STATISTICAL ANALYSIS PLAN
FOR PROTOCOL PRO 140_CD 03_GVHD

Sponsor:		
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Protocol Number:	PRO 140_CD 03_GVHD	
Protocol Title:	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 Date / Version:	Version 3.0 / 07-Jun-2016	

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SAP Version:	SAP – Final Version 1.0
SAP Date:	10 October 2016

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

Statistician, Amarex	Date
[redacted]	Date

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AML	Acute Myeloid Leukemia
ATC	Anatomic Therapeutic Classification
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
VAS	Visual Analogue Scale

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol PRO 140_CD03_GVHD, sponsored by CytoDyn Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objective of this plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

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

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

- Version 3.0, protocol 17 June 2016
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (1999)
- The Royal Statistical Society: Code of Conduct (1993)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guideline on General Considerations for Clinical Trials (ICH E8, 1997)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1997)

2. PROTOCOL DESIGN AND OBJECTIVES

2.1 Study Objectives

The primary objective 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.

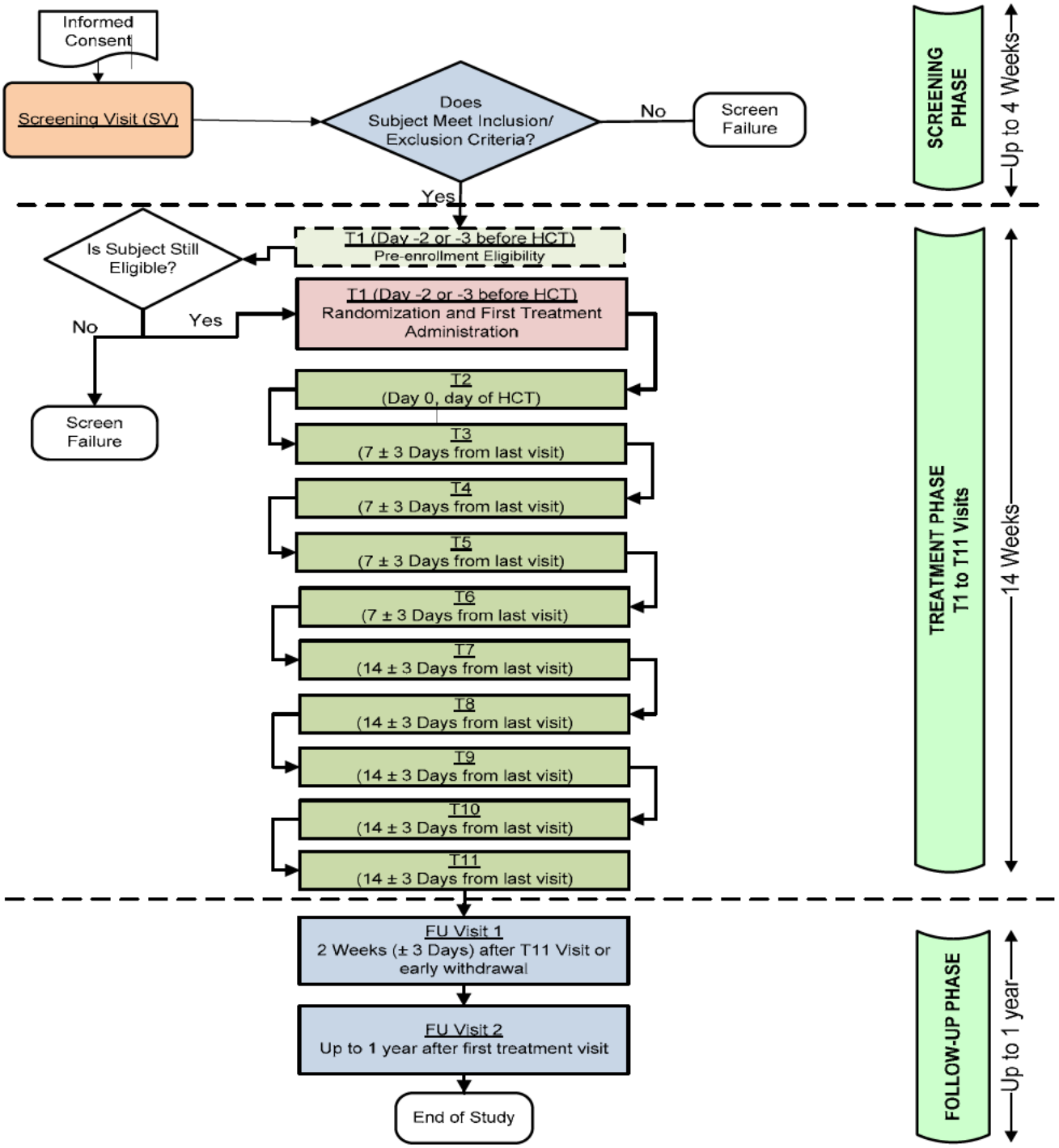
2.2 Design Overview

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.

The study will have three phases: Screening Phase, Treatment Phase and Follow-up Phase as shown in the study flow diagram Figure 2-1.

Figure 2-1 Clinical Trial Flow Diagram



2.3 Study Duration

A subject will be in this trial at maximum of around 56 weeks.

- **Screening Phase:** up to 4 weeks (28 days).
- **Treatment Phase:** up to 14 weeks ± allowed windows (up to 14 treatments).
- **Follow-up Phase:** up to one year after first treatment visit (T1), approx. 38 weeks from end of treatment visit].

2.4 Study Treatments

2.4.1 Treatment Groups

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

- Active Treatment Group: Standard GVHD prophylaxis + PRO140
- Control Treatment Group: Standard GVHD prophylaxis + Placebo

2.4.2 Randomization 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.

3. STUDY ASSESSMENTS/ ENDPOINTS

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

3.1.1 Primary Efficacy Endpoint

- Incidence of ≥ Grade II acute GVHD by Day-100

3.1.2 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

- 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)

3.1.3 Safety Assessments

Safety will be assessed by the below evaluations:

- 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

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

For this two arm clinical trial, it is planned to have a total of 60 subjects (30 per treatment group). This is a proof of concept study, and 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. Based on literature review, the incidence of GVHD in ablative transplant population range from 40-60%. Assuming that the control incidence of GVHD is 50% and that of the Active group is 15%, a sample size of 30 subjects per group produces a two-sided 95% CI for the difference in proportions with a width of 0.44 (i.e.,95% CI of 0.13 – 0.57).

