A Phase II, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of the Safety and Efficacy of PRO 140 for Prophylaxis of Acute Graft-Versus-Host Disease in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

Protocol Number:	**PRO 140_CD 03_GVHD**
Version:	**3.0**
Date:	**17 Jun 2016**

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

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**PRO 140_CD 03_GVHD**
Version:	**3.0**
Date:	**17 Jun 2016**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**PRO 140_CD 03_GVHD**
Version:	**3.0**
Date:	**17 Jun 2016**

INVESTIGATOR'S SIGNATURE

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

_____ _____
Principal Investigator's Signature Date

_____
Print Name

_____
Address

_____
Site Number

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytoDyn Inc.

Protocol Number: PRO 140_CD 03_GVHD

Investigational Product:
PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo

Indication:
Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

Title of Study

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of the Safety and Efficacy of PRO 140 for Prophylaxis of Acute Graft-Versus-Host Disease in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation.

Clinical Phase

Phase II

Concept and Rationale

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. The American Cancer Society estimates that in 2015, there will be 20,830 new cases of AML diagnosed in the United States, and about 10,460 deaths from AML have been projected. AML is generally a disease of older people with average age of a patient with AML being 66 years. The lifetime risk of being diagnosed with AML for the average American man is about 1 in 227 and for the average American woman the risk is about 1 in 278. The mainstay of induction therapy for AML for the past 40 years has been combination chemotherapy, which has resulted in approximately 60-70% complete remission rate and 30-40% 5-year overall survival.

Myelodysplastic Syndromes (MDS) is a heterogeneous group of clonal malignant hematopoietic stem cell disorders characterized by hyper- or hypocellular marrows, peripheral blood cytopenias, and cell function abnormalities resulting from failure of hematopoietic differentiation. MDS has a highly variable natural history with a variable risk of transformation to AML. The annual incidence of MDS in the US is 10-100 per million but might be higher in the elderly population.

Notwithstanding the use of combination chemotherapy for AML and MDS, these two, often related disorders remain the leading indications for allogeneic hematopoietic cell transplantation (HCT) in adults.

Even though allogeneic HCT is the treatment of choice for offering the curative option to patients with AML with unfavorable cytogenetics or molecular mutations as well as to patients with MDS, whether it should be offered to all patients in first remission of AML or to all patients with MDS is contested.

Transplantation-related mortality can be as high as 20-30%, which can counterbalance the potential advantages. Graft Versus Host Disease (GVHD) is one of the major causes of post-transplant morbidity and mortality.

Migration of donor cells, particularly T-cells, into different tissues including skin, liver and gastrointestinal

Name of Sponsor/Company: CytoDyn Inc.

Protocol Number: PRO 140_CD 03_GVHD

Investigational Product:
PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo

Indication:
Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

(GI) tract and recognition of the host histocompatibility antigens is critical in development of GVHD. Small molecules and monoclonal antibodies that block chemokine receptors such as CCR5, are in theory able to lessen the migration of donor cells into tissues. Therefore, blocking CCR5 after allogeneic HCT may reduce the occurrence rates of GVHD. PRO 140 is a humanized monoclonal antibody directed against CCR5. This study will investigate the safety and efficacy of pharmacologic inhibition of CCR5 in prevention of acute GVHD by administering PRO 140 as an add-on therapy to standard GVHD prophylaxis to adult patients with AML or MDS undergoing allogeneic HCT.

Study Objectives

- The primary objective of this study is to assess the efficacy of PRO 140 compared to placebo as an add-on therapy to standard GVHD prophylaxis in adult patients with AML or MDS undergoing allogeneic HCT
- The secondary objective of this study is to assess safety and tolerability of PRO 140 compared to placebo as an add-on therapy to standard GVHD prophylaxis in adult patients with AML or MDS undergoing allogeneic HCT

Study Endpoints

Primary Efficacy Endpoint

- Incidence of Grade II , Grade III or Grade IV acute GVHD by Day-100

Secondary Efficacy Endpoints

- Incidence of severe and life-threatening (Grade III and Grade IV) acute GVHD by Day-100
- Incidence of organ-specific acute GVHD by Day-100
- Donor engraftment evaluated by T-cell and myeloid chimerism in peripheral blood
- Neutrophil and platelet count recovery
- Changes in ECOG performance score
- GVHD-free survival (GFS)

Safety Assessments

- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale) and by investigator-evaluation of injection site reactions
- Frequency of treatment emergent adverse events and serious adverse events

Name of Sponsor/Company: CytoDyn Inc.

Protocol Number: PRO 140_CD 03_GVHD

Investigational Product:
PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo

Indication:
Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

- AML or MDS relapse rate by Day-100
- Changes and shifts in laboratory measurements over time
- Changes in Electrocardiogram (ECG) parameters over time

Study Design

This is a Phase II, randomized, double-blind, placebo-controlled, multi-center study to evaluate the feasibility of the use of PRO 140 as an add-on therapy to standard GVHD prophylaxis treatment for prevention of acute GVHD in adult patients with AML or MDS undergoing allogeneic HCT.

In this study, 60 subjects will be randomized to receive either PRO 140 or placebo in a 1:1 ratio (i.e. 30 subjects per arm). PRO 140 or placebo will be administered as a 350 mg subcutaneous injection on Day -3 or Day -2 prior to stem cell infusion, on the day of stem cell infusion (Day 0), and then weekly for 30 days (at Week 1, Week 2, Week 3 and Week 4) after which it will be administered every two weeks for up to 100±7 days (at Week 6, Week 8, Week 10, Week 12 and Week 14). Subjects will return to clinic for two Follow-up visits at 2 weeks after the last treatment visit, and one year after the first treatment visit.

Planned Number of Subjects

60

Planned Number of Center(s)

Multi-center study including up to 20 sites in the US

Inclusion Criteria

Subjects may be included in the study only if they meet all of the following inclusion criteria:

1. Patients diagnosed with AML or MDS per below:
    - Patients with a history of histologically or pathologically confirmed diagnosis of AML and < 5% blasts in the peripheral blood or bone marrow (per bone marrow aspiration and/or biopsy within 6 weeks prior to screening) scheduled to undergo allogeneic stem-cell transplantation
    - Patients with a histologically or pathologically confirmed diagnosis of MDS with < 10% blasts in the bone marrow (per bone marrow aspiration and/or biopsy within 6 weeks prior to screening) scheduled to undergo allogeneic stem-cell transplantation

Name of Sponsor/Company: CytoDyn Inc.

Protocol Number: PRO 140_CD 03_GVHD

Investigational Product:
PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo

Indication:
Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

2. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2
3. Patients must have normal organ function as defined below:
    - Myeloablative allogeneic HCT:
        - Males and females, age ≥18 and ≤ 65 years of age
        - Total bilirubin ≤ 2 mg/dL (except in patients with Gilbert's Syndrome)
        - AST/ALT ≤ 3 times institutional upper limit of normal (except in patients with leukemic infiltration of liver)
        - Serum creatinine ≤ 2 mg/dL and creatinine clearance ≥ 60 ml/hr
        - Diffusing capacity of the lung for carbon monoxide (DLCO) > 50% predicted with no symptomatic pulmonary disease
        - Cardiac ejection fraction ≥ 50%. If between 40-49% a cardiology consult is required
        - Clinically normal resting 12-lead ECG at screening visit or, if abnormal, considered not clinically significant by the PI
4. Patients must have a reasonable expectation of ≥ 6 months survival
5. The donor-recipient HLA match criteria required for participation in this protocol are not research subjects in this study and they must meet criteria as National Marrow Donor Program (NMDP) donors. Procedures for selection of donors and stem cell dose will follow FDA requirements for Blood Products (21 CFR 640) and Human Cellular and Tissue Based Products (21 CFR 1271). The standard institutional practices for stem cell transplants also will be followed. The donors are:
    - HLA-Identical Sibling (6/6): Minimal typing necessary is serologic typing for class I (AB) and molecular typing for class II (DRB1)
    - Matched Unrelated Donor (8/8): Molecular identity at HLA A, B, C and DRB1 by high-resolution typing
    - Matched Related and Unrelated Donor (7/8): high-resolution molecular typing at the following loci is required: HLA A, B, C and DRB1
6. Both male and female patients and their partners of childbearing potential must agree to use

Name of Sponsor/Company: CytoDyn Inc.

Protocol Number: PRO 140_CD 03_GVHD

Investigational Product:
PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo

Indication:
Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation

appropriate birth control methods (birth control pills, barriers, or abstinence) throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative serum pregnancy test at Screening visit and negative urine pregnancy test prior to receiving the first dose of study drug.

7. Patients must understand and voluntarily sign an informed consent form

Exclusion Criteria

Subjects will be excluded from the study if they meet one or more of the following exclusion criteria:

1. Patients not expected to be available for follow-up for at least 114 days after transplant
2. Patients who have received prior allogeneic stem cell-transplantation
3. Patients who receive post-transplant high dose cyclophosphamide
4. Patients with active central nervous system (CNS) involvement by malignant cells
5. Patients receiving other investigational drugs for GVHD. Co-enrollment in other clinical trials that do not include experimental GVHD therapies is allowed
6. Prior use of any experimental or approved CCR5 modulators including maraviroc and PRO 140
7. Patients with uncontrolled bacterial, viral or fungal infections including diagnosis of acute viral hepatitis (defined as any active infection with hepatitis A or a new diagnosis of hepatitis B or C within 24 weeks of transplant)
8. Currently active second malignancy other than non-melanoma skin cancers
9. Presence of fluid collection (ascites, pleural or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated
10. Patients who are HIV positive
11. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
12. Subjects on chronic steroid therapy > 5 mg/day within 2 weeks of screening except for inhaled, nasal, or topical steroids
13. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study

Name of Sponsor/Company: CytoDyn Inc. **Protocol Number:** PRO 140_CD 03_GVHD
Investigational Product: PRO 140 (Humanized monoclonal antibody to CCR5) or Placebo
Indication: Prophylaxis of Acute Graft-Versus-Host Disease (GVHD) in Patients With Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) Undergoing Allogeneic Stem-Cell Transplantation
compliance or the ability to evaluate safety/efficacy

Statistical Considerations

Sample Size Determination and Rationale:

For this two arm clinical trial, it is planned to have a total of 60 subjects (30 per treatment group). The sample size is on the basis of clinical judgment and not based on statistical power calculation. The number of subjects was deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Interim Analysis:

There will be a safety interim analysis after the first 10 subjects complete the treatment or withdraw from the study, whichever occurs first. The data from this interim analysis will be reviewed by an independent Data Monitoring Committee (DMC). The DMC responsibilities will be further elaborated in the study DMC charter.

There is no planned interim analysis for efficacy.

Statistical Analysis Considerations:

All data from the secondary endpoints will be summarized and tabulated according to the variable type:

- Continuous data summaries will include:
  - Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group
  - For inferential statistics, if the Normality assumption is met, t-test will be used and if the Normality assumption is not met, a non-parametric method will be used.
- Categorical data summaries
  - Frequencies and percentages will be presented by treatment group.
  - For inferential statistics Chi-square or fisher's exact test will be used.

