STATISTICAL ANALYSIS PLAN

TITLE:	**PROTECT: A Phase 1, Non-Randomized, Open-Label/Phase 2, Randomized, Blinded Study of ProTmune™ (*ex vivo* Programmed Mobilized Peripheral Blood Cells) Versus Non-Programmed Mobilized Peripheral Blood Cells for Allogeneic Hematopoietic Cell Transplantation in Adult Subjects with Hematologic Malignancies**
PROTOCOL NUMBER:	PT-001
INVESTIGATIONAL PRODUCT:	ProTmune
IND NUMBER:	016654
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PLAN VERSION NUMBER:	2.0
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SIGNATURE PAGE

Statistical Analysis Plan (SAP): Version 2.0, 09 February 2021.

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STATISTICAL ANALYSIS PLAN AMENDMENT SUMMARY OF CHANGES

Document History

Document	Date
Amendment Version 2.0	09 February 2021
Original Statistical Analysis Plan (Version 1.0)	28 April 2020

Statistical Analysis Plan PT-001, Version 2.0

Overall Rationale: Statistical Analysis Plan PT-001 has been amended to modify and clarify planned analyses. Additional minor modifications have been made to improve clarity and consistency.

A description of the major changes to the statistical analysis plan, along with a rationale for each change, follows.

Section Number	Description of Change and Rationale
3.3.2.3	Center for International Blood and Marrow Transplant Research (CIBMTR) Grade II-IV acute graft-versus-host disease (aGvHD) without skin involvement through Visit Day +100 and through Visit Day +180 has been added as an additional exploratory efficacy endpoint. CIBMTR Grade III-IV aGvHD without skin involvement through Visit Day +100 and through Visit Day +180 has also been added as an additional exploratory efficacy endpoint. The rationale for these analyses is to provide additional information on the ability of ProTmune to impact different clinicopathologic aspects of aGVHD given differences in biological mechanisms, differential patterns of organ involvement, and clinical management and outcomes of aGVHD with and without skin involvement.
5.1.6	The overall Type I error for the Phase 2 part of the study has been changed to 10%. The hypotheses regarding the primary and secondary endpoints will be independently tested, each at $\alpha = 0.05$ to render a family-wise Type I error rate of no more than 10%. The primary objective of the Phase 2 part of the study was to assess the efficacy of ProTmune. Decoupling the primary and secondary analyses would render an opportunity to perform robust statistical analysis of a key clinically relevant secondary analysis. In addition, it is common to set Type I error at 10% for randomized Phase 2 studies.
5.1.7	The subgroup analyses for the primary and key secondary efficacy endpoints have been updated to include the baseline Karnofsky Performance Status (KPS) score (90-100 vs. 80 or lower) as an indicator of a clinically relevant patient subgroup.
5.2.1.1	It has been clarified that donor demographic characteristics will be summarized for the intent-to-treat (ITT), modified intent-to-treat (mITT), and safety populations.
	(Continued)

