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STATISTICAL ANALYSIS PLAN
FOR PROTOCOL PRO 140_CD 02

Sponsor:

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Protocol Number:	PRO 140_CD 02
Protocol Title:	A Multi-center, Randomized, Double-blind, Placebo-controlled Trial, Followed by Single-arm Treatment of PRO 140 in Combination With Optimized Background Therapy in Treatment-Experienced HIV-1 Subjects
Protocol Date / Version:	9.0 / 08 Jan 2018

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Plan Version:	SAP - Version 3.0
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I have read and approve the Statistical Analysis Plan specified above and agree with its content:

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANCOVA	Analysis of Covariance
ART	Anti Retroviral Therapy
ASA	American Statistical Association
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HEENT	Head, Ears, Eyes, Nose, Throat
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
OBT	Optimized Background Therapy
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event

Abbreviation	Term
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SV	Screening Visit
TEAE	Treatment Emergent Adverse Events
TF	Treatment Failure
VAS	Visual Analogue Scale
VF	Virologic Failure
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol PRO 140 _CD02, sponsored by CytoDyn Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this Statistical Analysis Plan are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents and references [1-6], were reviewed in preparation of this Statistical Analysis Plan:

- Version 9.0, protocol 08 Jan 2018
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (1999)
- The Royal Statistical Society: Code of Conduct (1993)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guideline on General Considerations for Clinical Trials (ICH E8, 1997)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1997)

2. PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

The primary objective is to assess the efficacy, clinical safety and tolerability parameters of PRO 140 compared to placebo in reducing HIV-1 viral load in patients on their current ART (failing regimen) during the one week double-blind treatment period.

The secondary objectives are to assess the efficacy, clinical safety and tolerability parameters of PRO 140 in combination with optimized background therapy in patients during the 24-week single-arm, open-label treatment period.

2.2 Design Overview

This is a Phase 2b/3, multi-center, two part study, designed to evaluate the efficacy, safety, and tolerability of PRO 140 in conjunction with existing ART (failing regimen) for one week and Optimized Background Therapy (OBT) for 24 weeks respectively. The patient population for this trial are treatment-experienced HIV-infected patients with CCR5-tropic virus and demonstrates evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented genotypic or phenotypic resistance to ART drugs within three drug classes (or within two drug classes with limited treatment option).

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

Screening Phase (up to 6 weeks):

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

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

Treatment Phase (25 weeks ± allowed windows):

The Treatment Phase is divided into two parts:

- **Part 1**: 1-week randomized, double-blind, placebo-controlled period consisting of two treatment arms along with existing ART (failing regimen)
- **Part 2**: 24-week single-arm, open-label treatment period with all subjects receiving PRO 140 along with OBT

The first Treatment Visit will take place within 6 weeks of the Screening Visit.

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

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

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

Part 1: One-week double-blind, placebo-controlled period [IP (PRO 140 or Placebo) + existing ART]

Part 1 of treatment phase begins with an evaluation of results of laboratory samples collected at the Screening Visit. All subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without further evaluation. Subjects who meet all eligibility criteria, as per data gathered from Screening Visit, will be randomized to one of two treatment arms for one week.

Consenting patients will be randomized 1:1 to one of two treatment arms for one week:

- Group A: PRO140 350mg weekly SC Inj. + existing ART
- Group B: Placebo weekly SC Inj. + existing ART

Part 2: 24-week single-arm, open-label treatment period [PRO 140 + OBT]

After 7 days all subjects will enter the 24-week single-arm, open-label treatment period. During this period, all subjects will receive PRO 140 SC injection and Optimized Background Therapy. Optimized background therapy (OBT) is a standard-of-care regimen comprised of 3 or more antiretroviral agents selected by the investigator based on treatment history and genotypic and/or phenotypic assessments. OBT regimen will be initiated after completing one week of randomized, double-blind placebo-controlled period.

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

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

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

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

- *< 0.5 log_{10} copies/mL decrease in HIV-1 RNA at Day 7 of the Open-Label Treatment Period. [Assessment Timepoint: T3 and T4 visit]*
- *< 1.0 log_{10} copies/mL decrease in HIV-1 RNA at or after Week 4 of the Open-Label Treatment Period unless HIV-1 RNA <400 copies/mL [Assessment Timepoint: from T6 up to T25 visit].*
- *Confirmed plasma HIV-1 RNA levels ≥ 400 copies/mL at Week 24 of the Open-Label Treatment Period. [Assessment Timepoint: T25 and EOT visit]*

