CYTODYN

# Statistical Analysis Plan Cover Page

**Document Title:** Statistical Analysis Plan for Protocol PRO 140_CD03

**Protocol Number:** PRO 140_CD03

**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

**Version:** 1.0

**Document Date:** 27-Jan-2020

**NCT Number:** NCT02859961

# STATISTICAL ANALYSIS PLAN
# FOR PROTOCOL PRO 140_CD03

| | | |
|---|---|---|
| **Sponsor:** | | |
|  | CytoDyn, Inc.<br>1111 Main Street, Suite 660<br>Vancouver, Washington<br>98660 | (360) 980-8524-Work<br>(360) 980-8549-Fax<br>www.cytodyn.com |
| **Protocol Number:** | PRO 140_CD03 | |
| **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 Version / Date:** | 11.0 / 27-Nov-2019 | |


| | | | |
|---|---|---|---|
| **SAP Author:** | [redacted] | Telephone: | [redacted] |
| | | Facsimile: | [redacted] |


| | |
|---|---|
| **Plan Version:** | SAP - Version 1.0 |
| **Plan Date:** | 27-Jan-2020 |

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ART | Anti Retroviral Therapy |
| ASA | American Statistical Association |
| ATC | Anatomic Therapeutic Classification |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| CS | Clinically Significant |
| DAIDS | Division of AIDS |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| FDA | U.S. Food and Drug Administration |
| FU | Follow-Up |
| HEENT | Head, Ears, Eyes, Nose, Throat |
| HIV | Human Immunodeficiency Virus |
| ICH | International Conference on Harmonization |
| IP | Investigational Product |
| ITT | Intent-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PP | Per Protocol |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SV | Screening Visit |
| TEAE | Treatment Emergent Adverse Events |
| 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_CD03, 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:

- Protocol Version 11.0 / 27-Nov-2019
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

# 2. PROTOCOL DESIGN AND OBJECTIVES

## 2.1 Study Objectives

The objective of this study 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.

## 2.2 Design Overview

This study is a Phase 2b/3, multi-center, randomized, two-part, open-labeled study designed to evaluate 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

**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. More details are included in the protocol and Schedule of Assessments in Table 2-1, Table 2-2 and Table 2-3.

**Table 2-1: 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] | | | | | | | | | | | | | | | | | | | |
| – Group A (350mg SC) | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| – Group B (525mg SC) | | | | | | | | | | | | | | | | | | | |
| – Group C (700mg SC) | | | | | | | | | | | | | | | | | | | |
| 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 | | | | 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) | (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 | | | | | | | | | |
| (VAS)[16] | | | | | | | | | | | | | | | | | | | |
| 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 2-2: 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 |
| **CNS sub-study (n=20)** | | | | | | | | | | | | |
| CSF sample collection[17] | | | | | | | | | | | | 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 | | | | | | | | | | | |
| **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 2-3: 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

## 2.3 Study Duration

- **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 will be 58 weeks, which does not include additional follow-up time for virologic failure subjects.

## 2.4 Study Treatments

### 2.4.1 Treatment Groups

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

# 3. STUDY OUTCOME MEASURES

## 3.1 Primary Outcome Measures

The following outcome measures will be assessed for all subjects and within each treatment group for PRO 140 350mg, 525mg and 700mg dose.

### 3.1.1 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

### 3.1.2 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 (heterozygotes or homozygotes)
    - gp120 genotyping
    - Baseline HIV-1 RNA Single Copy levels
    - Immune Activation Markers
    - PhenoSense® Entry Assay

## 3.2 Secondary outcome measures

### 3.2.1 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).*
    - GenoSure Archive Assay will be performed at Baseline.
    - PhenoSense® GT ( PhenoSense Integrase and GeneSeq Integrase testing, if applicable), will be performed at the time of virologic failure.
- 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
    - The data will be from PhenoSense® Entry Assay

### 3.2.2 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)

**3.2.3 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)

## 4. SAMPLE SIZE DETERMINATION AND RATIONALE

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.

## 5. RANDOMIZATION AND BLINDING

There were no blinding requirements planned for this study.

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)

## 6. ANALYSIS POPULATIONS

### 6.1 Intent-to-Treat Population

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.

