.2.1 Re-screening

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

## 7.3 DEMOGRAPHIC INFORMATION

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

- Dates of ICF signature
- Date of birth
- Gender

- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

## 7.4 MEDICAL HISTORY

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

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

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

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

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

For each relevant history, the following will be documented:

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

## 7.5 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 Phase of the study EXCEPT for one week overlap of existing retroviral regimen and PRO 140 at the beginning of the study treatment and also one week overlap at the end of the treatment in subjects who do not experience virologic failure. Subject is allowed to re-initiate antiretroviral therapy during the Treatment 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.

- Use of short course of systemic corticosteroids (Medrol pack) after T2 will only be allowed with prior approval from the sponsor.

3. Use of radiation or cytotoxic chemotherapy, immunosuppressants and immunomodulating agents (e.g., interleukins, interferons) or agents with known anti-HIV activity (i.e., hydroxyurea, foscarnet) are NOT allowed during the study.
4. Use of any non-FDA approved/investigational therapy

### 7.5.2 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:

- General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Lymph Nodes
- Heart/Cardiovascular abnormalities
- Respiratory
- Abdomen
- Genitourinary
- Musculoskeletal and Extremities
- Neurologic abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety 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 Screening Visit (SV), Treatment Visit 48 (T48), and at Virologic Failure (VF) Visit. Only symptom-directed physical examination will be performed at treatment and follow-up visits conducted within the clinic, and at unscheduled visits within the Treatment and Follow-up Phases.

### 7.7 ELECTROCARDIOGRAM

A resting 12-lead ECG will be conducted at the Screening Visit (SV) and at T48 or Virologic Failure (VF) visit and the results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded.

Only those subjects who have normal or not-clinically significant results at the Screening Visit (SV) will be enrolled in this study.

### 7.8 NEUROLOGICAL ASSESSMENT

Neurological assessment will be performed by the Principal Investigator or Study Coordinator at Treatment Visits 1, 16 and 48 (T1, T16, T48) and at Virologic Failure (VF) Visit.

The neurological assessment tool is based on the three question survey used by Simioni et al. (Simioni S, 2010). Refer to Section 17.4 for further details. Additional neurological assessment modalities may be used as per Investigator's discretion.

### 7.9 VITAL SIGNS (INC. HEIGHT AND WEIGHT)

Vital signs will be collected at all study visits performed at the clinic. Vital signs collected during the Treatment Phase will be performed post-treatment, with the exception of pre-treatment vitals collected at T1, and assessed within 15 minutes following study treatment administration.

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

- Height (at SV)
- Weight (at SV, T48 and VF visits)
- BMI (derived from the height and weight measurements; at SV, T48 and VF visits)
- Seated blood pressure (taken after the subject has been seated for at least 5 minutes)
- Heart Rate
- Respiration Rate
- Temperature

### 7.10 CLINICAL LABORATORY ASSESSMENTS

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

### 7.10.1 Routine CBC

- Frequency of testing: At SV, T12, T22-25, T34-37, T48 or VF
- 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: At SV, T12, T22-25, T34-37, T48 or VF
- 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 Coagulation Indices

- Frequency of testing: At the Screening Visit, T12, at least once every 4 weeks between T22-25, T34-37, T48,and VF.
- Prothrombin time (PT) and International Normalized Ratio (INR)

### 7.10.4 Hepatitis B surface antigen (HBsAg)

- Frequency of testing: At SV
- To detect presence of Hepatitis B virus infection

### 7.10.5 PK sample for PRO 140

- Frequency of testing: At T1, T4, T8, T12, T16 and at least once every four weeks between T18-21, T26-29 and T34-37, T42-45 and at T48 and VF visits.

### 7.10.6 Anti-idiotypic antibodies to PRO 140

- Frequency of sample collection: At T1, T4, T8, T12, T16 and at least once every four weeks between T18-21, T26-29 and T34-37, T42-45 and at T48 and VF visits. Additionally, sample will be collected at Virologic Failure Follow-up Visit 1 (VF-FU1) and Non-Virologic Failure Follow-up Visit 2 (NVF-FU2)

### 7.10.7 Serum pregnancy test

- Frequency of testing: At SV

- 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.

### 7.10.8 Urine pregnancy test

- Frequency of testing: At T1 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.