5. INTERIM ANALYSIS

There will be a safety interim analysis after the first 10 subjects complete the treatment phase 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.

5.1.1 Procedures

- Cut-off dates for review of eCRFs, data cleaning, and analysis will be established based on an estimated target date of the first ten (10) treated subject completing pre-defined treatment period or withdraw from the study.
- All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.
- Data snapshot will be taken for the safety analysis.
- The statistician will generate planned data and information for the DMC, as described below.

5.1.2 Data and Information Provided to DMC

The DMC will receive: AEs, SAEs, labs, ECGs, vital signs, and all other safety related variables identified per the DMC Charter.

5.1.3 DMC Recommendation

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

5.1.4 Type I Error Rate Adjustment

There will be no impact on Type I error rate due to the safety interim analysis for this Phase 2 study.

6. ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

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

6.2 Per Protocol Population

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

the analysis of primary and secondary endpoints.

6.3 Safety Population

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

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

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

7.2 Duplicate Data

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

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

7.3 Handling of Missing Data

There will be no imputation of missing data for the analysis of efficacy and safety variables for this Phase II study.

7.4 Sensitivity Analysis

For the analysis of the primary endpoint, a tipping point analysis will be conducted to assess the robustness of the results of the primary analysis and the impact of missing data.

7.5 Multicenter Clinical Trials

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

7.6 Multiple Comparisons and Type I Error Rate Multiplicity adjustments

There is no need to adjust for multiplicity in this Phase II study.

7.7 Covariates and Prognostic Factors

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

7.8 Stratification Factors

Donor source (i.e., HLA-Matched Unrelated Donor (MUD) vs HLA-Mismatched Related Donor (MRD)) will be used as a stratification factor in this study.

7.9 Standard Calculations

7.9.1 Age

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

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

7.9.2 Height

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

Height (cm) = Height (in)*2.54

7.9.3 Weight

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

Weight (kg) = Weight (lb)/ 2.2046

7.9.4 Body Mass Index (BMI)

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

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

7.9.5 Definition and Duration of Platelet Recovery

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, the second platelet count should be at least as high as the first.