Section Number	Description of Change and Rationale
	(Continued)
5.3.1	Subject disposition was modified to provide more comprehensive information for the following: • To include the number of screen failures (overall, prior to randomization, and after randomization); • To remove the number of subjects who entered the conditioning period; • To summarize the impact of COVID-19 as a primary reason for withdrawal prior to completing the first year on study and prior to completing the 2-year follow-up based on U.S. Food and Drug Administration (FDA) guidance (FDA 2021); and • To include the summary of subject disposition for the mITT population.
5.3.2	Protocol deviations regarding study visits (missed visit, altered or partially completed visit, or out of window visit) impacted by COVID-19 will be summarized based on FDA guidance (FDA 2021).
5.3.3.2	CD34+ cells as the cumulative dose of investigational product (IP) will be summarized to describe the exposure to IP.
5.4.3.4	The definitions for complete chimerism and mixed chimerism were revised to reflect the following (Antin et al. 2001): • A ± 5% error in the assay detection methods will be applied for this study. • Chimerism determination is based on results obtained from unseparated peripheral blood or the T-cell fraction. • An additional category for chimerism <10% will be included to provide a more complete characterization of chimerism in this study. Based on the aforementioned changes, the definitions and thresholds for chimerism have been updated as follows: • Complete chimerism is defined as ≥95% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available). • Mixed chimerism is defined as ≥10 to <95% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available). • Chimerism <10% is defined as <10% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available). Further categorization of chimerism from T cells and unseparated peripheral blood will be described based on the following thresholds: ≥95% to 100%, 50% to <95%, 10 to <50%, and <10%. Summaries will be provided at multiple timepoints through Day +365. Summaries for overall chimerism and proportion of subjects with complete chimerism who subsequently developed mixed chimerism through Day +365 have been removed.
5.5.1, 5.5.2, 5.5.5	Timepoint estimates for the primary efficacy endpoint, first key secondary efficacy endpoint, and exploratory efficacy endpoints have been clarified using the target study day post- hematopoietic cell transplantation (HCT) as follows: • Target Study Day 101 post-HCT for Visit Day +100 • Target Study Day 181 post-HCT for Visit Day +180 • Target Study Day 366 post-HCT for Visit Day +365 and at 1 year • Target Study Day 731 post-HCT at 2 years Censoring rules have also been clarified.
	(Continued)

Section Number	Description of Change and Rationale
(Continued)	
5.5.5.1	The concordance rate between the investigator assessment and the Endpoint Adjudication Committee (EAC)-adjudicated assessment for the maximum CIBMTR Grade II-IV aGvHD and the maximum CIBMTR Grade III-IV aGvHD results through Day +100 and through Day +180 have been added.
5.5.6	Summaries for immune reconstitution data have been clarified and updated to describe each lymphocyte subset (NK cells, T cells, CD4+ T cells, CD8+ T cells, Treg, and B cells) on Visit Day +91 and Visit Day +365.

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides guidance and descriptions of the statistical methods and procedures to be implemented for the analyses of data from Fate Therapeutics, Inc., Protocol PT-001, PROTECT: A Phase 1, Non-Randomized, Open-Label/Phase 2 Randomized, Blinded Study of ProTmune™ (*ex vivo* Programmed Mobilized Peripheral Blood Cells) Versus Non-Programmed Mobilized Peripheral Blood Cells for Allogeneic Hematopoietic Cell Transplantation in Adult Subjects with Hematologic Malignancies (Version 6.0, 29 March 2019). Any deviations from this analysis plan will be justified by sound rationale and will be documented in the final Clinical Study Report (CSR).

This SAP will be finalized prior to the database lock after the completion of 1 year on study (Day +365) of the last patient or the date of last visit of the last patient (whichever occurs first), which is the cutoff date of the primary analysis. The final database lock will occur upon completion of the Day +730 follow-up and will conclude with the final analysis of the 2-year survival follow-up.

Unless otherwise specified, all statistical analyses and output will be produced using SAS® Version 9.3 or later.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Phase 1: The primary objective of the Phase 1 part of the study is to evaluate the safety and tolerability of ProTmune ex vivo programmed mobilized peripheral blood (mPB) cells for hematopoietic cell transplantation (HCT) in adult subjects with hematologic malignancies.

Phase 2: The primary objective of the Phase 2 part of the study is to assess the efficacy of ProTmune ex vivo programmed mPB cells for HCT in adult subjects with hematologic malignancies.

2.2 Secondary Objectives

Phase 1: The secondary objective of the Phase 1 part of the study is to assess the efficacy of ProTmune ex vivo programmed mPB cells for HCT in adult subjects with hematologic malignancies.

Phase 2: The secondary objective of the Phase 2 part of the study is to further evaluate the safety and tolerability of ProTmune ex vivo programmed mPB cells for HCT in adult subjects with hematologic malignancies.