### 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.

### 6.3 Safety Population

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

## 7. DATA CONVENTION AND RELATED DEFINITIONS

### 7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value prior to initiation of the first dose of PRO140.

### 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

There are no inferential statistics planned for this study, hence all data will be presented without imputation.

### 7.4 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

There are no inferential statistics planned for this study, hence there will be no adjustment for multiple comparisons.

### 7.5 Standard Calculations

#### 7.5.1 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] |
|---|

#### 7.5.2 Body Mass Index (BMI)

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

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

#### 7.5.3 Change from Baseline

For any of the effectiveness measurements change from baseline will be calculated using the formula noted below.

| Change from baseline =<br>Post Baseline Measurement – Baseline Measurement |
|---|

#### 7.5.4 Virologic Failure

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

#### 7.5.5 Time to Virologic Failure

The date of virologic failure is defined as the date of the second assessment of the two (2) consecutive plasma HIV-1 RNA levels of ≥ 200 copies/mL when virologic failure is confirmed.

For the censored subjects (i.e., subjects who do not have an event) the date of event will be:

- The time of the last visit data; if the subject completes the trial;

- The time of the early termination for those subjects who withdraw or early terminate from the trial.

***[for those with virologic failure]***
Time to virologic failure = (Date of first HIV-1 RNA levels of ≥ 200 copies/mL – Date of first treatment) +1
***[for those without virologic failure]***
Time to virologic failure = (Date of last visit/ early termination – Date of first treatment) +1

### 7.5.6 Viral Re-suppression

For all subjects with virologic failure, viral re-suppresion is defined as having a plasma HIV-1 RNA levels of <50 copies/mL after experiencing viroloic failure.

### 7.5.7 Time to Viral re-suppression

This will be assessed for all subjects experiencing viroloic failure. The date of viral re-suppression is defined as the date of first assessment where plasma HIV-1 RNA levels of <50 copies/mL after virologic failure.

Time to viral re-suppression = (Date of first HIV-1 RNA levels of < 50 copies/mL – Date of virologic failure) +1

### 7.5.8 Time to Viral re-suppression after re-initiation of oral combination antiretroviral regimen (Re-ART)

This will be assessed for all subjects experiencing virologic failure and oral combination antiviral therapy is re-initiated. The date of viral re-suppression is defined as the date of first assessment where plasma HIV-1 RNA levels of <50 copies/mL after virologic failure.

Time to viral re-suppression after Re-ART = (Date of first HIV-1 RNA levels of < 50 copies/mL – Date of first re-initiation of oral combination regimen) +1

## 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, rescreened, screen failure, 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.

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. 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, etc.) will be summarized using appropriate descriptive statistics.
Medical history of the subjects will also be summarized and also 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 and re-initiation of anti-retroviral therapy data 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.

In addition, Virologic failure subjects will have a long term safety follow up visit at 6 months and 1 year after the virologic failure visit. Any changes in ART regimen during this time will be captured and presented as a by-subject listing.

### 8.1.6 Treatment Exposure

All data from administration of study drug will be presented. In addition the following summaries will be included:

- Duration of PRO 140 treatment (in weeks)
    - At the Assigned dose
    - At the Rescue Dose (if applicable)
    - Combined Assigned and Rescue dose.
- Proportion of participants completing 24, 48 weeks of PRO 140 treatment.
    - At the Assigned dose
    - Combined Assigned and Rescue dose
- Duration of PRO 140 treatment (in weeks) at the time of virologic failure

## 8.2 Analysis of Study Outcome Measures

### *8.2.1 Safety Outcome Measures*

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

#### 8.2.1.1 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 (SOC), and preferred term (PT). The following TEAE summaries will be provided:

- Overall (*i.e.,* regardless of severity or relationship to treatment)
- 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.

*8.2.1.2 Injection Site Reaction assessment*

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

*8.2.1.3 Pain Assessment using Visual Analog Scale (VAS)*

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

8.2.1.4 Clinical Laboratory Evaluations

All available results of the clinical laboratory evaluations will be listed and summarized. Laboratory evaluations include hematology, biochemistry, serology and urinalysis.