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

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

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

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

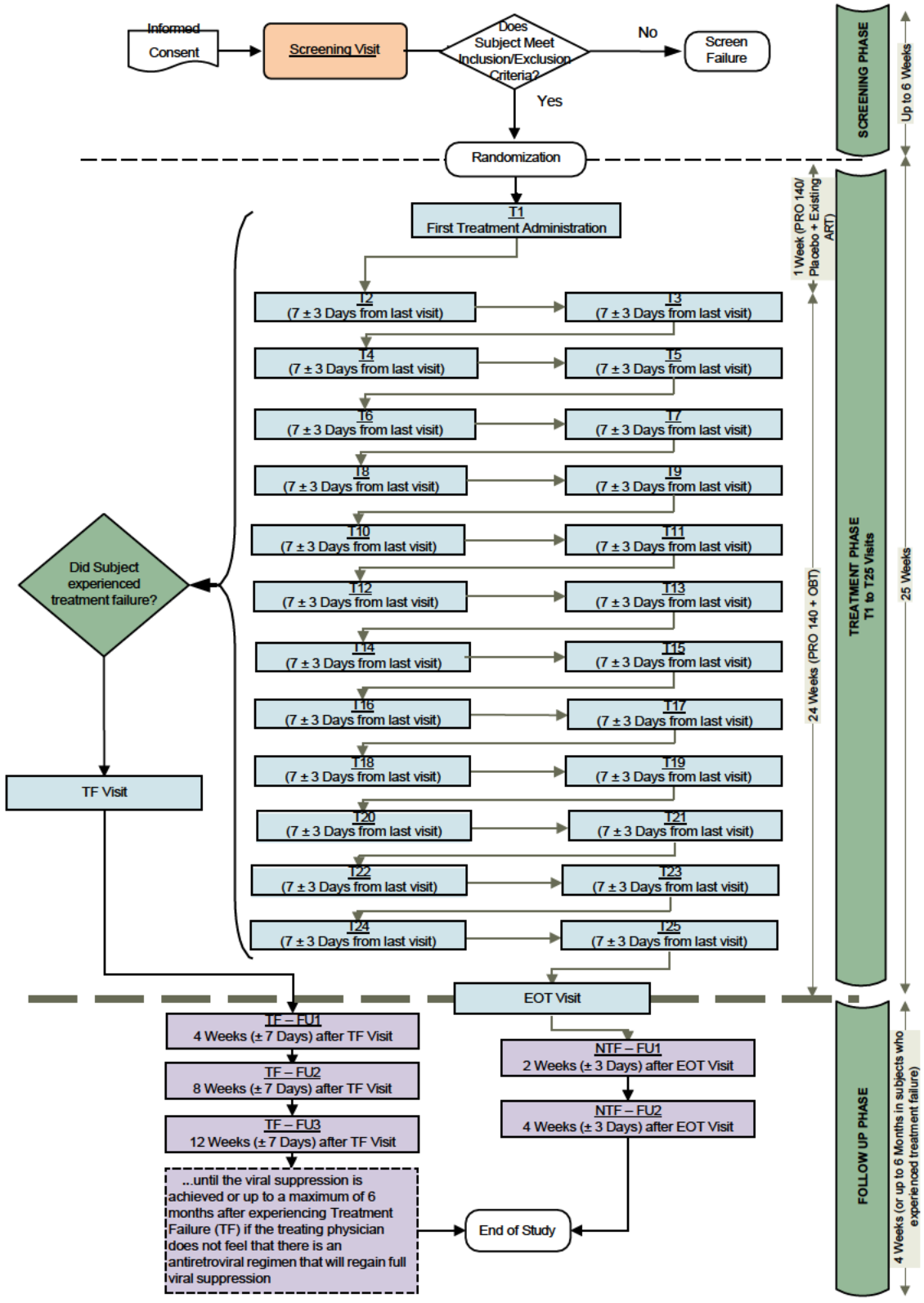
Safety Follow-up Visit:

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

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

All assessments are described in the protocol Table 4-1: Schedule of Assessments – Screening and Treatment Phase, and in the Appendix 1 of this SAP.

Figure 2-1: Study Flow Diagram



2.3 Study Duration

A subject will be in this trial at maximum of around 35 weeks (without the additional follow-up time for Virologic Failure subjects).

- **Screening Phase:** up to 6 weeks
- **Treatment Phase:** 25 weeks ± allowed windows (up to 25 treatments every week (±3 days)).
- **Follow-up Phase:**
  - Treatment Failure (TF): Until viral suppression is achieved
  - Non-Treatment Failure: 4 weeks

2.4 Study Treatments

2.4.1 Treatment Groups

For the Double-Blind part of the study the following treatment groups will be assessed:

Table 2-1: Part 1: One-week double-blind, placebo-controlled period [IP (PRO 140 or Placebo) + existing ART]

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
GROUP A				
PRO 140	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 X 1 mL/inj.) at T1 visit	SC injection
GROUP B				
Placebo	Parenteral solution	0 mg/mL	2 injections of placebo (2 X 1 mL/inj.) at T1 visit	SC injection

For the Open-Label part of the study the following treatment groups will be assessed:

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

Study Drug	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140	Parenteral solution	175 mg/mL	2 injections of PRO 140 (2 X 1 mL/inj.) per week for up to 24 weeks (T2 – T25)	SC injection

2.4.2 Randomization and Blinding

This trial is a two part treatment phase study with a one-week randomized, double-blind, placebo-controlled period, followed by a 24-week open label, single arm treatment period.