2.3 Exploratory Objectives

The exploratory objectives for the Phase 1 and Phase 2 parts of the study may include the following:

- To assess the incidence of neutrophil and platelet engraftment
- To assess the time to neutrophil and platelet engraftment
- To assess the cumulative incidence of acute graft-versus-host disease (aGvHD)
- To assess the incidence of, and time to, cytomegalovirus (CMV) viremia, incidence, and severity of CMV invasive disease, and incidence of CMV reactivation
- To assess time to first CMV-specific antiviral therapy
- To assess the incidence of confirmed bacterial, fungal, viral, and parasitic infections
- To assess the time to first use of an agent to treat an infection other than CMV as clinically indicated
- To assess the time to first use of steroids to treat aGvHD
- To assess the time to escalation of treatment to first use of second-line therapies for treatment of aGvHD
- To assess first episode, incidence, and duration of fever
- To assess biomarkers for aGvHD development
- To assess incidence and maximum severity of chronic graft-versus-host disease (cGvHD)
- To assess cumulative incidence of primary and secondary graft failure
- To assess neutrophil and T-cell chimerism
- To determine relapse-free survival (RFS)
- To determine the incidence of non-relapse mortality (NRM)
- To determine survival at one year and at two years
- To assess immune reconstitution (including B, T, dendritic, and natural killer [NK] cells)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 1, non-randomized, open-label/Phase 2, randomized, blinded, multicenter study of ProTmune ex vivo programmed mPB versus non-programmed mPB for allogeneic HCT in adult subjects with hematologic malignancies in the United States. All subjects in Phases 1 and 2 will have received a conditioning regimen comprising 1 of the following 5 preparative regimens: fludarabine and busulfan (FluBu4), busulfan and cyclophosphamide (BuCy), cyclophosphamide (Cy) and ≥12 Cy total body irradiation (Cy-TBI), TBI and etoposide, or fludarabine and melphalan (FluMel 140).

The Phase 1 part of the study is a non-randomized, open-label, single-arm study that will have treated 6 to 10 subjects who have an available 8/8 human leukocyte antigen (HLA)-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor. All eligible subjects enrolled in the Phase 1 part of the study will have received 1 unit of ProTmune ex vivo programmed mPB cells as the cell source for the HCT.

The Phase 2 part of the study is a randomized, blinded, 2-arm study that will have treated approximately 80 subjects who have an available 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor. After meeting eligibility, approximately 90 subjects (assuming a dropout rate of approximately 15% prior to treatment) will have been randomly assigned in a 1:1 ratio to receive either unmanipulated mPB cells (control arm) or ProTmune ex vivo programmed mPB cells (experimental arm). Subjects' CMV status (+/-) will be used as a stratification factor.

Refer to Protocol PT-001 for the study design schemas for each phase of the study (Appendix B for Phase 1 and Appendix H for Phase 2) and for the schedule of procedures (Appendix A).

For all treated subjects, the end of the 1 year on study is defined as the completion of follow-up through Day +365 for safety and efficacy. All treated subjects will additionally be followed for survival through Day +730 (i.e., 2 years).

Data will be cleaned and locked through the end of the 1 year on study when the last subject, last visit occurs or when the last data point is collected for the completion of 1 year on study (Day +365), whichever occurs later. The locked data will include Day +730 follow-up information from subjects who have reported data at the time of the database lock. All reporting of data and analyses for efficacy will be performed through the 1-year completion for the primary analysis. For safety analyses, all safety data (e.g., adverse events [AEs]) up to the cutoff date for the primary lock will be included.

The final database lock will occur when the last data point is collected for the completion of the Day +730 follow-up for the final analysis. The 2-year follow-up analysis will include updates to subject disposition, AEs, NRM, RFS, and survival.

The CSR will be completed based on the primary analysis of the 1-year on-study data. An addendum to the CSR will be provided to include the analysis of the 2-year follow-up data upon study completion.

3.2 Study Population

The study population comprises male and female subjects aged 18 years and older who have a hematologic malignancy for which allogeneic hematopoietic peripheral blood cell transplantation is deemed clinically appropriate. The Phase 1 part of the study will have treated 6 to 10 subjects who have an available 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor. The Phase 2 part of the study will have randomized approximately 90 subjects (assuming a dropout rate of approximately 15% prior to treatment) who have an available 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor in order to have treated approximately 80 subjects. Detailed inclusion and exclusion criteria are available in Section 4 of the protocol.