*8.2.1.4.1 Laboratory Values over Time*

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented. Data will be summarized as appropriate to the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

*8.2.1.4.2 Individual Subject Changes (Shift Tables)*

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, for shift (change) from baseline.

*8.2.1.1 Clinically Significant Abnormalities*

A by-subject listing of treatment-emergent clinically significant laboratory values, by treatment group, will be prepared.

8.2.1.2 Vital Signs

Tabulations of raw data and change from baseline values will be presented by visit for each vital sign parameter [*i.e.,* systolic BP (mmHg), diastolic BP (mmHg), temperature ($^0$C), heart rate (bpm), respiratory rate (rpm)].

8.2.1.3 Electrocardiogram (ECGs)

The ECG parameters include: ventricular rate (beats per minute), PR interval (msec), QRS interval

(msec), QT interval (msec), and QTcF interval (msec).

*8.2.1.3.1 ECG Values over Time*

Descriptive statistics of raw data and change from baseline values for each ECG measurement will be presented. For change from baseline summaries, subjects with an undefined change from baseline, because of missing baseline data, will be excluded.

*8.2.1.3.2 Individual Subject Changes (Shift Tables)*

Individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, for shift (change) from baseline.

8.2.1.4 Physical Examination

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

### *8.2.2 Efficacy Outcome Measures*

The primary analysis of efficacy outcome measures will be conducted on the ITT population. The Per Protocol (PP) population will be used as a supportive analysis.

8.2.2.1 Proportion of participants experiencing virologic failure at the assigned dose

The percentages of subjects with virologic failure (as defined in Section 7.5.6) will be presented descriptively by treatment groups for the ITT and PP populations.

Note: Assigned dose refers to the dose allocated at the time of randomization/enrollment.

8.2.2.2 Time to virologic failure at the assigned dose

The number of observations, mean, standard deviation, median, and minimum and maximum values will be presented to summarize time to virologic failure (as defined in Section 7.5.7) by treatment groups for the ITT and PP populations.

8.2.2.3 Proportion of participants moved to rescue arm or higher dose group

The percentages of subjects moved to a rescue arm or higher dose will be presented descriptively by treatment groups for the ITT and PP populations.

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.

8.2.2.4 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

The percentages of subjects with virologic re-suppression (as defined in Section 7.5.8) will be presented descriptively by treatment groups for the subset of the ITT and PP populations that moved to a rescue arm or higher dose group.

8.2.2.5 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

The number of observations, mean, standard deviation, median, and minimum and maximum values will be presented to summarize time to viral re-suppression (as defined in Section 7.5.9) by treatment groups for the subset of the ITT and PP populations that moved to a rescue arm or higher dose group.

8.2.2.6 Proportion of participants achieving viral re-suppression (HIV-1 RNA <50 copies/mL) after experiencing virologic failure (during the Treatment and Follow-up Phase)

The percentages of subjects with virologic re-suppression (as defined in Section 7.5.8) will be presented descriptively by treatment groups for the subset of the ITT and PP populations that experienced virologic failure.

8.2.2.7 Time to achieving viral re-suppression (for virologic failure subjects) after re-initiation of oral combination antiretroviral regimen during the Follow-up Phase.

The number of observations, mean, standard deviation, median, and minimum and maximum values will be presented to summarize time to viral re-suppression after re-initiation of oral combination antiretroviral regimen (as defined in Section 7.5.10) by treatment groups for the subset of the ITT and PP populations that experienced virologic failure and had re-initiation of oral combination antiviral therapy.

8.2.2.8 Proportion of participants completing 24, 48 weeks of PRO 140 treatment with HIV-1 RNA <50 copies/mL

The percentages of subjects with completing 24 and 48 weeks of PRO 140 treatment with HIV-1 RNA <50 copies/mL will be presented descriptively by treatment groups for the ITT and PP populations:

- At the Assigned dose
- Combined Assigned and Rescue dose

8.2.2.9 Mean change in CD4 cell count, at each visit within the Treatment Phase

The raw and change from baseline in CD4 cell count 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.