The primary analysis will be conducted on the intention-to-treat (ITT) population. The per-protocol (PP) population will be used for supportive analysis.

A Statistical Analysis Plan (SAP) will be developed to detail the statistical consideration and data convention prior to database lock.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
AUC	Area Under Curve
°C	Celsius
CBC	Complete Blood Count
CCR5	C-C chemokine receptor type 5
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
cm	Centimeter
C_{max}	Maximal Concentration
CNS	Central Nervous System
CRF	Case Report Form
CR	Complete remission
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Lung Diffusion Capacity Testing
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DO	Doctor of Osteopathic Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
E_{max}	Maximum drug effect
et al	et aliae; Latin for "and others"
°F	Fahrenheit
FDA	U.S. Food and Drug Administration
FDP	Fixed Dose Procedure
FU	Follow-Up
GCP	Good Clinical Practice

Abbreviation	Term
GI	Gastrointestinal
GVHD	Graft Versus Host Disease
HCT	Hematopoietic Cell Transplantation
Hb	Hemoglobin
HBsAg	Hepatitis B surface Antigen
HCT	Hematocrit
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IA	Interim Analysis
IB	Investigator's Brochure
IBMTR	International Bone Marrow Transplant Registry
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
i.e.	id est; Latin for "that is"
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reactions
ITT	Intent-to-treat
IV	Intravenous
LAR	Legally Acceptable Representative
LDH	Lactate dehydrogenase
LPN	Licensed Practical Nurse
LVEF	Left Ventricular Ejection Fraction
LVN	Licensed Vocational Nurse
mAb	Monoclonal Antibody
MD	Doctor of Medicine
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

Abbreviation	Term
mL	Milliliter
mm	Millimeter
MRD	HLA-Mismatched Related Donor
MUD	HLA-Matched Unrelated Donor
MUGA	Multi Gated Acquisition Scan
MW	Molecular Weight
NCS	Not Clinically Significant
NMDP	National Marrow Donor Program
NP	Nurse Practitioner
PA	Physician Assistant
PBSC	Peripheral Blood Stem Cell
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cells
RN	Registered Nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOP	Standard Operating Procedure
SOS	Sinusoidal Obstruction Syndrome
TBI	Total Body Irradiation
TEAE	Treatment Emergent Adverse Events
USA	United States of America
VAS	Visual Analogue Scale
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

1.1 STATEMENT OF INTENT

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

1.2 BACKGROUND

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. The American Cancer Society estimates that in 2015, there will be 20,830 new cases of AML diagnosed in the United States, and about 10,460 deaths from AML have been projected. AML is generally a disease of older people with average age of a patient with AML being 66 years. The lifetime risk of being diagnosed with AML for the average American man is about 1 in 227 and for the average American woman the risk is about 1 in 278. The mainstay of induction therapy for AML for the last 40 years has been combination chemotherapy with cytarabine and an anthracycline and sometimes with a third agent, which has resulted in approximately 60-70% complete remission rate and 30-40% 5-year overall survival.

Myelodysplastic Syndromes (MDS) is a heterogeneous group of clonal malignant hematopoietic stem cell disorders characterized by hyper- or hypocellular marrows, peripheral blood cytopenias, and cell function abnormalities resulting from failure of hematopoietic differentiation. It has a highly variable natural history with a variable risk of transformation to AML. The annual incidence of MDS in the US is 10-100 per million but might be higher in elderly.

Although chemotherapeutic agents including DNA methyltransferase inhibitors are used for treatment of AML and MDS, these two, often related, malignant disorders are the leading indications for allogeneic hematopoietic cell transplantation (HCT) in adults. The ability of the immune system to eliminate residual AML blasts or dysfunctional stem-cells in MDS has been demonstrated in the context of allogeneic stem cell transplantation with myeloablative as well as non-myeloablative conditioning regimens.

Even though allogeneic HCT is the treatment of choice for offering the curative option to patients with AML with unfavorable cytogenetics or molecular mutations as well as to patients with MDS, whether it should be offered to all patients in first remission of AML or to all patients with MDS is contested.

It is true that allogeneic HCT has the lowest risk of relapse of all therapeutic options for patients with AML and MDS, but transplantation-related mortality can be as high as 20-30%, which can counterbalance the potential advantages. The equilibrium between the increased anti-leukemic efficacy of allogeneic HCT and the risk of non-relapse mortality depends on many factors including the disease risk category, recipient age, donor type, and comorbidities.

In allogeneic HCT, even after histocompatibility matching, risk of recognizing the recipient cells as "foreign" by the donor cells exist. When this recognition happens, an immunological response is initiated by donor T-cells reacting against the recipient antigens. This phenomenon is known as the Graft Versus Host Disease (GVHD). GVHD is one of the major causes of post-transplant morbidity and mortality.

Novel conditioning regimens and immunosuppressive strategies for treatment of GVHD can and have extended the pool of patients eligible for transplantation at the same time as reducing toxic effects in these patients, however GVHD still remains as a significant complication for allogeneic HCT patients.

GVHD is categorized into two classes, acute and chronic, based on the timing of the onset after the transplant. Acute GVHD generally occurs within the first 100 days after the transplantation and often involves the skin, liver and the GI tract. Chronic GVHD occurs after 100 days post-transplant and can persist for several years.

There are two commonly used systems for grading of GVHD including the Glucksberg grade (I-IV) and the International Bone Marrow Transplant Registry (IBMTR) grading system (A-D) (Przepiorka D, et al., 1995, Rowlings, PA et al., 1997, Cahn JY et al., 2005). For the purpose of this study Glucksberg grading will be used (see section 7.18).

The current standard for initial GVHD therapy is methylprednisolone alone or in combination with immunosuppressive drugs, however, only 20-30 % of patients achieve complete responses (Deeg et al., 2001), where a complete response is a complete resolution of GVHD. The response to treatment of GVHD declines with increasing severity of the condition. Sixty to 95% of Grade II patients show some response to the 'standard of care,' but that declines to 15 to 40% for Grade III and to 0%-6% for Grade IV (Przepiorka et al., 1995). Failure of first line therapy of acute GVHD is a significant factor for poor 2-year survival: 10% survival rate for non-responders and 54% in responders (Pavletic et al., 1999).

A number of additional immunosuppressive drugs have been tested for the treatment of acute GVHD, but neither anti-thymocyte globulins (ATG), CD5-immunotoxins, Interleukin-1 (IL-1) antagonists nor monoclonal antibodies such as anti-IL-2 receptors and others have demonstrated an ability to control GVHD or improve overall patient survival (Martin et al., 1991; Remberger et al., 2001; Martin et al., 1996; Antin et al., 2002, Anasetti et al., 1994). Thus, development of new therapeutic agents and strategies are required to improve prophylaxis and management of acute GVHD and to decrease the toxicities of the immunosuppressive regimens.

1.3 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

PRO 140 is a humanized IgG4,κ monoclonal antibody (mAb) to the C-C chemokine receptor type 5 (CCR5), under development as a prophylactic agent for Acute Graft-Versus-Host Disease (GVHD).

Migration of donor cells, particularly T-cells, into different tissues including skin, liver and GI tract is critical in development of acute GVHD. Small molecules and monoclonal antibodies that block chemokine receptors such as CCR5, are in theory able to lessen the migration of donor cells into tissues. Therefore, blocking CCR5 after allogeneic stem cell transplantation may reduce the occurrence rates of GVHD. PRO 140 is a humanized monoclonal antibody directed against CCR5. This study will investigate the safety and efficacy of pharmacologic inhibition of CCR5 in prevention of acute GVHD by administering PRO 140 to adult patients with AML or MDS undergoing allogeneic HCT.

1.4 SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES

1.4.1 Pre-Clinical Studies with PRO 140

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

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

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

1.4.2 Impact of PRO 140 on homing of stem cells

From a previous in vitro study with PRO 140 (Insel et al., 2015) and from published research on the CCR5 (Robertson et al., 2006; Hutter et al., 2009), in addition to the discussions with the Key Opinion Leaders associated with this study, the evidence strongly suggests that binding of CCR5 by PRO 140 does not interfere with stem cell homing to the bone marrow given that:

iii) CCR5 does not seem to play a significant role in stem cell homing to the bone marrow, which is the target site in the treatment for acute myeloid leukemia and myelodysplastic syndromes;

iv) Complete absence of functional CCR5 does not preclude homing of stem cells to the bone marrow, which is the target site in the treatment for acute myeloid leukemia and myelodysplastic syndromes; therefore, a similar outcome is expected from cells expressing CCR5 and bound to PRO 140.

The in vitro study with PRO 140 (Insel et al., 2015) evaluated the antagonist/agonist activity of PRO 140 downstream of CCR5 binding in human CD4+ cells. Specifically, the study measured the levels of cAMP upon treatment of CD4+/CCR5+ human T-cells with G-protein-coupled receptor (GPCR) effectors and inhibitors in combination with PRO 140. The rationale was that, since CCR5 is a GPCR, a differential response in cAMP production or degradation would be observed in PRO 140, if it does interfere with CCR5 function in the context of G-protein-mediated modulation of cAMP and all associated downstream signaling pathways. The study concluded that PRO 140 does not interfere with the rolipram-activated synthesis of cAMP, but it does antagonize the RANTES-activated degradation of cAMP. Previous in vitro data from Progenics suggest that PRO 140 inhibits calcium transients downstream of CCR5 binding. Overall, these observations suggest that PRO 140 interferes with some but not all G-protein-dependent signaling pathways downstream of CCR5 binding.

The published study by Robertson et al. (Robertson et al., 2006) provides preclinical data suggesting that CCR5 is not involved in homing of stem cells to the bone marrow. This is evidenced by lower levels of CCR5 mRNA in cells homing to the bone marrow, compared to those homing to the thymus. Also, treatment with pertussis toxin (CXCR4 inhibitor) drastically reduced the number of cells homing to the thymus but did not alter the number of cells homing to the bone marrow. Finally, bone marrow cells lacking CCR5 showed no significant impairment in homing to either organ.

Furthermore, the published study by Hutter et al. (Hutter et al., 2009) refers to an HIV-1-positive subject who was treated for acute myeloid leukemia with two courses of allogeneic stem cell transplantation with CD34+ peripheral blood stem cells from an HLA-identical donor who was homozygous for CCR5-delta-32 (non-functional CCR5). In both instances, the treatment resulted in successful engraftment, suggesting that the absence of functional CCR5

receptors does not preclude stem cell homing.

1.4.3 Clinical Studies with PRO 140

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

1.4.3.1 PRO 140 1101 Study

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

1.4.3.2 PRO 140 1102 Study

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

1.4.3.3 PRO 140 1103 Study

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

1.4.3.4 PRO 140 1302 Study

The initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks. Subjects (n=39) were randomized to receive a single IV

injection of placebo or PRO 140 at doses of 0.5, 2, or 5 mg/kg. Subjects were monitored for antiviral effects, safety and PRO 140 pharmacokinetics (PK) for 58 days.

PRO 140 demonstrated potent, rapid, prolonged and dose-dependent antiviral activity. Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant effect on QTc intervals or other electrocardiographic parameters, and there were no remarkably laboratory findings.