Randomization will be conducted via a Web based system, and the process for the blinding requirements will be outlined in the study randomization plan. Resistance to ART drugs at the time

of randomization will be used as a stratification factor to ensure balance between each treatment group in this stratum.

3. STUDY ASSESSMENTS/ ENDPOINTS

There are multiple efficacy endpoints and assessments in this trial. These are partitioned in the primary and secondary endpoints.

3.1 Primary Efficacy Endpoint

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

3.2 Secondary Efficacy Endpoints

There are multiple secondary endpoints to be assessed in this study, to maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. The order of the endpoints will be as follows:

1. Proportion of participants with ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period, stratified to each group:

   a. resistance to ART drugs within three drug classes,

   b. resistance to ART drugs within two drug classes with limited treatment option.

2. Proportion of participants with ≥ 1 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period for all patients and within each stratum
3. Mean change from Baseline in HIV-1 RNA levels ($\log_{10}$ copies/mL) at the end of the 1-week double-blind treatment period for all patients and within each stratum
4. Percentage of participants achieving HIV-1 RNA < 400 copies/mL at week 25 for all patients and within each stratum
5. Percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 25 for all patients and within each stratum
6. Mean change from Baseline in HIV-1 RNA levels ($\log_{10}$ copies/mL) at week 25 for all patients and within each stratum

7. Mean change from Baseline in CD4 cell count at the end of the 1-week double-blind treatment period for all patients and within each stratum
8. Mean change from Baseline in CD4 cell count at week 25 for all patients and within each stratum

3.3 Safety Assessments

Safety measurements will include:

- Emergence of Dual/Mixed (D/M)- and CXCR4-tropic virus in patients who had exclusive CCR5-tropic virus at study entry.
- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale) and by investigator-evaluation of injection site reactions.
- Frequency of treatment-related adverse events resulting in study drug discontinuation
- Frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale
- Frequency of treatment–emergent serious adverse events

4. SAMPLE SIZE DETERMINATION AND RATIONALE, STATISTICAL POWER, AND SIGNIFICANCE LEVEL

For this two arm clinical trial, it is planned to have a total of 50 subjects (25 per treatment group) randomized and complete the clinical trial.

The nQuery 6.01 is used for this sample size calculation. The sample size calculation is based on the assumption that the proportion of participants with ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at Week 1 during the double-blind treatment period is 90% for the PRO 140 group vs 35% for the Placebo group.

Note: *Response rate of 90% is estimated for the PRO 140 group on the basis of results from PRO140 2101 study wherein 90% of participants with CCR5-tropic virus achieved* ≥ 0.5 $\log_{10}$ *reduction in HIV-1 RNA viral load in one week from baseline.*

Under the above assumptions, 25 subjects per treatment group will be required to meet the Type I error rate of 0.05 and more than 90% power; for a total of 50 subjects for the clinical trial.

5. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An independent data monitoring committee (IDMC) will be convened for this study and will act in an advisory capacity to the Sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and for monitoring the overall conduct of the study.

The membership criteria and other details of the IDMC are described in a separate IDMC Charter.

5.1 Interim Safety Reviews

The IDMC will convene from the beginning and at approximately six month intervals thereafter, based on enrollment to evaluate the overall progress of the study, perform reviews of safety data to assess the risk of the trial and provide recommendations to the sponsor accordingly.

The safety review includes data for AEs, SAEs, labs, ECGs, vital signs, and all other safety related variables identified per the DMC Charter. No inferential statistics will be conducted for the safety interim analysis tabulation of the data.

The DMC will receive: all safety signals including number of virologic non-response and virologic rebounds, unexpected AEs, all related AEs, all SAEs, and all deaths during the Treatment and Follow-Up Phases.

5.2 Interim Efficacy Review

An efficacy Interim Analysis (IA) is planned to be conducted when at least 40 patients have been randomized and completed the 1-week double-blind treatment period of the study or early terminated, whichever comes first.

The procedures for this IA will be based on a standard operating procedure (SOP) that has a well-established firewall to protect the integrity of the trial. The IA will be performed by an independent un-blinded statistician, who is not otherwise associated with the conduct of this trial.

The main objectives of this IA are:

- To evaluate the safety of PRO140.
- Sample size re-assessment to evaluate the final sample size needed to proceed with the study.

This meeting will be held by telephone and arranged by the IDMC Executive Secretary at the request of the IDMC Chairperson and in conjunction with Sponsor. IDMC interim analyses meeting will be in three sessions: an "open session", a "closed session", and another "open session" for recommendations unless otherwise specified by the Chairperson.