### 7.10.9 Plasma HIV-1 RNA level and TruCount T Assay

- Frequency of testing: At SV, T1, T2, T4, T6, T8, T10, T12, T14, T16 and T17, at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41, T42- 45, T48 and at VF visits when subject comes to clinic. In addition, blood sample will also be collected at all Virologic Failure Follow-up (VF-FU) Visits or Non-Virologic Failure Follow-up (NVF-FU) Visits.
- To assess antiretroviral therapeutic response to PRO 140 or cART regimen

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

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

### 7.10.10 HIV-1 Trofile® DNA Assay

- Frequency of testing: At SV, T10, and T48 Visits. In addition, Trofile® DNA may also be collected at VF, VF-6mFU and VF12mFU Visits, if last known HIV-1 RNA level is <1000 copies/mL.
- To assess HIV-1 co-receptor tropism. This test determines eligibility for CCR5 antagonist therapy for patients infected with HIV-1. Only those subjects who have exclusive CCR5-tropic virus will be eligible to participate in this study.
- Unlike the standard Trofile® assay (which uses viral RNA), Trofile® DNA Assay can determine the coreceptor tropism of a patient's HIV-1 strain when the patient's viral load is undetectable.

### 7.10.11 HIV-1 Trofile® RNA Assay

- Frequency of testing: At VF, VF-6mFU and VF12mFU Visits, if last known HIV-1 RNA level is >1000 copies/mL.

### 7.10.12 HIV-1 Drug Resistance Assay

a. GenoSure Archive Assay

GenoSure Archive assay provides HIV-1 antiretroviral drug resistance data when standard resistance testing cannot be performed due to inadequate plasma viral load.

- Frequency of sample collection: At SV, T1, and T48. Additionally, at VF, VF-6mFU and VF12mFU Visits, if last known HIV-1 RNA level is <1000 copies/mL.

b. PhenoSense® GT

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

- Frequency of sample collection: At VF, VF-6mFU and VF12mFU Visits, if last known HIV-1 RNA level is >1000 copies/mL.

c. PhenoSense Integrase and GeneSeq Integrase testing

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

*Samples for PhenoSense® GT (and PhenoSense Integrase and GeneSeq Integrase testing, if collected) will be stored at Lab and will be analyzed only if subject experiences virologic failure.*

### 7.10.13 Blood sample collection for evaluation of potential biomarkers

#### 7.10.13.1 gp120 genotypes

- Frequency of testing: At T1 visit
- To assess the baseline gp120 genotypes from each enrolled subject to identify potential polymorphisms that may decrease PRO 140 susceptibility and may affect response to PRO 140

#### 7.10.13.2 Plasma HIV-1 RNA Single Copy Assay

- Frequency of sample collection: At T1 prior to first treatment administration, T8 and T12 visits
- To assess antiretroviral therapeutic response to PRO 140 regimen

#### 7.10.13.3 Immune Activation Markers

- Frequency of testing: At T1, T48 and VF visit

- Immune activation markers (CRP, IL-6, D-Dimer)

#### 7.10.13.4 PhenoSense® Entry Assay

- Frequency of testing: At T1, T10, T48, VF, VF-6mFU and VF12mFU Visits
    - ***Note**: PhenoSense® Entry will be performed at T1 using the blood sample collected for Tropism at Screening for subjects who are found eligible and enrolled in the study.*
- With AMD3100 (X4 inhibitor drug), Maraviroc and PRO 140 (R5 inhibitor drugs).

#### 7.10.13.5 CCR5 expression levels

- Frequency of testing: At T1 visit
- Flow cytometry and the 2D7 MAb will be used to measure CCR5 expression levels on peripheral blood mononuclear cells (PBMCs)

#### 7.10.13.6 Quest Diagnostics Tropism Assay

- Frequency of testing: At SV or T1 and VF
- Includes:
    - HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing or HIV-1 Proviral Tropism.

      *The Quest Diagnostics HIV-1 coreceptor tropism test begins with standard Sanger sequencing of the third variable (V3) loop of the HIV-1 gene, the primary determinant of viral tropism. The next-generation DNA sequencing (ultradeep sequencing [UDS]) is performed if standard sequencing detects only R5 virus. HIV-1 Coreceptor Tropism, Proviral DNA test is used when the plasma viral load is < 1000 copies/mL.*
    - CytoDyn is currently investigating the possibility of developing a more accurate test for detection of poor response to PRO 140 in patients with early breakthrough or virologic failure during the treatment phase of the study.