1.4.3.5 PRO 140 2301 Study

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

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

1.4.3.6 PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks (Thompson, 2009). Placebo (n=10) and three PRO 140 doses were examined: 162 mg weekly for three weeks (n=11), 324 mg weekly for three weeks (n=11), and 324 mg biweekly (every other week) for two doses (n=12). Subjects were followed for 44 days after the final dose.

Potent, dose-dependent and highly statistically significant antiviral activity was observed. The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection (Thompson, 2009).

Subcutaneous PRO 140 was generally well tolerated both locally and systemically. There was no obvious dose-related pattern of toxicity. The most common adverse events (diarrhea, headache, lymphadenopathy and hypertension) were mild to moderate and self-resolving. These events are common in HIV infection and were reported with similar frequencies in the placebo and PRO

140 treatment groups. Administration-site reactions were mild, transient, and observed in a fraction of subjects.

1.4.3.7 PRO 140-CD01 Study

PRO 140_CD01 study (open-label, 40 subjects, multi-center) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution of antiretroviral therapy in HIV-1 infected patients (with exclusive CCR5-tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty (40) subjects (M/F: 37/3) with median age of 54.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-two out of 40 (55%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of≥ 400 copies/mL separated by at least 3 days. Of the 40 enrolled subjects, 3 subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37 subjects were found to have exclusive CCR5-tropic virus. Fifty-nine percent (59%) of R5-exclusive subjects compared to zero percent (0%) of D/M subjects experienced virologic success within 12 weeks of PRO140 monotherapy (p=0.0465). All virologic failure subjects who had available lab data in both studies achieved viral suppression to < 400 HIV-1 RNA copies/mL, as well as viral suppression to 'Non Detectable' or < 50 HIV-1 RNA copies/mL after re-initiation of ART.

The by-subject analysis of PhenoSense® Entry Assay data for PRO140, maraviroc, and AMD3100 shows no significant changes in the post-treatment IC50 and IC90 values were noted when compared with baseline values in virologic failure and non-virologic failure groups of subjects. As the aggregate analysis shows, the subjects who experienced virologic failure had higher IC90 value for PR0140 at baseline compared to subjects without virologic failure. The mean IC90 for subjects who experienced virologic failure was higher (10.84 µg/mL) than the IC90 for subjects without virologic failure (6.70 µg/mL) in the CD01 study (p=0.0115).

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

Safety data were analyzed for all 40 enrolled subjects. One (1) of 40 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-eight (28) of 40 subjects (70%) experienced one or more adverse events (AEs) after receiving at least

one dose of PRO140. The most commonly occurring AEs were infections and infestation conditions which were reported by 14 of 40 (35%) subjects. The majority of the reported AEs (63/89; 70.7%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported AEs (72/89; 80.8%) were deemed mild in nature.

This clinical study is complete and results are pending publication.

1.4.3.8 PRO 140-CD01 Extension Study

PRO 140_CD01-Extension study (open-label, 28 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 108 weeks) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels of≥ 400 copies/ mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy for up to 108 weeks.

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

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

PRO140 was generally well tolerated, and no drug-related SAEs were observed. Results for PhenoSense® Entry Assay, ADA and PK assessments and Serum Concentration of ART Drugs for the ongoing CD01-Extension study are expected to be available in 2017.

This clinical study is currently ongoing.

1.4.3.9 PRO 140-CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 150 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 in combination with either existing ART (failing regimen) or Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 150 adult patients with a documented history of genotypic or phenotypic resistance to ART drugs within one or more drug classes who demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy and have limited treatment options.

The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, potential for hypersensitivity to one or more ART drugs, or potential drug interactions with treatment for co-morbid conditions.

In Part 1 of double-blind treatment period, virally non-suppressed subjects will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days until HIV-1 genotypic drug resistance assay results are available to construct an OBT. The primary efficacy endpoint is proportion of participants with≥ 0.7 log10 reduction in HIV -1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

In Part 2 of double-blind treatment period, subjects will continue treatment with either PRO 140 or Placebo in combination with OBT for an additional 3 weeks until HIV-1 co-receptor tropism assay results are available, at which time subjects will move into the 24-week open-label period.

During the 24-week open-label period, subjects infected with only CCR5-tropic HIV-1 will receive PRO 140 + OBT, whereas subjects infected with D/M- or CXCR4-tropic HIV-1 will receive OBT alone during the 24-week open-label treatment period.

This clinical study is currently ongoing.

1.4.3.10 PRO 140-CD03 HIV Study

PRO 140_CD03 study (open-label, 300 subjects, multi-center) seeks to evaluate the 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. This clinical study is ready to start, pending approval.

Table 1-1: Clinical Studies with PRO 140

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

Protocol Number	Phase	No. of Subjects (Planned/ Analyzed)	Doses	Cell line used to make PRO-140	Subject Population	Comments
PRO 140 CD01	2b	40/40	350 mg SC weekly dose for 12 weeks of monotherapy (total treatment duration 14 weeks)	CHO	HIV-1 positive	Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; Open-label administration of PRO 140 demonstrated favorable tolerability, and potent, long-acting, antiviral activity.
PRO 140 CD_01-Extension	2b	16/16	350 mg SC weekly dose for 108 weeks of monotherapy (total treatment duration 109 weeks)	CHO	HIV-1 positive	This clinical study is currently ongoing with results expected to be available by the end of Q1 2017.
PRO 140 CD02	2b/3	150/Ongoing	350 mg SC weekly dose of PRO 140 or placebo along with existing ART for 1 week then PRO 140 along with optimized background therapy for 28 weeks (total treatment duration 29 weeks)	CHO	HIV-1 positive, treatment-experienced	This study is ongoing
PRO 140 CD03	2b/3	300/TBD	350 mg SC weekly dose for 46 weeks of monotherapy (total treatment duration 48 weeks)	CHO	HIV-1 positive, treatment-experienced	The study has been submitted to clinical sites and the start-up process is ongoing.

1.5 RATIONALE FOR DOSE SELECTION

For this proof of concept study with the indication of GVHD, the dose of 350 mg administered SC was chosen in light of dosages used in previous and ongoing human studies on HIV indication (especially PRO140-CD01 and PRO 140-CD02). Table 1-1 provides the summaries of clinical studies completed or ongoing using PRO 140. The dose of 350 mg weekly used in these studies was well tolerated with no dose limiting toxicities (DLT). The results of this study will determine the next steps to be taken in terms of dose selection to further develop PRO 140 for the indication of GVHD.

1.6 RISKS / BENEFITS ASSESSMENT

PRO 140 or placebo will be administered as add-on therapy to the standard GVHD prophylaxis treatments, thus there is no risk of discontinuing anti-GVHD therapy.

1.6.1 RISKS/DISCOMFORT TO SUBJECTS AND PRECAUTIONS TO MINIMIZE RISK

1.6.1.1 Allergic Reaction

PRO 140 belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions (fatigue, diarrhea, fever, vomiting, headache, nausea, pain at the site of injection, low blood pressure, rash, itching, and chills) or flu-like reactions such as fever, chills, and aches. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of PRO 140, infusion of proteins always carries with it the theoretical risk for anaphylactic shock. Accordingly, whenever PRO 140 is administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

1.6.1.2 Immune Response

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

1.6.1.3 Pregnancy

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

1.6.1.4 Venipuncture

Blood sampling is required as part of the study protocol. Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

1.6.1.5 Unknown Risks

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

1.6.1.6 Theoretical risk for increased severity of West Nile virus infection

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

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

1.6.2 Intended Benefit for Subjects

This is a proof of concept study for the purpose of evaluating safety and efficacy of PRO 140 for further clinical testing in acute GVHD indication. The most significant limitation with the current GVHD prophylaxis treatments has been the necessity and challenge of continued adherence to the medications, along with relatively high risk of occurring GVHD. This study provides opportunity to the subjects to have supervised SC treatments with PRO 140 as an add-on to their current GVHD prophylaxis regimen. Subjects participating in the present add-on therapy study will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

2 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of PRO 140 compared to placebo as an add-on therapy to standard GVHD prophylaxis in adult patients with AML or MDS undergoing allogeneic HCT.

The secondary objective of this study is to assess safety and tolerability of PRO 140 compared to placebo as an add-on therapy to standard GVHD prophylaxis in adult patients with AML or MDS undergoing allogeneic HCT.

Study Endpoints

Primary Efficacy Endpoint

- Incidence of Grade II, Grade III or Grade IV acute GVHD by Day-100

Secondary Efficacy Endpoints

- Incidence of severe and life-threatening (Grade III and Grade IV) acute GVHD by Day-100
- Incidence of organ-specific acute GVHD by Day-100
- Donor engraftment evaluated by T-cell and myeloid chimerism in peripheral blood
- Neutrophil and platelet count recovery
- Changes in ECOG performance score
- GVHD-free survival (GFS)

Safety Assessments

- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale) and by investigator-evaluation of injection site reactions
- Frequency of treatment emergent adverse events and serious adverse events
- AML or MDS relapse rate by Day-100
- Changes and shifts in laboratory measurements over time
- Changes in Electrocardiogram (ECG) parameters over time

3 STUDY DESIGN

3.1 STUDY CENTER(S)

Approximately up to 20 centers in the United States will enroll patients in this study.

3.2 STUDY POPULATION

This study will recruit 60 subjects with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes (MDS) undergoing allogeneic stem-cell transplantation.

3.3 ELIGIBILITY CRITERIA

3.3.1 Inclusion Criteria

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

1. Patients diagnosed with AML or MDS per below:
    - Patients with a history of histologically or pathologically confirmed diagnosis of AML and < 5% blasts in the peripheral blood or bone marrow (per bone marrow aspiration and/or biopsy within 6 weeks prior to screening) scheduled to undergo allogeneic stem-cell transplantation
    - Patients with a histologically or pathologically confirmed diagnosis of MDS with < 10% blasts in the bone marrow (per bone marrow aspiration and/or biopsy within 6 weeks prior to screening) scheduled to undergo allogeneic stem-cell transplantation
2. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2
3. Patients must have normal organ function as defined below:
    - <u>Myeloablative allogeneic HCT:</u>
        - Males and females, age ≥18 and ≤ 65 years of age
        - Total bilirubin ≤ 2 mg/dL (except in patients with Gilbert's Syndrome)
        - AST/ALT ≤ 3 times institutional upper limit of normal (except in patients with leukemic infiltration of liver)
        - Serum creatinine ≤ 2 mg/dL and creatinine clearance ≥ 60 ml/hr
        - Diffusing capacity of the lung for carbon monoxide (DLCO) > 50% predicted with no symptomatic pulmonary disease
        - Cardiac ejection fraction ≥ 50%. If between 40-49% a cardiology consult is required

- Clinically normal resting 12-lead ECG at screening visit or, if abnormal, considered not clinically significant by the PI

4. Patients must have a reasonable expectation of ≥ 6 months survival
5. The donor-recipient HLA match criteria required for participation in this protocol are not research subjects in this study and they must meet criteria as National Marrow Donor Program (NMDP) donors. Procedures for selection of donors and stem cell dose will follow FDA requirements for Blood Products (21 CFR 640) and Human Cellular and Tissue Based Products (21 CFR 1271). The standard institutional practices for stem cell transplants also will be followed. The donors are:

    - HLA-Identical Sibling (6/6): Minimal typing necessary is serologic typing for class I (AB) and molecular typing for class II (DRB1)
    - Matched Unrelated Donor (8/8): Molecular identity at HLA A, B, C and DRB1 by high-resolution typing
    - Matched Related and Unrelated Donor (7/8): high-resolution molecular typing at the following loci is required: HLA A, B, C and DRB1

6. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods (birth control pills, barriers, or abstinence) throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized). Females of childbearing potential must have a negative serum pregnancy test at Screening visit and negative urine pregnancy test prior to receiving the first dose of study drug.
7. Patients must understand and voluntarily sign an informed consent form

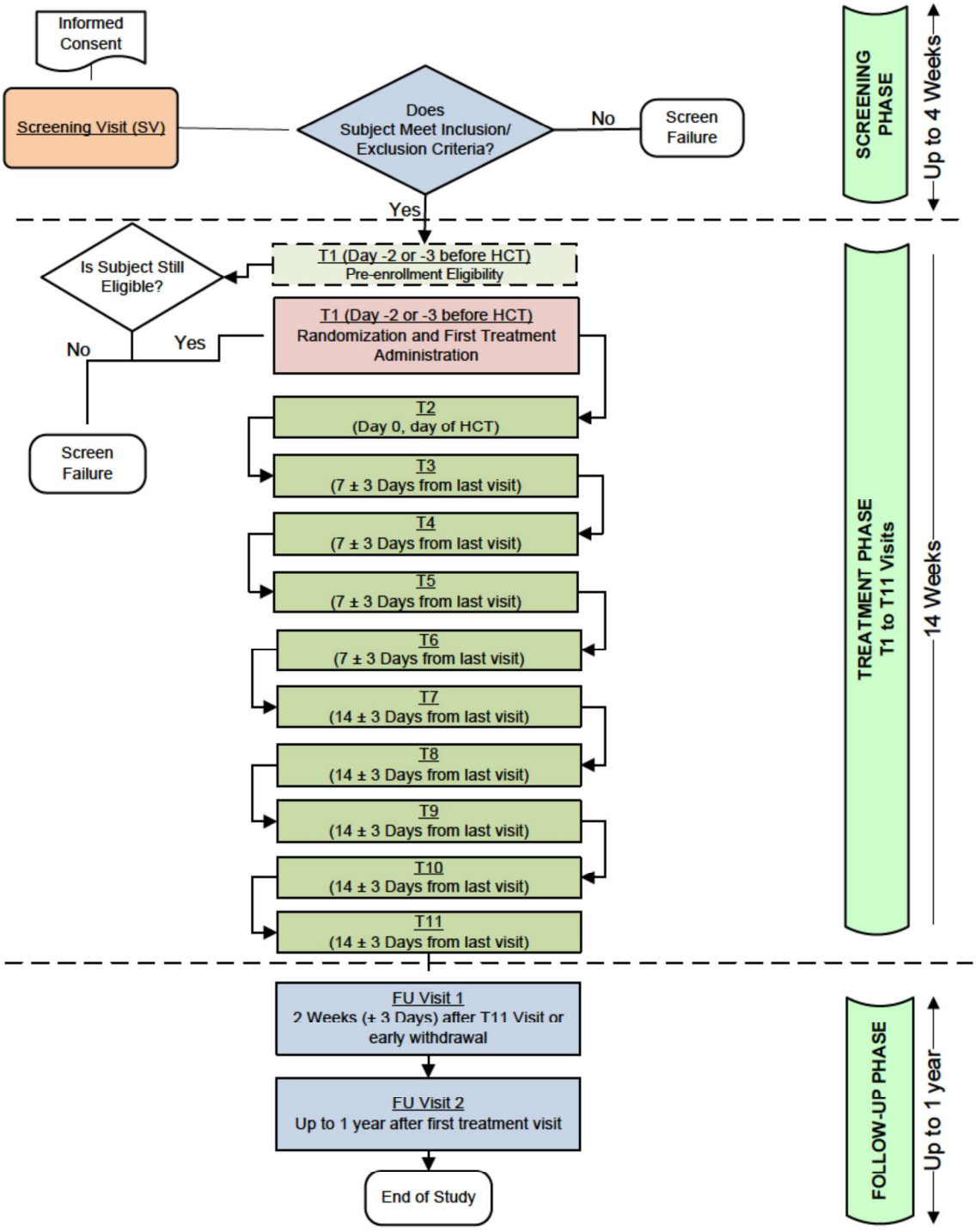
3.3.2 Exclusion Criteria

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

1. Patients not expected to be available for follow-up for at least 114 days after transplant
2. Patients who have received prior allogeneic stem cell-transplantation
3. Patients who receive post-transplant high dose cyclophosphamide
4. Patients with active central nervous system (CNS) involvement by malignant cells
5. Patients receiving other investigational drugs for GVHD. Co-enrollment in other clinical trials that do not include experimental GVHD therapies is allowed

6. Prior use of any experimental or approved CCR5 modulator including maraviroc and PRO 140
7. Patients with uncontrolled bacterial, viral or fungal infections including diagnosis of acute viral hepatitis (defined as any active infection with hepatitis A or a new diagnosis of hepatitis B or C within 24 weeks of dosing)
8. Currently active second malignancy other than non-melanoma skin cancers
9. Presence of fluid collection (ascites, pleural or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated
10. Patients who are HIV positive
11. Females who are pregnant, lactating, or breastfeeding, or who plan to become pregnant during the study
12. Subjects on chronic steroid therapy > 5 mg/day within 2 weeks of screening except for inhaled, nasal, or topical steroids
13. Any other clinical condition that, in the Investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy

Figure 3-1: Study Flow Diagram



4 STUDY SCHEDULE

This research study is divided into three study phases:

(1) **Screening Phase** (Screening to T1 Visit) begins with signing of Informed Consent and lasts up to 4 weeks (28 days).

(2) **Treatment Phase** (up to 14 weeks ± allowed windows). Eligible subjects will be randomized and receive up to 11 study treatments (PRO 140 or placebo), given on Day -3 or Day -2 prior to stem cell infusion, on the day of stem cell infusion (Day 0), and then weekly for 30 days (at Week 1, Week 2, Week 3 and Week 4) after which it will be administered every two weeks for up to 98 days (at Week 6, Week 8, Week 10, Week 12 and Week 14).

(3) **Follow-Up Phase** (up to one year). Subjects who have completed the Treatment phase or who have withdrawn from the study will be followed-up at 2 weeks after the last treatment visit and one year after first treatment visit.

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

Table 4-1: Schedule of Assessments

Study Phase		Screening Phase (up to 4 weeks)	Treatment Phase (14 weeks)											Follow-Up Phase (up to one year)		Unscheduled Visit
Visit		**Screening Visit**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**Follow-up Visit 1**	**Follow-up Visit 2**	
Weeks		**Up to -4 weeks**			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**52**	
Days		**Up to -28 days**	**Day -3/-2**	**Day 0**	**Day 7±3**	**Day 14±3**	**Day 21±3**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±3**	**Day 98±3**	**Day 112±3**	**Day 365±14**	
Procedures	**Protocol Section**															
Informed Consent[1]	Section 7.1	X														
Eligibility Evaluation[2]	Section 7.2	X	X													
Medical History[3]	Section 7.4	X	X													
Subject Demographic	Section 7.3	X														
Physical Examination	Section 7.6	X		X						X			X			X
Vital Signs[4]	Section 7.9	X	X	X		X		X	X	X	X	X	X	X	X	X
ECOG performance score	Section 7.10	X	X			X			X		X		X	X		X
Height and Weight	Section 7.9	X														X
ECG	Section 7.7	X	X					X			X		X	X		
Complete Blood Count (CBC)[5]	Section 7.11.1	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum Biochemistry[6]	Section 7.11.2	X	X			X		X	X	X	X	X	X	X		X
PPK	Section 7.11.3	X	X					X		X		X		X	X	
Urinalysis[7]	Section 7.11.8	X							X				X			
Serum Pregnancy Test[8]	Section 7.11.7	X							X				X			
Anti-idiotypic antibodies to PRO 140	Section 7.11.6		X[9]						X				X			

Study Phase		Screening Phase (up to 4 weeks)	Treatment Phase (14 weeks)											Follow-Up Phase (up to one year)		Unscheduled Visit
Visit		**Screening Visit**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**Follow-up Visit 1**	**Follow-up Visit 2**	
Weeks		**Up to -4 weeks**			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**52**	
Days		**Up to -28 days**	**Day -3/-2**	**Day 0**	**Day 7±3**	**Day 14±3**	**Day 21±3**	**Day 28±3**	**Day 42±3**	**Day 56±3**	**Day 70±3**	**Day 84±3**	**Day 98±3**	**Day 112±3**	**Day 365±14**	
Procedures	**Protocol Section**															
HIV rapid antigen test	Section 7.8	X														
Lymphocyte Phenotype Panel	Section 7.11.4			X		X		X		X			X			
T-cell and myeloid chimerism	Section 7.11.5							X		X			X		X	
Randomization	Section 7.12		X													
Administration of PRO 140 or Placebo	Section 7.13		X	X	X	X	X	X	X	X	X	X	X			
Grading GVHD – skin, gut, liver[10]	Section 7.17			X[1]	X	X	X	X	X	X	X	X	X	X		X
Injection Site Reaction Evaluation	Section 7.15		X	X	X	X	X	X	X	X	X	X	X			X
Injection Site Pain Assessment (VAS)[12]	Section 7.16			X	X	X	X	X	X	X	X	X	X			
Adverse Events	Section 9.1		X[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Meds	Section 7.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[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 will be recorded as Medical History up to the first randomized Treatment at Visit T1
[4] Post treatment vital signs will be recorded (sitting blood pressure, heart rate, respiration rate, and temperature)
[5] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, Absolute Neutrophil Count (ANC) and platelets
[6] Serum Biochemistry:

- Hepatic function indicators: total and direct bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total

protein, Lactate dehydrogenase (LDH)
- Renal function indicators: Blood Urea Nitrogen (BUN), creatinine
- Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
- Other: glucose (random), cholesterol (total)

[7] ONLY for women of childbearing potential
[8] Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, RBC, WBC, epithelial cells, bacteria, casts, crystals
[9] Anti-idiotypic antibodies to PRO 140 at visit T1 to be performed prior to dosing
[10] For GVHD diagnosis and grading refer to sections 7.17 and 7.18
[11] After PRO 140 or Placebo dosing
[12] Injection Site Pain Assessment (VAS) will be performed prior to study treatment administration beginning at visit T2 (to assess the average pain felt at the injection site since the last injection)

4.1 SCREENING PHASE

4.1.1 Screening Visit

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent. The subject screening number will incorporate a two-digit Study Center number (01, 02 or 03….) and a three-digit numeric ID assigned in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site (e.g. 01-001 or 02-001).