5.2.1 Data Snapshot

a. Cutoff dates for collection of eCRFs, data querying, database lock and analysis will be established based on an estimated target date of when 40 of the subjects completed 1-week double-blind treatment period.
b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.
c. Snapshot of the dataset will be taken for the IA. This snapshot will not contain the treatment assignments (i.e., will be blinded).
d. The locked data snapshot will be saved in a drive to which only the independent statistician responsible for the IA has access.
e. The randomization code to un-blind the data will be delivered to the independent statistician by the randomization code generator.
f. The independent statistician will merge the randomization code with the validated data and will generate the planned statistical analyses for the IA.

5.2.2 Metrics to be Calculated for the IA

Using the validated data with the unblinded treatment allocations, the independent statistician will calculate the following metrics:

1. The proportion of subjects with a $\geq 0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period in the PRO140 group (Pa) the observed number of subjects in the group
2. The proportion of subjects with a $\geq 0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period in the Placebo group (Pc) the observed number of subjects in the group
3. The difference in rates of HIV-1 RNA viral load reduction between the treatment groups (Pa – Pc)
4. The Conditional Power (CP) of the trial at the time of the IA (Chen YH, 2004). (The method for this calculation is provided in Section 5.2.3).
5. The revised sample size requirement based on this IA (The rule and method for sample size

recalculation and p-value adjustment are provided in the below sections).

5.2.3 Conditional Power (CP)

The CP will be calculated according to the below formula (Chen YH, 2004) using the HIV-1 RNA viral load reduction rates in the PRO140 and Placebo groups

$$CP(f_1,z_1) = \Phi \{ z_1 / \sqrt{f_1 (1 - f_1)} - z_\alpha / \sqrt{(1 - f_1)} \}$$

Where:

- $CP(f_1,z_1)$ is the conditional power at the IA
- **Φ{.}** is the cumulative distribution function of a standard Normal distribution ($\mu=0$, $\sigma^2 = 1$)
- f_1 is the fraction of patients enrolled and used in the interim analysis before decision of increasing the sample size ($f_1 = (n_a + n_c) / N_0$, *where n_a and n_c are the number of subjects used for the interim analysis in the PRO140 & Placebo groups, respectively, and N_0 is the original sample size*)
- z_α is the upper α quintile for standard Normal distribution
- z_1 is the standardized Normal, since the original sample size is based on proportions the z-score will be obtained from the following formula:

$$z_1 = (P_a - P_c) / \sqrt{[P_a (1 - P_a) / n_a + P_c (1 - P_c) / n_c]}$$

Where:

- P_a = the number of subjects with a ≥ $0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline in the Active group divided by the number of subjects in Active group (i.e., n_a)
- n_a = the number of subjects in the Active group used in the IA
- P_c= the number of subjects with a ≥ $0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline in the Control group, divided by number of subjects in the Control group (i.e., n_c)
- n_c= the number of subjects in the Control group used in the IA
- a = the Active group
- c = the Control group

5.2.4 Protection of integrity of the trial

This IA will be conducted under strict SOP to protect the integrity of the trial. Only masked summary data specifically for basic baseline characteristics, conditional power and safety summaries will be released only to the IDMC members.

5.2.5 Rules and Method for Increasing Sample Size

Rule: Regardless of the size of the CP at IA, the original sample size will not be reduced nor will the trial be stopped early.

The sample size for the study will be adjusted only if the Interim Analysis CP is less than 80%. The adjustment would be an increase in the sample size in order to bring the CP to at least 80% up to a maximum increment of 70 subjects using the observed difference at the time of the interim analysis. The sample size will be maintained as the original sample size, if the CP is larger than or equal to 80%.

Method: This sample size recalculation will be made by adjusting the f_2 in the CP equation below, until the CP is 80%.

$$CP(f_2, Z) = \Phi\{ - Z_\alpha / \sqrt{(1 - f_2)} + Z / \sqrt{f_2 (1 - f_2)} \}$$

Where:

- CP(f_2, Z) is the CP at the IA to be increased to 80% by adjusting f_2
- f_2 is the fraction of patients enrolled and used in the IA before decision of increasing the sample size relative to the new sample in the adjusted trial. It is defined as:

  $$f_2 = (n_a + n_c) / (N_0 + n_{added})$$

- **Φ{.}**, Z_α , Z, n_a , n_c *and* N_0 are the same as those defined above

The number of subjects to be added to the trial is then calculated from the f_2 that yields the CP of 80% as follows:

$$n_{added} = (n_a + n_c - N_0 * f_2) / f_2$$

5.2.6 Data Provided to IDMC

The IDMC will receive a statistical report. The details on the content of the report are described in the IDMC Charter.