3.3 Study Endpoints

3.3.1 Safety Endpoints

The safety endpoints for both the Phase 1 and Phase 2 parts of the study include the assessment of AEs as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE, v4.03), vital signs, physical examination findings, engraftment, graft failure, chimerism, clinical laboratory assessments, and electrocardiographic data obtained by 12-lead electrocardiogram (ECG).

3.3.2 Efficacy Endpoints

3.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint for both the **Phase 1 and Phase 2** parts of the study is the cumulative incidence of Center for International Blood and Marrow Transplant Research (CIBMTR) Grade II-IV aGvHD through Visit Day +100 based on investigator assessment. Death and relapse without CIBMTR Grade II-IV aGvHD will be considered competing risks.

Each study site will determine the presence or absence of aGvHD by assigning the clinical stage for the target organs of the skin, liver, and gut along with assigning an overall grade according to the CIBMTR aGvHD Grading Scale (see Appendix E of the protocol).

3.3.2.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for both the **Phase 1 and Phase 2** parts of the study are as follows:

- 1-year GvHD-free, relapse-free survival (GRFS), a composite endpoint in which events include Grade III-IV aGvHD, cGvHD requiring systemic immunosuppressive therapy, relapse, or death from any cause (Holtan et al. 2015)
- Proportion of subjects alive without relapse and without moderate or severe cGvHD per National Institutes of Health (NIH) Consensus Criteria at Visit Day +365

3.3.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for both the **Phase 1 and Phase 2** parts of the study are as follows:

- Cumulative incidence through Visit Day +100 and through Visit Day +180 of:
  - CIBMTR Grade III-IV aGvHD
  - Maximum CIBMTR Grade II-IV aGvHD
  - Maximum CIBMTR Grade III-IV aGvHD
  - Maximum CIBMTR Grade II-IV aGvHD based on Endpoint Adjudication Committee (EAC)-adjudicated results
  - Maximum CIBMTR Grade III-IV aGvHD based on EAC-adjudicated results
  - CIBMTR Grade II-IV aGvHD without skin involvement
  - CIBMTR Grade III-IV aGvHD without skin involvement
- 1-year cGvHD-free, relapse-free survival (CRFS), a composite endpoint in which events include any cGvHD requiring systemic immunosuppressive therapy, relapse, or death from any cause (Pasquini et al. 2018)
- Cumulative incidence of NRM at 1 and 2 years
  - All deaths in the absence of relapse of the primary malignancy will be considered NRM, where relapse will be considered a competing risk.
- Cumulative incidence of moderate or severe cGvHD per NIH Consensus Criteria for the global severity score cGvHD through Visit Day +365
  - Death and relapse without moderate or severe cGvHD will be considered competing risks.
- GRFS will also be assessed at Day +180
- Cumulative dose of systemic steroid for GvHD, converted to cumulative systemic prednisone equivalent dose in mg
- Proportion of subjects with steroid refractory aGvHD, defined as subjects who have started a new systemic immunosuppressive therapy after initial systemic steroid use for the treatment of aGvHD
- RFS at 1 and 2 years
- Overall survival (OS) at 1 and 2 years
- GvHD biomarkers, assessed as actual values at each visit
- Immune reconstitution evaluated with B cells, T cells, dendritic cells, and NK cells, assessed as actual values and change from baseline values at each visit

All summaries for aGvHD and cGvHD will be based on the investigator assessment, unless noted otherwise.

4 DEFINITION OF ANALYSIS POPULATIONS

4.1 Intent-to-Treat Population

The intent-to-treat (ITT) population for Phase 1 will include all subjects who received ProTmune ex vivo programmed mPB cells.

The ITT population for Phase 2 will include all randomized subjects. The ITT population will include each subject in their randomized treatment group, regardless of actual treatment received.