Subject Screening # : **XX - YYY**

XX=Study Center YYY=Subject Numeric ID

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

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

1. Medical history (section 7.4),
2. Subject demographics (section 7.3),
3. Physical examination (section 7.6),
4. Vital Signs (section 7.9),
5. Body Weight & Height measurements (section 7.9)
6. Eastern Cooperative Oncology Group (ECOG) performance status (section 7.10)
7. Prior and current medications review (section 7.5),
8. Electrocardiogram (ECG) (section 7.7)
9. Collection of Blood Specimens for:
    - Complete Blood Count (CBC) w/diff (section 7.11.1)

- Biochemistry (section 7.11.2)
- Serum pregnancy test, for female subjects of childbearing potential (section 7.11.7). Childbearing potential is defined as someone who is not surgically sterile or is not more than one year past complete cessation of menstrual cycles.

10. Collection of Urine Specimen for Urinalysis (section 7.11.8)
11. HIV rapid antigen testing (section 7.8)

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

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

Eligible subjects that are not enrolled within 28 days of Screening Visit will have screening lab assessments repeated to reconfirm eligibility.

4.2 TREATMENT PHASE

Subjects who meet all eligibility criteria, as per data gathered from Screening Visit and who stay eligible for the study are to be randomized and treated.

4.2.1 Treatment Visit-1 (T1)

Treatment Visit 1 (T1) will happen -2/-3 days prior to the transplant. The following assessments will be performed at the T1.

Pre-Treatment

- Confirmation of eligibility criteria by reviewing test results and other criteria assessments performed at the Screening Visit (section 7.2)
- Any changes in concomitant medications (section 7.5)
- Any changes in medical history since Screening Visit (section 7.4),
- ECOG performance status (section 7.10)

12. ECG (section 7.7),

- Collection of Blood Specimens for:
  - CBC w/diff (section 7.11.1)
  - Serum Biochemistry (section 7.11.2)
- Randomization (see section 7.12)

Administration of Study treatment (PRO 140 or Placebo)

All eligible subjects who are randomized will receive either PRO 140 350 mg or placebo as subcutaneous injection in the abdomen. A total of 350 mg (175 mg/mL) is delivered as two 1 mL injections on opposite sides of the abdomen. The study treatment (PRO 140 or placebo SC injections) will be administered by a licensed medical professional (MD, DO, PA, LPN, LVN, NP, or RN).

Post-Treatment

- Injection Site Reaction Assessment (see section 7.15)
  - **Note:** *To assess injection site reactions, refer to the investigator injection site reaction table (refer to section 17.1).*
- Injection Site Pain Assessment (VAS) (section 7.16)
- Vital Signs (see section 7.9) will be assessed within 15 minutes of study treatment administration.
- Assessment of Adverse Events (AE) (see section 9)

4.2.2 Treatment Visit-2 (T2) - Stem Cell Infusion (Day 0)

The following assessments will be performed on Treatment Visit-2:

- Assess for any Adverse Events and changes in Concomitant medications (section 9 and 7.5)
- Physical examination (section 7.6)
- Vital Signs (section 7.7)
- Collection of Blood Specimens for
  - CBC (section 7.11.1)
  - Lymphocyte Phenotype Panel (section 7.11.4)
- Study Treatment Administration (PRO 140 or Placebo) (section 7.13)

- Stem cell infusion will be conducted post-study treatment administration (as per institutional guidelines; see section 7.19)
- Diagnosis and Grading of GVHD (section 7.17 and 7.18)
- Injection Site Reaction Assessment (section 7.15)
  - **Note:** *To assess injection site reactions, refer to the investigator injection site reaction table (refer to section 17.1).*
- Injection Site Pain Assessment (VAS) (section 7.16)

4.2.3 Treatment Visit-3 to Treatment Visit-11 (T11)

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

- Assess for any Adverse Events and changes in Concomitant medications (section 9 and 7.5),
- Diagnosis and Grading of GVHD (section 7.17 and 7.18)
- Physical examination (section 7.6) (at T8, T11)
- Vital Signs (section 7.9), (at T4, T6, T7, T8, T9, T10, T11)
- ECOG performance status (section 7.10) (at T4, T7, T9, T11)
- ECG (section 7.7) (at T6, T9, T11)
- Collection of Blood Specimens for:
  - CBC w/diff (section 7.11.1)
  - Serum biochemistry (section 7.11.2) (at T4, T6, T7, T8, T9, T10, T11)
  - Serum pregnancy test, for female subjects of childbearing potential (section 7.11.7) (at T7 and T11)
  - Anti-idiotypic antibodies to PRO 140 (section 7.11.6) (at T7 and T11)
  - Lymphocyte Phenotype Panel (section 7.11.4) (at T4, T6, T8 and T11)
  - T-cell and myeloid chimerism (section 7.11.5) (at T6, T8 and T11)
- Collection of Urine Specimen for Urinalysis (section 7.11.8) (at T7 and T11)
- Study Treatment Administration (PRO 140 or Placebo) (section 7.13)
- Injection Site Reaction Assessment (section 7.15)

- **Note:** *To assess injection site reactions, refer to the investigator injection site reaction table (refer to section 17.1).*

- Injection Site Pain Assessment (VAS) (section 7.16)

4.3 FOLLOW-UP PHASE

4.3.1 Follow-Up Visit 1

The follow-up visit 1 will occur two (2) weeks after the last treatment visit. The following assessments will be performed at the follow-up visit 1, unless otherwise specified:

- Assess for any Adverse Events and changes in Concomitant medications (section 9 and 7.5),
- Vital Signs (section 7.9),
- ECOG performance status (section7.10)
- Collection of Blood Specimens for
  - CBC w/diff (section 7.11.1)
  - Serum biochemistry (section 7.11.2)
- ECG (section 7.7)
- Grading GVHD – skin, gut, liver (section 7.17)

4.3.2 Follow-up Visit 2

The follow-up visit 2 will occur one year after the first treatment visit. The following assessments will be performed at the follow-up visit 2, unless otherwise specified:

- Assess for any Adverse Events and changes in Concomitant medications (section 9 and 7.5),
- Vital Signs (section 7.7),
- Collection of Blood Specimens for:
  - T-cell and myeloid chimerism (section 7.11.5).

5 SUBJECT COMPLETION AND WITHDRAWAL

5.1 SUBJECT COMPLETION

A subject who completes the 14-week Treatment Phase and 2-week Follow-Up Phase will be considered as having completed the study.

5.2 SUBJECT WITHDRAWAL

A subject who is randomized but does not complete the study, as defined in section 5.1, is considered to have prematurely withdrawn from the Study.

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

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

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

- A subject is significantly non-compliant with the requirements of the protocol.
- The investigator determines that it is in the best interest of the subject.
- Subject chooses to withdraw or is withdrawn due to an adverse event specified in section 9.1.9
- A subject becomes pregnant

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

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

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

5.2.1 Data Collected for Withdrawn Subjects

Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Patients who have study treatment discontinued will continue to be followed, per protocol, whenever possible. Patients who have study treatment

discontinued due to a serious adverse event will be followed until resolution or stabilization of the event.

In the event that a subject is withdrawn from the study at any time due to an adverse event or serious adverse event (SAE), the procedures stated in Section 9.1.1 or 9.2.1, respectively must be followed.

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

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

5.3 SCREEN FAILURES

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

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

6 STUDY TREATMENTS

6.1 INVESTIGATIONAL PRODUCT DESCRIPTION

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

Kits will be labeled with a unique identification number. Each kit used during the Treatment Phase will contain two vials of PRO 140 or Placebo for SC injection. One milliliter (1 mL) of PRO 140 or placebo solution will be drawn from each vial and loaded into the syringe. A total of 350 mg (175 mg/mL) of PRO 140 or placebo is delivered as two 1 mL injections administered subcutaneously on opposite sides of the abdomen. One study injection kit will be assigned per subject per treatment visit.

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

Each vial of the Placebo contains 5mM Histidine, 15 mM Glycine, 95 mM Sodium Chloride, 0.3% (w/v) Sorbitol, 0.005% (w/v) Polysorbate 20 at a pH of 5.5.

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

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

Table 6-1: Investigational Product - PRO 140/Placebo at Treatment visits

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.) on opposite sides of abdomen	SC injection
Placebo	Parenteral solution	0 mg/mL	2 injections of placebo (2 X 1 mL/inj.) on opposite sides of abdomen	SC injection

6.2 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

The contents of each vial are described in section 6.1. PRO 140 and placebo kits will be labeled with information such as: study protocol #; fill volume; concentration; storage condition; a “use

as per study protocol" statement; a cautionary statement; Sponsor's name and address; and the kit number.

Below are representative samples of the Investigational Product individual vial (Figure 6-1), syringe label (Figure 6-2), and kit labels (Figure 6-3) designated for use in this clinical protocol. Each kit contains two labeled vials and two syringe labels.

Figure 6-1: Investigational Product - Vial Label

Protocol: PRO 140_CD 03_GVHD Kit No. xxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) or placebo solution for subcutaneous injection Store at 2°C to 8°C (36°F to 46°F) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA	Protocol: PRO 140_CD 03_GVHD Kit No. xxx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) or placebo solution for subcutaneous injection Store at 2°C to 8°C (36°F to 46°F) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-2: Investigational Product - Syringe Label

Protocol: PRO 140_CD 03_GVHD Contents of Kit No. xxx This syringe contains 1 mL PRO 140 (175 mg/mL) or placebo solution for subcutaneous injection USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-3: Investigational Product - Kit Label

Protocol: PRO 140_CD 03_GVHD Kit No. xxx

Site No. _____ Subject No. _____

This kit contains 2 single-use vials

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

Store at 2°C to 8°C (36°F to 46°F)

USE AS PER STUDY PROTOCOL

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

CytoDyn Inc., Vancouver, WA, USA

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

6.3 INVESTIGATIONAL PRODUCT STORAGE

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

The site must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

6.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

Guidelines for dose preparation can be found in the study pharmacy manual.

PRO 140 will be provided to the administering personnel in single-use syringes prepared from vials of study drug stored at 2-8°C at the site pharmacy prior to use. Each of two syringes is filled to deliver 1.0 mL of study drug.

Equivalent volumes of study drug will be administered subcutaneously on opposite sides of the abdomen.

A 25-guage needle should be used to remove IP from vial and for administration of IP to subjects. IP should be administered slowly over 15 seconds per mL.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as described in section 17.1.

All doses of study drug will be prepared by the credentialed pharmacist and will be administered as SC injection by a licensed medical professional (MD, DO, PA, LPN, LVN, NP, or RN).

Note: It is preferred that the same injection site be used throughout the study. At the same time, it is not recommended to inject the study drug into areas where skin shows signs of a previous injection site reaction(s). It is advised to change the injection site if any previous injection site reaction remains unresolved.

6.5 Investigational Product Receipt and Accountability

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

6.6 Investigational Product Disposition

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

7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1 INFORMED CONSENT

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

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

7.2 ASSESSMENT OF ELIGIBILITY

During the Screening Phase and at T1 Visit (prior to randomization), the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and Exclusion criteria of this Protocol are described in sections 3.3.1 and 3.3.2. If the subject is not suitable or eligible for the trial then the subject will be a screen failure. Screen failure subjects may be re-entered into the study at a later time and re-screened.