All expedited safety reports will be provided in real time to the DMC chair upon being reported to FDA. At each meeting, the DMC will be authorized to unblind the study upon unanimous vote in the event of any concerns about safety or lack of efficacy. Unblinded CRO personnel, separate and independent of the blinded CRO personnel, will supply the DMC with all necessary tables and listings to perform their independent review.

5.2.7 Stopping Rule

There will be no intention to stop the study based on the efficacy interim results; however, the DMC may stop the study at any time based on review of safety data such as incidence of treatment

failure (i.e., virologic non-response and virologic rebound) in the open-label phase of the study.

5.2.8 Information Provided to Sponsor by IDMC

The IDMC will make recommendations to sponsor on the sample size adjustment and any safety concerns.

5.2.9 Protection of Type I Error Rate

Adjustments are made to protect the trial-wise Type I error rate due to Interim Analysis and potential increase in the sample size after the IA. To preserve the Type I error rate, the following steps will be followed:

a. If the statistical power is larger than 50%, then the sample size will be adjusted upward and no Type I error rate adjustment will be made to the final analysis (Chen YH, 2004).

b. If the statistical power is less than 50%, the Type I error rate will be inflated and statistical adjustment will be made to the final analysis if the decision to increase the sample size is made. That is, the observed p-value, as well as the point estimate of the response rates, and the 95% CIs will be based on [Proschan Liu, Hunsberger, 2003]:

   $p\text{-value} = 2*\{1 - T_{2(n1+n2-1)}(|z_1 + z_2|/\sqrt{2})\}$,

   Response rate for each treatment group: $\hat{S} = (\sqrt{n_1} \times \hat{S}_1 + \sqrt{n_2} \times \hat{S}_2)/(\sqrt{n_1} + \sqrt{n_2})$,

   95% Confidence Intervals $= (\hat{S} - 2\, t_{\alpha/2\ 2(n1+n2-1)}\sigma,\ \hat{S} + 2\, t_{\alpha/2\ 2(n1+n2-1)}\sigma)$

where n1, is the sample size in the treatment group before interim analysis and n2 is the sample size in treatment group after the interim analysis; T2(n1+n2 - 1) (.) is t distribution with 2 (n1+ n2-1) degrees of freedom. The $\hat{S}1$ is the responder rate of the n1 observation before the interim analysis and $\hat{S}2$ is the responder rate of the n2 observation after the interim analysis. The $(\sqrt{n_1} + \sqrt{n_2})\sigma$ is the observed pooled standard deviation before and after the interim analysis.

6. ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as the set of subjects who are randomized and have received at least one dose of PRO 140 or placebo. This population will be used as a primary analysis population for the primary and secondary endpoints.

6.2 Per Protocol Population

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population

requirements, and were not associated with a major protocol violation. This population will be identified before the database lock. This analysis using this population will be supportive.

6.3 Safety Population

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

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before treatment.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit, the last measured value will be used for the analysis. If it is not possible to identify the "last measured value" the average of the duplicate values will be used.

No data will be excluded. All collected data will be listed.

7.3 Handling of Missing Data

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

7.4 Multicenter Clinical Trials

This is a multicenter clinical trial that includes up to 60 centers in the United States.

7.5 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

For the primary endpoint only one hypothesis will be tested, hence there is no adjustment for Type I error rate.

For the secondary endpoints, the closed test procedure will be used to protect the trial-wise error rate. The order of the endpoints is specified in Section 3.2.

7.6 Covariates and Prognostic Factors

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

7.7 Stratification Factors

Resistance to ART drugs at the time of randomization will be used as a stratification factor to ensure balance between each treatment group in this stratum.

7.8 Subgroups and Exploratory Analysis

All planned subgroups by the stratification factor that are part of secondary endpoints will be summarized. Any additional subgroup/ exploratory analyses may be conducted as post hoc analyses.

7.9 Standard Calculations

7.9.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) = integer of[(date of informed consent – date of birth)/ 365.25+ 0.5]

7.9.2 Height

For summary purposes height will be expressed in centimeters. Entries made in inches will be converted to centimeters using the formula noted below.

Height (cm) = Height (in)*2.54

7.9.3 Weight

For summary purposes weight will be expressed in kilograms. Entries made in pounds will be converted to kilograms using the formula noted below.

Weight (kg) = Weight (lb)/ 2.2046

7.9.4 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

$$BMI\ (kg/m^2) = weight\ (kg) / [[height\ (cm)/100]^2]$$

8. STATISTICAL METHODS

All data collected during this study will be presented in subject data listings. All statistical analyses

will be performed using SAS® for Windows, version 9.4 or later.

8.1 Summarizing and Tabulating the Collected Data

All data collected will be summarized according to the variable type:

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

8.1.1 Subject Disposition and Withdrawals

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.