#### 7.10.13.7 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: At T1, T2, T4, T6, T8, T10, T12, T14, T16, T17, and at least once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41, T42-45, (when subject comes to clinic), at T48, and VF visits.

- Samples will be shipped overnight to IncellDx Lab. No samples should be collected on Fridays due to IncellDx Lab being closed Saturdays.

#### 7.10.13.8 CCR5 Genotyping

- To correlate the CCR5 homozygous or heterozygous status with virologic response to PRO 140 reported during the treatment phase.
- No new sample collection is needed. The residual whole blood sample collected for tropism assessment at Screening or at post-treatment visits will be used for testing of CCR5 genotyping (homozygous or heterozygous status).

### 7.10.14 Urinalysis

- Frequency of testing: At the Screening Visit (SV), T12, T22-25, T34-37, T48 or VF visit
- Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, and microscopic examination of urine sediment

### 7.10.15 CSF sample collection for CNS sub-study

- Frequency of testing: At the T1 (prior to first dose of PRO 140), T4 and VF visits.
- In a subset of participants (n=20) to assess the extent of PRO 140 entry into the CNS compartment, and to evaluate virologic responses in CSF.

### 7.10.16 Genital Secretion sample collection for GU sub-study

- Frequency of testing: At the T1 (prior to first dose of PRO 140), T4, T16 and VF visits.
- In a subset of participants (n=20) to assess the extent of PRO 140 entry into the genitourinary compartment, and to evaluate virologic responses in genital secretion.

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

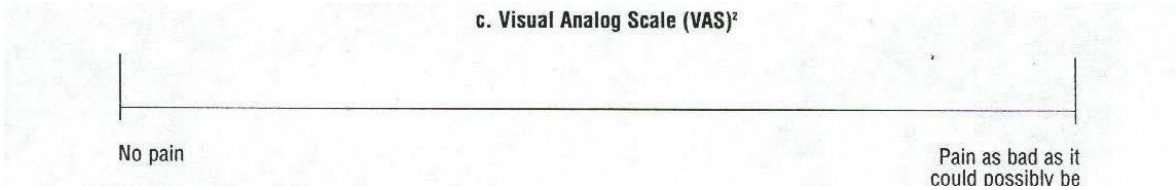
At each treatment visit that occurs at the clinical site, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded by the Investigator starting after the first injection is given. Refer to Sections 9.1.8 and 17.3 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). This assessment will be performed each time subjects arrive to the clinic for the study visit.

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

**Figure 7-1: Visual Analog Scale**




### 7.14 MEASUREMENT OF TREATMENT ADHERENCE

Adherence to assigned regimen during Treatment Phase will be self-reported by subject at T4, T8, T12, T16, and once every four weeks between T18-21, T22-25, T26-29, T30-33, T34-37, T38-41 and T42-45 visits followed by at T48 and VF visits when subject comes to clinic.

# 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

All eligible subjects in the study will receive PRO 140 as a 350 mg or 525 mg or 700mg subcutaneous injection weekly for up to 48 weeks.

## 8.2 DESCRIPTION OF STUDY OUTCOME MEASURES

### 8.2.1 Primary Safety Outcome Measures

The following metrics will be analyzed to assess the clinical safety of PRO 140 monotherapy regimen:

- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of Treatment-Emergent Serious Adverse Events
- Incidence of Injection Site Reactions by Investigator evaluation
- Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale
- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale)
- Changes and shifts in laboratory measurements over time
- Changes in vital signs and weight over time
- Changes and shift in Electrocardiogram (ECG) parameters over time
- Incidence of Physical Examination abnormalities over time

### 8.2.2 Primary Efficacy Outcome Measures:

- Proportion of participants experiencing virologic failure at the assigned dose

  *Note: (1) Virologic failure is defined as two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL. (2) Assigned dose refers to the dose allocated at the time of randomization/enrollment.*
- Time to virologic failure at the assigned dose
- Proportion of participants moved to rescue arm or higher dose group

*Note: Rescue is defined as subjects who were unable to maintain viral suppression, or experienced virologic failure, and moved to a higher dose of PRO 140*