7.2.1 Re-screening

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

7.3 DEMOGRAPHIC INFORMATION

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

- Date of birth
- Gender

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

7.4 MEDICAL HISTORY

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

- All ongoing medical conditions
- Baseline diagnosis requiring stem cell transplant, including AML or MDS
- Date of diagnosis
- Any prior medical conditions that have resolved within the last year

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

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

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

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of onset/diagnosis
- History status (resolved or ongoing)
- Date of resolution, if applicable

7.5 PRIOR / CONCOMITANT MEDICATIONS AND NON-STUDY TREATMENTS

A complete history of current therapies will be recorded in the source documents and on the appropriate page of the eCRF.

In addition to this, all other medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded. Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing)

Please refer to Exclusion Criteria (section 3.3.2) for a list of prohibited treatments and/or procedures. All other medications that are appropriate for the care of the subject may be prescribed. If concomitant medications are started during the study, the indication for the concomitant medication should be recorded as an AE if it meets the criteria.

7.5.1 Excluded Medications and Therapies

Cyclophosphamide and CCR5 inhibitors other than PRO 140 (ex. maraviroc) are prohibited during this study.

7.5.2 Allowable Medications and Therapies

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

7.6 PHYSICAL EXAMINATION

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

- Head, Ears, Eyes, Nose, Throat (HEENT)
- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject; i.e., the abnormality is clinically significant (CS).

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance. After administration of the first dose of study treatment, each physical exam abnormality that is considered to be clinically significant will be recorded as an AE.

7.7 ELECTROCARDIOGRAM

12-lead ECG will be conducted and 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. Each treatment-emergent abnormality that is considered to be clinically significant will be recorded as an AE. Each ECG should be signed by a physician.

7.8 HUMAN IMMUNODEFICIENCY VIRUS (HIV) RAPID ANTIGEN TEST

Test should be performed per the site standard kits and procedures. The result reports will need to be reviewed and signed by the Investigator.

7.9 VITAL SIGNS, HEIGHT AND WEIGHT

Vital signs collected during the Treatment Phase will be performed post-treatment, assessed within 15 minutes following study treatment administration. Height and weight will be assessed only at Screening and unscheduled visits.

The following will be collected:

- Height and weight; BMI will be calculated using high and weight measurements

- Systolic and diastolic blood pressure (taken after the subject has been seated for at least 5 minutes)
- Heart Rate (HR)
- Respiration Rate (RR)
- Temperature

7.10 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status test is used to evaluate the patients' level of functioning per Table 7-1 below:

Table 7-1: ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

7.11 Clinical Laboratory Assessments

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

7.11.1 Routine CBC

- Includes hemoglobin, hematocrit (HCT), red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count (%), absolute neutrophils count (ANC) and platelets count.
    - *Note: Platelet recovery will be defined as post-transplant increase in platelet levels to greater than 20,000/µL on two consecutive counts at least 2 days apart, if no platelet transfusion is given on or between the days of the two counts and the second platelet count is at least as high as the first. The date of platelet recovery will be defined as the day of the first eligible count per above. Neutrophil*

recovery will be defined as an increase in absolute neutrophil count (ANC) to greater than 500/µL on 2 consecutive days. The date of neutrophil recovery will be defined as the day of the first count above the threshold.

7.11.2 Biochemistry

- Biochemistry profile includes assessment of:

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

  Renal function indicators: Blood Urea Nitrogen (BUN), creatinine

  Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

  Other: glucose (random), cholesterol (total)

7.11.3 Population Pharmacokinetics

- Blood samples will be collected and evaluated per the study schedule of assessments.

7.11.4 Lymphocyte phenotype panel

- Lymphocyte phenotype panel will be performed and evaluated per the study schedule of assessments.

7.11.5 T-cell and Myeloid chimerism evaluation

- T-cell and myeloid chimerism tests will be evaluated per the institutional standards.

7.11.6 Anti-idiotypic antibodies to PRO 140

- The first samples for anti-idiotypic antibodies for PRO 140 may be collected at the T1 prior to first dose of PRO 140

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

7.11.7 Serum pregnancy test

- Only for female subjects of childbearing potential. Childbearing potential is defined as someone who is not surgically sterile or is not more than one year past complete cessation of menstrual cycles.

7.11.8 Urinalysis

- Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, RBC, WBC, epithelial cells, bacteria, casts, crystals

All laboratory reports will be reviewed by the Investigator.

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

7.12 RANDOMIZATION

Subjects who are eligible to participate in the trial will be randomized to one of the treatment groups via IWRS (Interactive Web Based Randomization System) at the T1 Visit prior to IP administration. The randomization will be central and will use mixed block size of 2 and 4 with a 1:1 ratio of Active Treatment to Control Treatment to ensure even distribution of Active and Control subjects. A randomization plan that details the stratification and randomization will be developed.

7.13 PRO 140 ADMINISTRATION

PRO 140 will be administered -2/-3 days before the stem cell infusion, on the day of stem cell infusion (Day 0) and thereafter on days 7, 14, 21, 28, 42, 56, 70, 84 and 98 as per the study schedule of assessments (Table 4-1).

Refer to section 6.4 for details on the procedure of PRO 140 administration.

7.14 STANDARD OF CARE

For the purpose of this study, the combination regimen of tacrolimus plus methotrextate per below will be considered as standard of care (Ratanatharathorn et al., 1998 and Ruutu et al., 2014):

- For tacrolimus the starting dose of 0.02-0.03 mg/kg/day will be initiated on day -1 of transplant by continuous IV infusion to target whole blood levels of tacrolimus between 5 and 10 ng/ml. The route of administration will be converted from IV to oral at the ratio of 1:3 to 1:4 when patients are able to tolerate oral intake. When a patient is switched from IV to oral tacrolimus, the target for blood levels of tacrolimus will be kept at approximately 10 ng/ml. For dose modifications institutional standards will be followed.
- For methotrexate the initial dose will be a minimum of 5 mg/m^2 on day +1 after the transplant. Three additional doses of minimum 5 mg/m^2 are given on days +3, +6 and +11 after the transplant. The day +11 dose is omitted in case of any toxicity of grade II or higher. The drug is given as bolus IV injection. For dose modifications institutional standards will be followed.

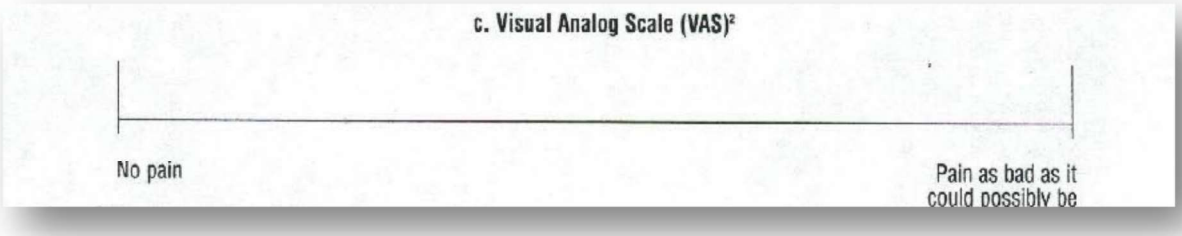
7.15 Injection Site Reaction assessment

At each visit during the Treatment Phase, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded by the Investigator starting after the first injection is given. Refer to sections 9.1.8 and 17.1 for more details.

7.16 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). Subjects will be asked to mark the point that best represents the average pain intensity at the injection site over the past week 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. The first VAS assessment will occur prior to study treatment administration at visit T2.

Figure 7-1: Sample Visual Analog Scale



7.17 ACUTE GVHD DIAGNOSIS

GVHD diagnosis will be confirmed by biopsies of organs involved per the institutional standards, when the clinical features are consistent with GVHD. The diagnosis and biopsy results must be confirmed by the PI on the source documents and entered into the eCRF.

7.18 ACUTE GVHD CLINICAL GRADING AND STAGING

Acute GVHD grading and staging will be performed by the Investigator as per procedures described in the Technical Manual of Procedures version 3.0 and dated 19 March 2013 (Blood and Marrow Transplant Clinical Trials Network):

- Assessment of the clinical acute GVHD using the form Clinical Acute GHVD (see Figure 7-2);
- Assessment of the GVHD staging using the GVHD Staging table (see Table 7-2);
- Assessment of the GVHD grading using the GVHD Grading Scale (see Table 7-3);
- Assessment of the GHVD index using the CIBMTR GHVD Index (see Table 7-4).

Figure 7-2: Clinical Acute GVHD Assessment

Clinical Acute GVHD Assessment

Date _____ Patient ID _____ Karnofsky/Lansky _____

	Code							Differential Diagnosis						
	0	1	2	3	4	5		GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	☐	☐	☐	☐	☐		% body rash:____	☐	☐	☐		☐		_____
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____	☐	☐	☐	☐	☐		_____
Upper GI	☐	☐						☐	☐	☐	☐	☐		_____
Liver	☐	☐	☐	☐	☐		Max bili: _____	☐	☐	☐	☐	☐	☐	_____

Treatment: ☐ CSA ☐ Tacrolimus ☐ Pred ☐ Methylpred ☐ Ontak
☐ Pentostatin ☐ MMF ☐ Etanercept ☐ Other _____

Code Definitions:

Skin:
0 No rash
1 Maculopapular rash, <25% of body surface
2 Maculopapular rash, 25-50% of body surface
3 Generalized erythroderma
4 Generalized erythroderma with bullous formation and desquamation

Lower GI (Diarrhea):
0 None
1 ≤500 mL/day or <280 mL/m²
2 501-1000 mL/day or 280- 555 mL/m²
3 1001-1500 mL/day or 556- 833 mL/m²
4 >1500 mL/day or >833 mL/m²
5 Severe abdominal pain with or without ileus, or stool with frank blood or melena

Upper GI:
0 No protracted nausea and vomiting
1 Persistent nausea, vomiting or anorexia

Liver (Bilirubin):
0 <2.0 mg/dl
1 2.1-3.0 mg/dl
2 3.1-6.0 mg/dl
3 6.1-15.0 mg/dl
4 >15.1 mg/dl

Signature _____

Table 7-2: GVHD Staging

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500ml/d or persistent nausea	Bilirubin 2-3mg/dl
2	25-50%	> 1000 ml/d	Bilirubin 3-6 mg/dl
3	> 50%	> 1500 ml/d	Bilirubin 6-15 mg/dl
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dl

Table 7-3: CONSENSUS GVHD Grading (Przepiorka D, et al., 1995)

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

Table 7-4: CIBMTR GVHD Index (Rowlings et al., 1997)

Stage	Skin	GI	Liver
A	Stage 1	0	0
B	Stage 0-2 or	0-2 or	0-2
C	Stage 3 or	3 or	3
D	Stage 4 or	4 or	4

7.19 STANDARD INSTITUTIONAL PRACTICES FOR STEM CELL INFUSION

Procedures for selection of donors and stem cell dose will follow FDA requirements for Blood Products (21 CFR 640) and Human Cellular and Tissue Based Products (21 CFR 1271). The standard institutional practices for cell transplants will also be followed including the use of G-CSF, irradiations and infection prophylaxis. The inclusion criteria for peripheral blood stem cell (PBSC) donors are detailed in section 3.3.1 of this study.