There will be a detailed accounting of all subjects that signed the informed consent to participate in this trial. The following will be summarized:

- The number of subjects who signed the informed consent
- The number of subjects who are screen failures
- The number of subjects who are randomized for the first part of the study
- The number of subjects who are randomized but not treated
- The number of subjects who are treated
- The number of subjects who completed the double blind treatment phase
- The number of subjects who completed both treatment phases
- The number of subjects who completed the follow up phase
- The number of subjects who discontinued

Reasons for discontinuation will also be summarized.

In addition, there will also be a listing of all discontinued subjects, which will provide the clinical trial center and the specific reason for discontinuation.

8.1.2 Protocol Deviations

The deviations occurring during the clinical trial will be summarized descriptively according to the following categories:

- Entrance criteria deviation
- Withdrawal criteria deviation
- Received wrong treatment or incorrect dose
- Received an excluded medication
- All other deviations

Additionally a by-subject listing of all deviations will also be prepared.

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Gender, Time since HIV diagnosis, Viral load at Screening Visit, Tropism, etc.) will be summarized and/or listed, descriptively for the Safety Population.

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

8.1.4 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.

8.1.5 Anti-Retroviral Therapy (ART)

Anti-retroviral therapy will be summarized for the Safety Population. All such 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 anti-retroviral therapy recorded in the eCRFs will also be listed.

8.1.6 Optimized Background Therapy (OBT)

Optimized background therapy will be summarized for the Safety Population. All such 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 optimized background therapy recorded in the eCRFs will also be listed.

8.1.7 Treatment Administration

All treatment PRO-140 administration data will be listed. In addition, the number and percentage of the subjects who received PRO-140 injection along with the summary of volume of injection will be presented for the safety population for each week during the treatment period.

8.2 Analysis of Efficacy Data

8.2.1 Primary Endpoint

The primary efficacy endpoint for this study is proportion of participants with a $\geq 0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period.

The number and percentage of subjects with a $\geq 0.5\log_{10}$ or greater reduction in HIV-1 RNA viral load from baseline will be presented for the two treatment groups. Fisher's Exact test will be used to test the primary endpoint if the count in any cell (of the contingency table) is less than 5; otherwise Chi-Square test will be used assess the difference in the primary endpoint between treatment groups. In addition, the odds ratio and its 95% CI will also be presented.

8.2.2 Secondary Endpoints

There are multiple secondary endpoints to be assessed in this study, to maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. The order of the secondary endpoints will be as discussed in the below sections:

8.2.2.1 Proportion of participants with ≥ 0.5 $\log_{10}$ reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period

Similar analysis methods used for the primary endpoint specified in Section 8.2.1.1 will be used to analyze the below subgroups:

a. resistance to ART drugs within three drug classes

b. resistance to ART drugs within two drug classes with limited treatment option.

8.2.2.2 Proportion of participants with ≥ 1 log_{10} reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period

The number and percentage of subjects with a ≥ 1log_{10} or greater reduction in HIV-1 RNA viral load from baseline will be presented for the two treatment groups. Fisher's Exact test will be used to test the endpoint if the count in any cell (of the contingency table) is less than 5; otherwise Chi-Square test will be used assess the difference in the endpoint between treatment groups. In addition, the odds ratio and its 95% CI will also be presented.

8.2.2.3 Mean change from Baseline in HIV-1 RNA levels (log_{10} copies/mL) at the end of the 1-week double-blind treatment period

The raw and change from baseline in HIV-1 RNA levels (log_{10} copies/mL) at the end of the 1-week double-blind treatment period will be summarized by treatment group for the first week during the double-blind treatment phase. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded. The change from baseline in HIV-1 RNA levels will be compared between the two groups using Analysis of Covariance (ANCOVA) with the stratification factor (i.e., Resistance to ART drugs at the time of randomization) included in the model.

8.2.2.4 Percentage of participants achieving HIV-1 RNA < 400 copies/mL at week 25

The number and percentages of subjects achieving HIV-1 RNA < 400 copies/mL at week 25 will be presented.

8.2.2.5 Percentage of participants achieving HIV-1 RNA < 50 copies/mL at week 25

The number and percentages of subjects achieving HIV-1 RNA < 50 copies/mL at week 25 will be presented.

8.2.2.6 Mean change from Baseline in HIV-1 RNA levels (log_{10} copies/mL) at week 25

The raw and change from baseline in HIV-1 RNA levels (log_{10} copies/mL) at week 25 will be

summarized for each week during the treatment phase. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.2.2.7 Mean change from Baseline in CD4 cell count at the end of the 1-week double-blind treatment period

The raw and change from baseline in CD4 cell count at the end of the 1-week double-blind treatment period will be summarized by treatment group for the first week during the double-blind treatment phase. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded. The change from baseline in CD4 cell count will be compared between the two groups using Analysis of Covariance (ANCOVA) with the stratification factor (i.e., Resistance to ART drugs at the time of randomization) included in the model.