8.2.2.10 To evaluate the prognostic factors of therapeutic success of PRO 140 monotherapy during the Treatment Phase

- CCR5 Receptor Occupancy: To confirm occupancy of CCR5 receptors on T-cells and monocytes or both while subjects are on PRO 140 Monotherapy and to monitor changes in CCR5 receptor occupancy status associated with changes in HIV-1 RNA levels and CD4 counts.

  Data for CCR5 Receptor Occupancy will be provided from the external vendor InCell Dx. All data will be presented as a by-subject listing.
- CCR5 Genotyping Status (heterozygotes or homozygotes)

  Data for CCR5 Genotyping Assay will be provided from the external vendor InCell Dx. All data will be presented as a by-subject listing.
- gp120 genotyping: To identify potential polymorphisms that may decrease PRO 140 susceptibility and may affect response to PRO 140

  Data for gp120 genotype will be provided by external vendor Monogram Biosciences. All data from Monogram Biosciences will be presented as a by-subject listing.
- Baseline HIV-1 RNA Single Copy levels: To monitor changes in HIV-1 RNA single copy levels while subjects are on PRO 140 Monotherapy.

  Data for HIV-1 RNA single copy assay will be provided by external vendor bioMontor Lab. All data from will be presented as a by-subject listing.

- Immune Activation Markers: To monitor changes in CRP, IL-6, and D-Dimer levels while subjects are on PRO 140 Monotherapy.
  Data for immune activation markers will be provided by external vendor Covance. All data will be presented as by-subject listings.

- PhenoSense® Entry Assay: Baseline IC50, IC90 and maximal inhibition for PRO 140 and change from baseline while subjects are on PRO 140 Monotherapy
  Data for PhenoSense Entry assay will be provided by external vendor Monogram Biosciences. All data will be presented as by-subject listings.

### 8.2.3 Exploratory outcome measures

Exploratory outcome measures 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.

### *8.2.4 Additional Data listings and tabulations*

8.2.4.1 Neurological Assessment

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

8.2.4.2 HIV-1 Trofile® DNA/RNA Assay

Data for HIV-1 trofile® DNA/RNA assay will be provided by external vendor Monogram Biosciences. All data will be presented as by-subject listings.

8.2.4.3 TruCount Assay (including CD4 Counts)

Data for TruCount assay will be provided by external vendor Covance. All data will be presented as by-subject listings.

8.2.4.4 Drug Resistance, Genotypic and Phenotypic data

Data for drug resistance, genotypic and phenotypic will be provided by external vendor Monogram Biosciences. All data from Monogram Biosciences will be presented as a by-subject listing.

#### 8.2.4.5 HIV-1 Co-Receptor Tropism (exploratory assay)

Data for HIV-1 co-receptor tropism will be provided by external vendor Quest Diagnostics. All data will be presented as a by-subject listing.

#### *8.2.4.6* Anti-Idiotypic Antibodies to PRO 140

Data for Anti-idiotypic antibodies to PRO 140 will be provided by external vendor *QPS*. All data will be presented as by-subject listings.

#### 8.2.4.7 PK Concentration of PRO140

Data for PK concentration of PRO 140 will be provided by external vendor *QPS*. All data will be presented as by-subject listings.

#### 8.2.4.8 Serum Concentration of ART Drugs

All serum concentration of ART drugs will be provided from the external vendor CLS. All data will be presented as a by-subject listing.

#### *8.2.4.9* Notific**a**tion and Outcome Pregnancy

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

#### 8.2.4.10 Weight

Weight data will be summarized and presented as by-subject listing.

#### 8.2.4.11 Height

Height data will be summarized and presented as by-subject listing.

#### 8.2.4.12 Urine drug test

All available urine drug test data will be presented as by-subject listing.

#### 8.2.4.13 Pregnancy test

All available pregnancy data will be presented as by-subject listing.

# 9. APPENDIX – PLANNED TLG

## 9.1 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.X)

## 9.2 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
- PE
- ECG
- TOLERABILITY
- NEUROLOGICAL ASSESSMENT
- OTHER SAFETY

## 10. VERSION HISTORY

***This is the first version of the SAP.***

## 11. REFERENCES

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2016.
2. The Royal Statistical Society: Code of Conduct (2014).
3. E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
4. E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1998
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.