The sources of stem cells to be used in this study will consist only of bone marrow and peripheral blood. The cord blood will be excluded as graft source to avoid confound incidence of GVHD. Minimum recommended doses for each of stem cells source will be as follows:

- Bone marrow: minimum of 2 x 10^6 $CD34^+$ cells/kg of recipient's body weight;
- Peripheral blood: minimum of 2 x 10^6 $CD34^+$ cells/kg of recipient's body weight.

7.19.1 Conditioning Regimen of Stem Cells

For the purpose of this study, only myeloablative conditioning regimens will be used. Total Body Irradiation (TBI) and chemotherapy conditioning regimens can be used in concordance with the clinical site's standard procedures. The clinical sites should use chemotherapy with or without TBI with the minimum cumulative dosages mentioned below:

- TBI at 1200 cGy;
- Cyclophosphamide at 120 mg/kg;
- Etoposide at 60 mg/kg;
- Melphalan at 100 mg/m^2;
- Busulfan at 12 mg/kg;
- Fludarabine at 160 mg/m2;
- In case that TBI is used with combination of Busulfan and fludarabine, the minimum dose of TBI will be 400 cGy.

8 STATISTICAL CONSIDERATIONS

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

8.1 TREATMENT GROUPS

This is a placebo-controlled study. The following treatment groups will be assessed:

Group	Description
Active Treatment	Standard GVHD prophylaxis + PRO140
Control Treatment	Standard GVHD prophylaxis + Placebo

8.2 DESCRIPTION OF STUDY ENDPOINTS

8.2.1 Primary Efficacy Endpoint

- Incidence of Grade II, Grade III or Grade IV acute GVHD by Day-100

8.2.2 Secondary Efficacy Endpoints

- Incidence of severe and life-threatening (Grade III and Grade IV) acute GVHD by Day-100
- Incidence of organ-specific acute GVHD by Day-100
- Effect of PRO 140 or Placebo on donor engraftment by T-cell and myeloid chimerism in peripheral blood
- Effect of PRO 140 or Placebo on neutrophil and platelet count recovery
- Changes in ECOG performance score
- GVHD-free survival (GFS)

8.2.3 Safety Assessments

- Tolerability of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale) and by investigator-evaluation of injection site reactions
- Frequency of treatment emergent adverse events and serious adverse events

- AML or MDS relapse rate by Day-100
- Changes and shifts in laboratory measurements over time
- Changes in Electrocardiogram (ECG) parameters over time

8.3 SAMPLE SIZE DETERMINATION AND RATIONALE

For this two arm clinical trial, it is planned to have a total of 60 subjects (30 per treatment group). The sample size is on the basis of clinical judgment and not based on statistical power calculation. The number of subjects was deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

8.4 RANDOMIZATION, STRATIFICATION AND BLINDING

This is a double-blind, multi-center randomized clinical trial. The randomization will be central and will use mixed blocks of 2 and 4 with a 1:1 ratio of Active to Control to ensure even distribution of Active and Control subjects.

Randomization will be conducted via a Web based system, and the process for the blinding requirements will be outlined in the study randomization plan. To decrease the effect of HLA-Matched Unrelated Donor (MUD) vs HLA-Mismatched Related Donor (MRD) as a confounding factor in this study, the donor source will be used as a stratification factor. This stratification will allows us to achieve a balanced randomization scheme with more reliable interpretation.

8.5 INTERIM ANALYSIS

There will be a safety interim analysis after the first 10 subjects complete the treatment or withdraw from the study, whichever occurs first. The data from this interim analysis will be reviewed by an independent Data Monitoring Committee (DMC). The DMC responsibilities will be further elaborated in the study DMC charter.

There is no planned interim analysis for efficacy.

To protect the integrity of the blinded data, the IA will be conducted based on a Standard Operating Procedure for Interim Analysis that has a well-established firewall to protect the integrity of the trial. The details of the IA, including the below bullet points, are included in the Statistical Analysis Plan (SAP) for the study.

- The goals of the IA
- IA procedures for data preparation
- IA procedures for conduct of the analysis
- Data to be shared with the DMC

- Information to be shared with the sponsor after the IA
- The stopping rule
- Protection of Type I error rate and adjustments

8.6 GENERAL STATISTICAL CONSIDERATIONS

8.6.1 Analysis Populations

8.6.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as the set of subjects who are randomized to PRO 140 or placebo. The ITT population will be the primary analysis population for the analysis of primary and secondary endpoints.

8.6.1.2 Per Protocol Population

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

8.6.1.3 Safety Population

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

8.6.2 Statistical Methods

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later.

8.6.3 Prognostic Factors/Covariates

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

8.6.4 Handling of Missing Data

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

8.7 DATA SUMMARY

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

All statistical tests will be 2-sided and a 0.05% significance level will be used throughout the analyses.

8.7.1 Subject Disposition

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

8.7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Gender, HIV rapid antigen test, etc.) will be summarized using appropriate descriptive statistics.

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

8.7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Safety population. All prior and concomitant medications recorded in the CRFs will be coded to matching Anatomic Therapeutic Classification (ATC) codes using World health Organization (WHO) drug dictionary. Summaries will be prepared using the coded terms. All prior and concomitant medications recorded in the eCRFs will also be listed.

8.7.4 Administration of Study Drug

All the data from administration of study drug will be summarized and/or listed appropriately.

8.7.5 Efficacy Analysis

8.7.5.1 Primary Analysis

The primary analysis will be conducted on the ITT population.

The primary efficacy endpoint for this study is the incidence of ≥ Grade II acute GVHD by Day +100.

Chi-square/ Fisher's exact test will be used to compare the primary endpoint between the treatment groups.

All data from the secondary endpoints will be summarized and tabulated according to the variable type:

- Continuous data summaries will include:
  - Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group
  - For inferential statistics, if the Normality assumption is met, t-test will be used and if the Normality assumption is not met, a non-parametric method will be used.
- Categorical data summaries
  - Frequencies and percentages will be presented by treatment group.
  - For inferential statistics Chi-square or fisher's exact test will be used.

8.7.5.2 Supportive Analysis

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

8.7.6 Safety Analysis

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

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

8.7.6.1 Adverse Events

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

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

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

8.7.6.2 Tolerability Assessment

All data from tolerability assessments of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale) and by investigator-evaluation of injection site reactions will be summarized.

8.7.6.3 Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized.

8.7.6.4 Physical Examination

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

8.7.6.5 Vital Signs

All vital sign assessment findings will be listed and summarized.

8.7.6.6 ECG Examination

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

8.7.6.7 AML or MDS relapse rate by Day-100

AML or MDS relapse rate by Day-100 will be presented.

9 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

9.1 ADVERSE EVENT

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the Investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

9.1.1 Reporting of Adverse Events

Report initiation for all AEs and SAEs will begin at the time of the first treatment and continue up until the final study visit (i.e. up to the Follow-up visit). All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

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

9.1.2 Impact of Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol, or if the outcome of the event was "death".

9.1.3 CTCAE Grade (Severity) Assessment

The investigator will carefully evaluate the comments of each subject and the response to treatment in order to judge the true nature and severity of the AE. To assess severity, the

investigator will use the guidelines outlined in CTCAE v4.03. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 9-1: CTCAE v4.03 General Guidelines

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

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

9.1.4 Causality Assessment

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

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a

known response pattern to treatment with the study treatment.

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

9.1.5 Treatment Given as a Result of the Event

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

9.1.6 Outcome Assessment

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

9.1.7 Expected / Anticipated Adverse Events

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

9.1.8 SC Injection-related Events

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

SC Injection-site reactions thought to be directly related to the injection are considered to be AEs of special interest, and a separate guideline for the acquisition of data related to this AE of special interest is provided in section 17.1.

9.1.9 Stopping Rules for PRO 140

Subjects who develop Grade 1 or Grade 2 adverse events will continue per protocol. If a subject chooses to discontinue study treatment, the site should notify the protocol team leadership, and encourage the subject to complete any remaining study visits until the toxicity resolves.
For subjects who develop Grade 3 or higher adverse events per below, or experience graft failure or relapse the study treatment will be permanently discontinued:

- Grade 3 or higher liver toxicity not attributable to other causes such as infection, GVHD or Sinusoidal Obstruction Syndrome (SOS);
- Grade 3 or higher toxicity which is assessed by the investigator to be definitely, probably or possibly related to the study drug;
- Graft failure or relapse;

9.1.10 Study Stopping Rules

Upon occurrence of any of the following events, data will be reviewed by the Data Monitoring Committee (DMC):

1. Occurrence of a Grade 4 toxicity or two (2) occurrences of Grade 3 toxicities that are assessed to be definitely, probably or possibly study drug-related by the treating investigator;
2. Occurrence of more than 20 percent mortality by day +100;
3. Occurrence of more than 5 percent graft failures by day +100;
4. Occurrence of 5 or more of the first 10 subjects experiencing acute Grade II-IV GVHD.

The DMC will make a recommendation to the study investigators, who, in consultation with the sponsor will decide whether to stop enrollment in the study.

9.2 SERIOUS ADVERSE EVENTS (SAE)

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the AE)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.1 Reporting of SAE

The Investigator is required to report all SAEs that occur during the time period specified in section 9.1.1. Once the Investigator becomes aware of an SAE, he/she must report the SAE to [redacted]

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

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)).

9.2.2 SAE Follow-Up

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

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

9.2.3 Pregnancy

If a pregnancy occurs in a subject or partner of a male subject during the study, it must also be reported to CytoDyn, Inc. Any pregnant subject must be followed up by the Investigator or designee until the child is born. Any complication experienced through the end of the pregnancy should be considered as an adverse event (AE), and should be recorded, and if it meets the seriousness criteria, it must be reported CytoDyn, Inc/designated CRO promptly.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

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

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

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 MONITORING REQUIREMENTS

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

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

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

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

11.2 ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

Electronic CRFs must be completed for each subject who has signed an informed consent form. For subjects who are screen failures, this would be limited to the screen failure eCRF page. All source documents and eCRFs will be completed as soon as possible after the subject's visit. Corrections to data on the eCRFs will be documented. The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Electronic CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

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

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

11.4 REPORTING PROTOCOL DEVIATIONS

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

12 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee (DMC), independent of the study operations will be established to consider safety data generated during the study and to make recommendations about IA data. The details of the DMC responsibilities will be included in the DMC charter. The DMC charter will be developed and operated in adherence to the current FDA guidance on DSMC (Establishment and Operation of Clinical Trial Data Safety Monitoring Committees [March 2006]). The DMC meetings will take place at least once after the IA, and at other time-points as determined by the DMC charter, if necessary. In addition to the pre-specified time-points, the DMC may also decide to schedule a meeting whenever they decide a review of emergent safety data is warranted. The charter will detail the roles and responsibilities of the DMC members once they have been appointed. The study data will be provided to the Committee members in the form of a data report. Meetings to discuss the data will be held in person or by teleconference, based on the DMC Chair's decision. The meetings will be in two stages: an "open stage" which will involve discussion on general aspects of the trial, and a "closed stage" between the DMC members only. The remit of the DMC will be primarily to assess the safety aspects of the trial.