8.2.2.8 Mean change from Baseline in CD4 cell count at week 25

The raw and change from baseline in CD4 cell count at week 25 will be summarized for each week during the treatment phase. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3 Analysis of Safety Data

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

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

8.3.1 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent MedDRA dictionary.

All Treatment Emergent Adverse Events (TEAEs) will be summarized by treatment group, by System Organ Class and Preferred Term. TEAEs are defined as events with an onset on or after the first treatment administration. The following TEAE summaries will be provided, using frequency counts and percentages:

- Overall (*i.e.,* regardless of severity or relationship to treatment)
- By impact of study treatment (none, study treatment interrupted, study treatment discontinued, or not applicable[1])
- By severity grade (mild, moderate, severe, life threatening or death for SAEs)
- By relationship to study treatment (definitely related, probably related, possibly related, remotely related or unrelated)

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

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

8.3.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected according to the time points in the schedule of assessments for analysis. All available results of the clinical laboratory evaluations (e.g., Routine CBC, Biochemistry, etc.) will be listed and summarized by treatment group.

8.3.3 Urine and Serum Pregnancy Test

All the results for serum pregnancy test will be presented as a by-subject listing.

8.3.4 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

[1] 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".

- 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), End of Treatment (EOT) Visit, and at Treatment Failure (TF) Visit. Only symptom-directed physical examination will be performed at treatment and follow-up visits conducted within the clinic, and at unscheduled visits within the Treatment and Follow-up Phases.

All physical examination findings will be listed and/or summarized by treatment group.

8.3.5 Vital Signs

Vital signs will be collected at all study visits performed at the clinic. Vital signs collected during the Treatment Phase will be performed post-treatment, assessed within 15 minutes following study treatment administration.

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

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

- Respiration Rate
- Temperature

All vital sign assessment findings will be listed and summarized.
Tabulations of raw data and change from baseline values will be presented by time point and treatment group for each vital sign parameter [*i.e.,* pulse (beats/min), temperature (^{0}C), systolic BP (mmHg), diastolic BP (mmHg)]. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.6 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.

8.3.6.1 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.

All data from the injection site reaction assessments of the repeated subcutaneous administration of PRO 140 will be descriptively summarized by treatment group.

8.3.6.2 Pain Assessment Using Visual Analog Scale (VAS)

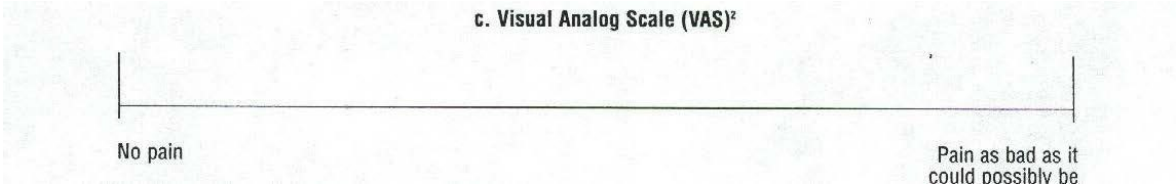
Tolerability of repeated subcutaneous administration of PRO 140 is evaluated based on assessment of subject-perceived injection site pain using the Pain Visual Analog Scale (VAS). This assessment will be performed each time subjects arrive to the clinic for the study visit.

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.

All data from the VAS assessment of the repeated subcutaneous administration of PRO 140 will be summarized descriptively by treatment group.

Figure 8-1: Visual Analog Scale



8.3.7 ECG Assessment

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

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

8.3.8 Neurological Assessment

Neurological assessment will be performed by the Principal Investigator (or delegated personnel) or a Neurologist at Treatment Visits 1, 3, 7, 11, 15, 19 and 23 (T1, T3, T7, T11, T15, T19, T23), End of Treatment (EOT) and at Treatment Failure (TF) Visit.

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

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

8.3.9 Tropism and Drug Resistance from Monogram Biosciences

All Trofile® assay data from Monogram Biosciences will be presented as a by-subject listing.

8.3.10 Tropism from Quest Diagnostics

All tropism data from Quest diagnostics will be presented as a by-subject listing.

8.3.11 Anti-Idiotypic Antibodies to Pro 140

Anti-idiotypic antibodies to PRO 140 will be performed at T1, T7, T15, EOT and TF visits. All data will be presented as by-subject listings.

8.3.12 PK Concentration of PRO140

PK sample for PRO 140 will be taken at T1, T7, T15, EOT and TF visits. All data will be presented as by-subject listings.

8.3.13 Serum Concentration of ART Drugs

All serum concentration of ART drugs will be presented as a by-subject listing.

8.3.14 Notification and Outcome Pregnancy

All the results for Notification and Outcome Pregnancy will be presented as a by-subject listing.