- Proportion of participants achieving viral re-suppression (HIV-1 RNA <50 copies/mL) during Treatment Phase after moving to rescue arm or higher dose group
- Time to achieving viral re-suppression (HIV-1 RNA <50 copies/mL) during Treatment Phase for subjects who moved to rescue arm or higher dose group
- Proportion of participants achieving viral re-suppression (HIV-1 RNA <50 copies/mL) after experiencing virologic failure (during the Treatment and Follow-up Phase)
- Time to achieving viral re-suppression (for virologic failure subjects) after re-initiation of oral combination antiretroviral regimen during the Follow-up Phase.
- Proportion of participants completing 24, 48 weeks of PRO 140 treatment with HIV-1 RNA <50 copies/mL
- Mean change in CD4 cell count, at each visit within the Treatment Phase
- To evaluate the prognostic factors of therapeutic success of PRO 140 monotherapy during the Treatment Phase.
    a. CCR5 Receptor Occupancy
    b. CCR5 Genotyping Status
    c. gp120 genotyping
    d. Baseline HIV-1 RNA Single Copy levels
    e. Immune Activation Markers
    **f.** PhenoSense® Entry Assay

8.2.3 **Secondary Exploratory Outcome Measures:**

- Measurement of treatment adherence to the PRO 140 monotherapy regimen; this will be assessed using number of missed PRO 140 administrations
- Loss of future drug options
  *The first occurrence of intermediate to high level resistance to any one or more of the standard antiretroviral drugs to which the patient's virus was considered to be sensitive at trial entry (i.e. excluding drug resistance present at baseline).*
- Proportion of participants overall and within each treatment group experiencing emerging resistance exhibited by fold increase in maraviroc and PRO 140 FC (Fold Change in $IC_{50}$ and $IC_{90}$ relative to wild-type virus) between baseline and the time of virologic failure, as a measure of post-baseline phenotypic resistance

  **Note:** *Virologic failure is defined as two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL.*

**Central Nervous System (CNS) sub-study:** In a subset of participants (n=20):

- Level of HIV-1 RNA in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits
- PRO 140 concentration in CSF at T1 (prior to first dose of PRO 140), T4 and VF visits
- Relationship between PRO 140 concentration in plasma and CSF
- Relationship between PRO 140 concentration in CSF and HIV-1 RNA in CSF
- Relationship between plasma and CSF HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities)

**Genitourinary (GU) sub-study:** In a subset of participants (n=20):

- Level of HIV-1 RNA in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits.
- PRO 140 concentration in genital secretion at T1 (prior to first dose of PRO 140), T4, T16 and VF visits.
- Relationship between PRO 140 concentration in plasma and genital secretion
- Relationship between PRO 140 concentration and HIV-1 RNA in genital secretion,
- Relationship between plasma and genital secretion HIV-1 RNA suppression and HIV disease progression and safety parameters (i.e., adverse events and laboratory abnormalities)

### 8.2.4 Safety Assessments

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

Three hundred (300) subjects will be enrolled in this study. The sample size is selected on the basis of clinical judgment.

## 8.4 Randomization and Blinding

All subjects enrolled under this version of the protocol will be randomized in two treatment arms. The study is open label with no blinding requirements.

## 8.5 INTERIM ANALYSIS

The interim analysis will be directed and conducted by an independent DMC, which will include clinicians with expertise in HIV disease, a neurologist or psychiatrist and at least one biostatistician who is not otherwise involved in the trial. The iDMC will monitor the safety of the trial from the beginning and at approximately six month intervals based on enrollment thereafter. The main purpose of this IA is to ensure the safety of the subjects in the trial and to recommend whether the trial should be stopped early to protect the safety of the participants.

The iDMC will closely monitor the following:

- Virologic failure and viral re-suppression (after oral combination therapy is re-instituted).
- Long-term safety follow-up data for one year after completion of treatment phase
- In addition to other safety parameters, all baseline/post-treatment tropism, resistance, prognostic factors such as, HIV-1 RNA single copy assay, immune activation markers etc. and any potential cardiovascular events (that may occur from inflammatory bursts post-drug withdrawal)

A detailed interim analysis plan will be prepared and presented to the DMC prior to the conduct of the interim analysis.

The details of the IA, including the below bullet points, will be included in the Statistical Analysis Plan (SAP) for the study.