Duration of platelet recovery will be defined as the difference between the date of transplant and the date of the first eligible count of the two consecutive counts.

Duration of Platelet Recovery = (Date of first eligible count – Date of transplant) +1

7.9.6 Definition and Duration of Neutrophil Recovery

Neutrophil recovery will be defined as an increase in absolute neutrophil count (ANC) to greater than 500/μL on two consecutive days.

Duration of neutrophil recovery will be defined as the difference between the date of transplant and the date of the first count above the threshold (i.e., 500/μL) of the two consecutive days.

Duration of Neutrophil Recovery = (Date of first count above the threshold – Date of transplant) +1

7.9.7 Duration of GVHD-Free Survival (GFS)

GFS is defined as the duration from the day of transplant (Day 0/T2) until GVHD related death. Survivors, lost to follow-up and non-GVHD death are censored.

[for those with GVHD related death]
Days to event = (Date of death – Date of transplant) +1
[for those who completed the study]
Days to censoring = (Date of completion – Date of transplant) +1
[for those who lost to follow-up]
Days to censoring = (Date of last response assessment – Date of transplant) +1

[for those with non-GVHD related death]
Days to censoring = (Date of death – Date of transplant) +1

7.9.8 Donor Engraftment Failure

Donor engraftment failure is defined as T-cell or myeloid has, or both have less than 5% chimerism from the donor at anytime in the study duration after transplant.

8. STATISTICAL METHODS

All data collected during this study will be presented in subject data listings. All statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

8.1 Summarizing and Tabulating the Collected Data

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

- Continuous data summaries will include:
  - 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.
- Time-dependent data: Kaplan Meier methods will be used to analyze time dependent data and to depict the time to event data.

8.1.1 Subject Disposition and Withdrawals

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

- The number of subjects who signed the informed consent
- The number of subjects who are screen failures
- The number of subjects who are treated
- The number of subjects who completed the study
- The number of subjects who discontinued

Reasons for discontinuation will also be summarized.

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

8.1.2 Protocol Deviations

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

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

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

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (i.e., Age, Gender, 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.

8.1.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Safety population. All prior and concomitant medications recorded in the CRFs will be coded to match Anatomic Therapeutic Classification (ATC) codes using the most recent version of 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.

8.1.5 Treatment Administration

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

8.2 Analysis of Efficacy Data

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

8.2.1 Primary Endpoint

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.

8.2.2 Secondary Endpoints

All data from the secondary endpoints will be summarized as follows:

8.2.2.1 Incidence of severe and life-threatening (Grade III and Grade IV) acute GVHD by Day-100

The number and percentages of subjects with severe and life-threatening (Grade III and Grade IV) acute GVHD by Day-100 will be presented. Chi-square/ Fisher's exact test will be used to compare the incidence between the treatment groups.

8.2.2.2 Incidence of organ-specific acute GVHD by Day-100

The number and percentages of subjects with organ-specific acute GVHD by Day-100 will be presented by organ category. Chi-square/ Fisher's exact test will be used to compare the incidence between the treatment groups.

8.2.2.3 Donor engraftment evaluated by T-cell and myeloid chimerism in peripheral blood

The number and percentages of subjects with donor engraftment failure evaluated by T-cell and myeloid chimerism in peripheral blood will be presented by different treatment groups. The definition of donor engraftment failure is presented in Section 7.9.8. Chi-square/ Fisher's exact test will be used to compare the incidence of donor engraftment failure.

8.2.2.4 Neutrophil and platelet count recovery

The number and percentages of subjects with neutrophil and platelet count recovery will be presented. The definition of neutophil and platelet count recovery is presented in Sections 7.9.5 and 7.9.6, respectively. Chi-square/ Fisher's exact test will be used to compare the incidence of neutrophil recovery and of platelet recovery between treatment groups.

8.2.2.5 Changes in ECOG performance score

The raw and change from baseline in ECOG performance score will be summarized for each assessment scheduled visit (i.e., Screening visit, Treatment Visits 1, 4, 7, 9, 11, Follow-up Visit 1

and Unscheduled Visit(s)). Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group. If the Normality assumption is met, t-test will be used to compare the mean of ECOG performance score between the treatment groups and if the Normality assumption is not met, a non-parametric method will be used.