9. APPENDIX 1: SCHEDULE OF ASSESSMENTS

TABLE 1: SCHEDULE OF ASSESSMENTS – SCREENING AND TREATMENT PHASE

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

Procedure/Assessments	Screening Visit	Treatment Phase (25 weeks)																In case of Treatment Failure
		Double-blind (1 week)		Open-label (24 weeks)														
Visit	SV	T1 (Pre-Rx)	T1 (Post-Rx)	T2	T3	T4-6	T7	T8 - 10	T11	T12-14	T15	T16-18	T19	T20-22	T23	T24-25	EOT	TF
Window Period		Within 6 weeks of the Screening visit		1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	
TruCount T assay[12]	X	X		X	X		X		X		X		X		X		X	X
PK conc. to PRO 140[13]		X					X				X						X	X
Serum conc. of ART Drugs[14]		X					X				X						X	X
Urine Pregnancy Test[10]		X																
Pre-enrollment Eligibility		X																
Randomization [15]		X																
PRO 140 or Placebo plus Existing ART Regimen		X																
PRO 140 + OBT Administration				X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Reaction Assessment[16]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Pain Assessment (VAS)[17]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 Trofile® Assay[18]	X																	X
HIV-1 Drug Resistance Assay[19]	X	X		X	X		X		X		X		X		X			X
HIV-1 PhenoSense® Entry Assay[20]	X																	X
Anti-idiotypic antibodies to PRO 140		X					X				X						X	X
Blood sample collection for	X																	X

Procedure/Assessments	Screening Visit	Treatment Phase (25 weeks)															In case of Treatment Failure
		Double-blind (1 week)		Open-label (24 weeks)													
Visit	SV	T1 (Pre-Rx)	T1 (Post-Rx)	T2	T3	T4-6	T7	T8 - 10	T11	T12-14	T15	T16-18	T19	T20-22	T23	T24-25	EOT	TF
Window Period		Within 6 weeks of the Screening visit		1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	1 week ±3 days since last treatment	
exploratory analysis[21]																		
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Foot Notes:

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

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

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

[4] Symptom-directed physical examination

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

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

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

[8] Serum Biochemistry

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

Renal function indicators: BUN, creatinine

Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: glucose (random), cholesterol (total)

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

[10] ONLY performed on women of childbearing potential.

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

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

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

[14] Serum conc. of ART Drugs prior to IP administration at the T1, T7, T15, EOT and TF visits.
[15] Randomization via WebView CTMS system
[16] Injection Site Reaction Assessment as assessed by Investigator at the clinic visits at T1, T2, T3, T7, T11, T15, T19 and T23 visits.
[17] Subject-perceived injection site pain (average pain since last treatment) will be assessed using the Pain Visual Analog Scale (VAS) prior to each study treatment administration
[18] Monogram Biosciences Trofile® (DNA or RNA Assay based on viral load)
[19] Monogram Biosciences PhenoSense® GT (and PhenoSense Integrase and GeneSeq Integrase testing, if applicable)
[20] Monogram Biosciences HIV-1 PhenoSense® Entry assay with AMD3100 (CXCR4 inhibitor drug), Maraviroc and PRO 140 (CCR5 inhibitor drugs).
[21] Quest Diagnostics HIV-1 Coreceptor Tropism with Reflex to Ultradeep Sequencing or HIV-1 Proviral Tropism

TABLE 2: SCHEDULE OF ASSESSMENTS – FOLLOW-UP PHASE

(a) Subjects who do NOT experience treatment failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2
	NTF-FU1	NTF-FU2
Window Period	2 weeks (±3 days) after EOT visit	4 weeks (±3 days) after EOT visit
Physical Examination	X[1]	X[1]
Vital Signs	X	X
Plasma HIV-1 RNA level	X	X
TruCount T assay	X	X
Adverse Events	X	X
Concomitant Medications	X	X
Anti-idiotypic Antibodies to PRO 140		X

[1] Symptom-directed physical examination

(b) Subjects who experience treatment failure

Procedure/Assessments	Follow-Up Visit -1	Follow-Up Visit -2	Follow-Up Visit -3[1]
	TF-FU1	TF-FU2	TF-FU3
Window Period	4 weeks (±7 days) after TF visit	8 weeks (±7 days) after TF	12 weeks (±7 days) after TF
Physical Examination	X[2]	X[2]	X[2]
Vital Signs	X	X	X
Plasma HIV-1 RNA level	X	X	X
TruCount T assay	X	X	X
Adverse Events	X	X	X
Concomitant Medications	X	X	X
Anti-idiotypic Antibodies to PRO 140	X		

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

[2] Symptom-directed physical examination

10. APPENDIX 2 – PLANNED TLG

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILTY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)

TREATMENT ADMINISTRATION LISTINGS (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.1.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS

POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS

CONCOMITANT MEDICATION USAGE

EFFICACY SUMMARIES

SAFETY SUMMARIES

- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS AND PE
- OTHER SAFETY

11. REFERENCES

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5. Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 1988.
6. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.