- The goals of the IA
- IA procedures for data preparation
- IA procedures conduct of the analysis
- Futility analysis and stopping rule
- Data to be shared with the DMC
- Information to be shared with the sponsor after the IA

## 8.6 GENERAL STATISTICAL CONSIDERATIONS

### 8.6.1 Analysis Populations

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

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.

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 study, other than the baseline of the dependent variable (i.e., Baseline CD4 cell counts for assessing changes in CD4)

### 8.6.4 Handling of Missing Data

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

### 8.6.5 Multicenter Study

This is a multicenter clinical trial.

## 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

All data from the primary and secondary outcome measures will be summarized and tabulated according to the variable type:

- Time to event data will be depicted using Kaplan-Meier plots
- 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.

#### 8.7.4.1 Primary Analysis

Primary Analysis of the primary and secondary outcome measures will be conducted on the ITT population. A statistical analysis plan will be developed to detail the statistical methods used for the primary analysis.

#### 8.7.4.2 Supportive Analysis

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

### 8.7.5 Safety Analysis

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

For continuous variables data will be summarized using n, mean, Standard Deviation (SD), minimum and maximum values. For categorical variables data will be summarized using frequency and percentage.

#### 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.

# 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-FU2 for subject who do not experience virologic failure or until viral suppression is achieved for subjects who experience virologic failure). Additionally, virologic failure subjects will have a long-term follow-up visits at 6 months and at one year from the time of the Virologic Failure Visit. Only SAEs and any AE that is considered possibly or probably or definitely related to the study treatment by the Investigator will be captured during the Long-term Follow-up Phase of the study. All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

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

### 9.1.2 Impact of Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will

be used only when the subject is no longer in the treatment phase of the protocol, or if the outcome of the event was "death".

### 9.1.3 DAIDS AE Grade (Severity) Assessment

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

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

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

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

DAIDS AE Grading Table Version 2.0- November 2014

### 9.1.4 Causality Assessment

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

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

three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

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

### 9.1.5 Treatment Given as a Result of the Event

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

### 9.1.6 Outcome Assessment

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

### 9.1.7 Expected / Anticipated Adverse Events

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

### 9.1.8 SC Injection-related Events

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

SC injection-related events will be monitored according to the guidelines provided in Section 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 event or first occurrence of grade 2 event, 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 2 events following study drug injection, the subject should be reevaluated closely until the AE returns to Grade ≤1, at which time study treatment may be reintroduced at the discretion of the site Investigator. If the *same* Grade 2 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 the study, it must also be reported to CytoDyn, Inc. Any pregnant subject must be followed up by the Investigator or designee until the child is born. Any complication experienced through the end of the pregnancy should be considered as an adverse event (AE), and should be recorded, and if it meets the seriousness criteria, it must be reported to CytoDyn, Inc/designated CRO promptly. Participants who become pregnant will be entered into the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

### 9.2.1 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, the SAE should be submitted to Amarex Safety Department within 24 hours:

| | |
|---|---|
| **CRO Medical Monitor** | [redacted] |

The [redacted] 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)).

### 9.2.2 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, 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.

The DMC will monitor the safety of the trial from the beginning and at approximately six month intervals thereafter based on enrollment. In addition, an Interim Analysis (IA) will be conducted when approximately 50% (~200 subjects) have been enrolled and completed the Treatment Phase of the study or early terminated, whichever comes first. The interim analysis will be directed and conducted by the DMC. The main purpose of this IA is to ensure the safety of the subjects in the trial and to recommend whether the trial should be stopped early to protect the safety of the participants. The DMC will review safety and efficacy data including the fraction of study participants who develop virologic failure and the fraction of those whose virus is successfully suppressed after re-initiation of oral combination antiviral therapy. However the decision to continue the trial will not be based on the efficacy analysis. The DMC will consist of at least three independent members (including clinicians with expertise in HIV disease, a neurologist or 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.

All expedited safety reports will be provided in real time to the DMC chair upon being reported to FDA. The DMC will make the following recommendations at each 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 in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure (IB), clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of CytoDyn, shall not be disclosed to others without the written consent of CytoDyn, and shall not be used except in the performance of this study.

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

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

study report is signed off, or with respect to any outcome measures 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/DAIDS_AE_Grading_Table_v2_NOV2014.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 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.