8.2.2.6 GVHD-free survival (GFS)

GFS will be defined as the elapsed time between the date of transplant until GVHD related death. Duration of GVHD-free survival will be measured as in Section 7.9.7.

GVHD-free survival will be compared between the treatment groups using Log-rank test and Kaplan-Meier methods will be used to depict the survival curves.

8.3 Supportive Analysis

The PP population will be used for the 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.

8.4 Analysis of Safety Data

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.

8.4.1 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

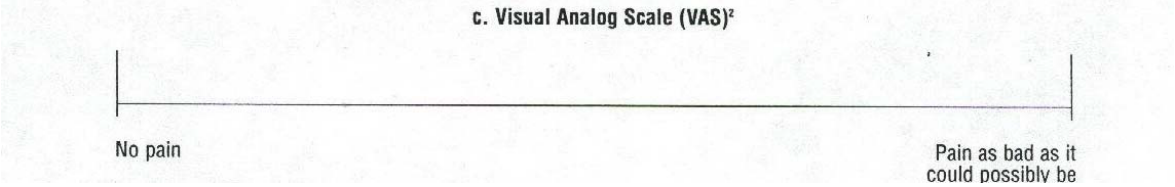
- TEAEs by relationship to study treatment.

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

8.4.2 Tolerability of repeated subcutaneous administration as assessed by Visual Analogue Scale

All data from tolerability assessments of repeated subcutaneous administration of PRO 140 as assessed by study participants (using Visual Analogue Scale, as presented in Figure 8-1: Visual Analog Scale below) and by investigator-evaluation of injection site reactions will be summarized using n, mean, Standard Deviation (SD), minimum and maximum values.

Figure 8-1: Visual Analog Scale



8.4.3 Clinical Laboratory Evaluations

The changes in laboratory values will be summarized descriptively for each visit. Changes will be calculated relative to the values collected at baseline.

- Serum chemistry
- Complete blood count (CBC)
- Urinalysis

Laboratory data will be summarized as appropriate to the variable type.

- For continuous data, summaries will include the number of observations, mean, standard deviation, median, minimum and maximum values.
- For categorical data, frequency counts and percentages will be used.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded. All available laboratory data will be included in individual subject listings.

8.4.4 Physical Examination

Physical examination results will be listed and summarized in terms of the number and percentage of subjects with abnormal and normal findings at the scheduled protocol assessment visit.

8.4.5 Vital Signs

Vital sign results (systolic and diastolic blood pressure, heart rate, respiration rate and temperature) will be summarized descriptively for each scheduled protocol visit. Changes will be calculated relative to the assessments at baseline. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.4.6 ECG Assessment

ECG results will be listed and summarized in terms of the number and percentage of subjects with abnormal and normal findings at the scheduled protocol assessment visit. Additionally, descriptive statistics will be tabulated for the reported ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec) values along with changes from baseline at each visit. Subjects with missing data for a given time point will not contribute to the tabulations for that time point.

8.4.7 AML or MDS relapse rate by Day-100

AML or MDS relapse rate by Day-100 will be summarized and present by treatment groups.

8.4.8 PK

PK results will be descriptively summarized for each scheduled protocol visit.

8.4.9 Anti-idiotypic antibodies

Anti-idiotypic antibodies will be descriptively summarized and presented by treatment groups.

8.4.10 Injection Site Reactions

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

9. APPENDIX 1: SCHEDULE OF ASSESSMENTS

TABLE 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			

TABLE 1: SCHEDULE OF ASSESSMENTS– CONTINUED FROM PREVIOUS PAGE

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[11]	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)

10. APPENDIX 2 – PLANNED TLG

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILITY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

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

TREATMENT ADMINISTRATION LISTINGS (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.1.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS

POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS

CONCOMITANT MEDICATION USAGE

EFFICACY SUMMARIES

SAFETY SUMMARIES

ADVERSE EVENT SUMMARIES

SERIOUS ADVERSE EVENTS

LABORATORY

VITAL SIGNS AND PE

OTHER SAFETY

11. VERSION HISTORY

Final version 1.0 based on the information from Protocol v3.0 (19Jun2016)

12. REFERENCES

1. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999.
2. The Royal Statistical Society: Code of Conduct (1993).
3. E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
4. E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1997
5. Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 1988.
6. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.