13 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR Part 312, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. Procedures for selection of donors and stem cell dose will follow FDA requirements for Blood Products (21 CFR 640) and Human Cellular and Tissue Based Products (21 CFR 1271). No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable GMP and the products provided for this study will be used only in accordance with this protocol.

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

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

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

13.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

13.3 SUBJECT INFORMED CONSENT REQUIREMENTS

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

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

14 DATA HANDLING AND RECORD KEEPING

14.1 RECORDING AND COLLECTION OF DATA

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

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

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

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

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

14.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control (QC) of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data QC, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

14.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- Product (e.g., IP supplies) and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening and enrollment log
- SAE reports
- IRB approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator.

15 PUBLICATION PLAN

All information supplied by the Sponsor or designee in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure (IB), clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to others without the written consent of Sponsor, and shall not be used except in the performance of this study.

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

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

study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

16 REFERENCES

Anasetti C, Hansen JA, Waldmann TA et al. Treatment of acute graft-versus-host disease with humanized anti-Tac: an antibody that binds to the interleukin-2 receptor. Blood 1994; 84: 1320-7.

Antin JH, Weisdorf D, Neuberg D et al. Interleukin-1 blockade does not prevent acute graft versus-host disease: results of a randomized, double-blind, placebo-controlled trial of interleukin-1 receptor antagonist in allogeneic bone marrow transplantation. Blood 2002; 100 :3479-82Antignani PL. (2001). Classification of chronic venous insufficiency: a review. *52(Suppl 1)*, 517-526.

Arribas JR, P. F.-G. (2005). Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J Acquir Immune Defic Syndr. , 40*, 280-287.

Baker SR, S. M. (1992). Aetiology of chronic leg ulcers. *6(3)*, 245-51.

Baker SR, S. M.-M. (1991). Epidemiology of chronic venous ulcers. *78(7)*, 864-7.

Boffito M, B. D. (2003). Intra-individual variability in lopinavir plasma trough concentrations supports therapeutic drug monitoring. *AIDS , 17*, 1107-1108.

Brem H, K. R. (2004). Protocol for the successful treatment of venous ulcers. *188* (1), 1-8.

Browse NL. (1982). The cause of venous ulceration. *2(8292)*, 243-5.

Cahn P, M. J.-V.-M. (2011). Pilot, randomized study assessing safety, tolerability and efficacy of simplified LPV/r maintenance therapy in HIV patients on the 1st PI-based regimen. *PLoS One. , 6*, e23726.

Callam MJ, R. C. (1985). Chronic ulceration of the leg: extent of the problem and provision of care. *290(6485)*, 1855-66.

Calza L, M. R. (2012). Protease inhibitor monotherapy as maintenance regimen in patients with HIV infection. *Curr HIV Res. , 10*, 661-72.

Cameron DW, d. S. (2008). A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. *Infect Dis. , 198*, 234-240.

Chen YH, D. D. (2004). Increasing the sample size when the unblinded interim result is promising. *23(7)*, 1023-38.

Coleridge Smith PD, T. P. (1988). Causes of venous ulceration: a new hypothesis. *296*, 1726-1727.

Cornwall JV, D. C. (1986). Leg ulcers: epidemiology and aetiology. *73(9)*, 693-6.

Cullum N, F. A. (2000). Compression bandages and stockings in the treatment of venous ulcers. *CD000265* . Cochrane Database Syst Rev .

Danon D, M. J. (1997). Treatment of human ulcers by application of macrophages prepared from a blood unit. *32(6)*, 633-41.

de Laat EH, S. o. (2005). Pressure ulcers: diagnostics and interventions aimed at wound-related complaints: a review of the literature. *14(4)*, 464-72.

Demeter LM, S. R.-W. (2000). Delavirdine susceptibilities and associated reverse transcriptase mutations in human immunodeficiency virus type 1 isolates from patients in a phase I/II trial of delavirdine monotherapy (ACTG 260). *Antimicrob.Agents Chemother. , 44*, 794-797.

Falanga V, M. D.-Y. (1998). Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *134(3)*, 293-300.

Guarnera G, T. G. (2007). Pain and quality of life in patients with vascular leg ulcers: an Italian multicentre study. *16(8)*, 347-51.

Guiguet M, G. J., & CO4., F.-A. (2012). Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS , 26*, 2345-50.

Gulick RM, L. J. (2008). Maraviroc for Previously Treated Patients with R5 HIV-1 Infection. *NEJM , 359* (14), 1429-1441.

Gutmann C, C. A. (2010). Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. *AIDS , 24*, 2347-2354.

Hankin CS, K. J. (2012). Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *18(5)*, 375-84.

Hutter, G.(2009). Long-term control of HIV by CCR5 delta32/delta32 stem-cell transplantation. *N Engl J Med*, 360(7), 692-698.

Insel, P., Franco, A. (2015). Evaluation of Antagonist/Agonist Activity of PRO 140 Downstream of CCR5 Binding Using Human CD4+ Cells. *Sponsor commissioned study*.

Jacobson JM, L. J. (2010). study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. *Antimicrob Agents Chemother. , 54*, 4137-42.

Jacobson JM, S. M. (2008). Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. *J Infect Dis. , 198*, 1345-52.

Jacobson JM, T. M. (2010). Anti-HIV-1 activity of weekly or biweekly treatment with subcutaneous PRO 140, a CCR5 monoclonal antibody. *J Infect Dis. , 201*, 1481-7.

Katlama C, V. M.-G. (2010). Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial MONOI-ANRS 136. *AIDS , 24*, 2365-2374.

Marozsan, A. J. (2008). Clonal analysis of HIV-1 co-receptor tropism change following treatment with PRO 140, a CCR5 monoclonal antibody. *48th Annual ICAAC / IDSA 46th Annual Meeting*, *Abstract H-1218.* Washington, DC.

Meynard JL, B. V. (2010). Lopinavir/ritonavirmonotherapy versus current treatment continuation for maintenance therapy of HIV-1infection: the KALESOLO trial. *J Antimicrob Chemother. , 65*, 2436-2444.

Moltó J, S. J. (2007). Lopinavir/ritonavir monotherapy as a simplification strategy in routine clinical practice. *J Antimicrob Chemother.* (60), 436-439.

Moyle G, G. J. (2008). Potential for new antiretrovirals to address unmet needs in the management of HIV-1 infection. *AIDS Patient Care STDS* , 459-471.

Nelzen O, B. D. (1991). Leg ulcer etiology - a cross sectional population study. *14(4)*, 557-64.

Nelzen O, B. D. (1994). Venous and non-venous leg ulcers: clinical history and appearance in a population study. *81(2)*, 182-7.

Nishikawa M, T. K. (2005). Analysis of binding sites for the new small-molecule CCR5 antagonist TAK-220 on human CCR5. *Antimicrob Agents Chemother , 49(11)*, 4708-4715.

Nunes EP, S. d. (2009). Monotherapy with Lopinavir/Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study). *HIV Clin Trials. , 10*, 368-374.

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

Orenstein A, K. E.-S. (2005). Treatment of deep sternal wound infections post-open heart surgery by application of activated macrophage suspension. *13(3)*, 237-42.

Przepiorka D, Weisdorf D, et al. (1995). 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 15 (6): 825-828.

Pulido F, A. J.-G.-E. (2008). Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS , 22*, F1-9.

Richman, D. D. (1994). Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. *J Virol. , 68*, 1660-1666.

Robertson, P. (2006). CXCR4 and CCR5 mediate homing of primitive bone marrow-derived hematopoietic cells to the postnatal thymus. *Exp Hematol*, 34(3), 308-319.

Rowlings PA, Przepiorka D, et al. (1997). IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol*. 97: 855-864.

Saag, M. S. (1993). A short-term clinical evaluation of L-697,661, a non-nucleoside inhibitor of HIV-1 reverse transcriptase. *N.Engl.J Med. , 329*, 1065-1072.

Shai A, H. S. (2005). Direct triggers for ulceration in patients with venous insufficiency. *44(12)*, 1006-9.

Shukla D, T. A. (2005). Pain in acute and chronic wounds: a descriptive study. *51(11)*, 47-51.

Simioni S, C. M. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *24*, 1243-1250.

Tang MW, S. R. (2012). HIV-1 Antiretroviral Resistance: Scientific Principles and Clinical Applications. *Drugs* , e1-e25.

Technical Manual of Procedures version 3.0 dated March 19, 2103, Blood and Marrow Transplant Clinical Trials Network.

Thompson MA, A. J. (2012). Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society–USA Panel. *JAMA , 308*, 387-402.

Thompson, M. L. (2009). Weekly and bi-weekly subcutaneous PRO 140 demonstrates potent, sustained antiviral activity. *16th Conference on Retroviruses and Opportunistic Infections*, *Abstract #571a.* Montreal QE, Canada,.

Zuloff-Shani A, A. A.-Z. (2010). Hard to heal pressure ulcers (Stage III-IV): Efficacy of injected activated macrophage suspension as compared with standard of care (SOC) treatment controlled trial. *51(3)*, 268-71.

Zuloff-Shani A, D. D. (Submitted for publication). Treatment of infected wounds following saphenous vein harvesting for coronary bypass surgery by injection of activated macrophage suspension.

Ruutu T, Gratwohl A, De Witte T, et al. Prophylaxis and treatment of GVHD: EBMT–ELN working group recommendations for a standardized practice. Bone Marrow Transplant. 2014 Feb;49(2):319

17 APPENDICES

17.1 APPENDIX I: ADVERSE EVENTS OF SPECIAL INTEREST: INJECTION SITE REACTIONS

The following table should be used to characterize injection-site reactions and provide appropriate grading of severity.

Injection-site Reactions				
Parameter	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life-threatening)**
Injection-site pain	Pain without touching or pain when area is touched: no or minimal limitation of use of limb	Pain without touching or pain when area is touched limiting use of limb OR causing greater than minimal interference with usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform basic self-care function OR hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Characterization of the injection site, if not normal	Erythema OR induration of 5x5 cm - 9x9 cm (or 25 cm2-81 cm2)	Erythema OR induration OR Edema >9 cm any diameter (or >81 cm2)	Ulceration OR secondary infection OR Phlebitis or Sterile abscess OR drainage	Necrosis (involving dermis and deeper tissue)
Pruritus associated with injection	Itching localized to injection site AND relieved spontaneously or <48 hours of treatment	Itching beyond the injection site but not generalized OR itching localized to injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social and functional activities	N/A
Bleeding	Initial bleed that does not exceed bandage and spontaneously stops	Bleeding that exceeds bandage and spontaneously stops	Continued bleeding that requires change of dressing and alternative injection site	N/A
Absorption of drug	Minor elevation of skin at injection site but no leakage of injection material	Leakage at injection site ceases with decrease in injection rate	Leakage at injection site that does not cease with decrease in injection rate	

17.2 APPENDIX II: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03

For complete detailed information please refer to the link below

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