4.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all subjects in the ITT population who received Investigational Product (IP; defined as either ProTmune or Control mPB units). Subjects who are randomized but do not receive IP because the incoming donor mPB unit did not meet criteria for manufacturing, or because their health status deteriorated and they no longer met eligibility criteria, will be considered screen failures and will not be part of the mITT population. Despite the exclusion of these subjects, the ITT principle would be considered preserved because the decision of whether or not to receive treatment is not expected to be influenced by knowledge of the assigned treatment and would be expected to occur equally in either treatment group. Summaries and analyses utilizing the mITT population will include each subject in their randomized treatment group, regardless of actual treatment received.

4.3 Per-Protocol Population

The per-protocol (PP) population will include all Phase 2 subjects in the mITT population who received the planned treatment and do not have any major protocol deviations. Sensitivity analyses of the primary and key secondary endpoints will be performed based on the PP population.

The PP population should exclude subjects with any of the following:

- Major eligibility deviations that may affect the assessment of efficacy, i.e., eligible diseases or HLA matching
- Not receiving the planned treatment
- Use of prohibited concomitant medications that may affect the assessment of efficacy, e.g., GvHD prophylaxis not specified per the protocol
- No documented GvHD assessments

4.4 Safety Population

The safety population will include all subjects who received IP. All safety analysis will be based on the safety population. Summaries and analyses utilizing the safety population will include each subject in the treatment group representing the actual treatment received, regardless of the treatment the subject was allocated to receive at randomization. For example, if a single ProTmune mPB unit is received by a subject randomized to the control arm then the subject will be analyzed in the ProTmune arm.

5 STATISTICAL METHODOLOGY

5.1 General Considerations

For information on table, figure, and listing reporting standards, please see Appendix 1.

5.1.1 Visit Windowing and Mapping

Information on the mapping and windowing of subject visits is provided in Appendix 2.

5.1.2 Definition of Baseline

Baseline is defined as the last non-missing assessment value obtained prior to infusion of IP (either ProTmune or Control mPB units). The day of the infusion of IP will be defined as Study Day 1. Study days prior to Study Day 1 will be expressed as negative integers relative to Study Day 1. There will be no Study Day 0.

5.1.3 Handling of Missing Data

In general, data will be analyzed and presented as observed and will not be imputed for the analysis of efficacy or safety data in this study unless otherwise specified in Sections 5.2, 5.3, 5.4, and 5.5. Handling of partial dates is described in Appendix 3.

5.1.4 Interim Analyses

There are no formal interim analyses for efficacy planned.

5.1.5 Independent Data Monitoring Committee Review

During Phase 1, an Independent Data Monitoring Committee (IDMC) will convene to assess safety data as outlined in the IDMC Charter. At that time, the Sponsor, in consultation with and based on recommendations from the IDMC, will decide whether the study should stop or whether the Phase 2 study can begin. If the IDMC and Sponsor determine that there are no safety concerns based on Phase 1 safety data, Phase 2 study enrollment will begin.

During Phase 2, the IDMC will convene according to the guidelines outlined in the IDMC Charter.

5.1.6 Adjustment for Multiplicity

Formal statistical tests are planned for the primary and key secondary efficacy endpoints of the Phase 2 portion of the study.

To control the family-wise type 1 error rate at 10%, the primary and key secondary endpoints will be tested, each at $\alpha = 0.05$, using the methods described in Sections 5.5.1 and 5.5.2, respectively.

For any other comparisons that are not subjected to multiplicity adjustment, nominal two-sided p-values (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

5.1.7 Subgroup Analyses

The primary and key secondary efficacy analyses will be performed for the following subgroups (if there is sufficient sample size) based on the mITT and PP populations:

- Primary indication for transplant
  - Acute lymphoblastic leukemia
  - Acute myeloid leukemia
  - Myelodysplastic syndrome
- Age (<65 vs. ≥65 years)
- Sex (female, male)
- Race (white vs. all other races)
- Baseline Karnofsky Performance Status (KPS) score (90-100 vs. 80 or lower)

A forest plot for the primary and key secondary efficacy endpoints will be presented to compare the treatment effects overall and for each subgroup. Hazard ratios will be displayed for the primary endpoint and the first key secondary endpoint, and odds ratios for the second key secondary endpoint along with the 95% confidence interval.

5.1.8 Randomization and Blinding

5.1.8.1 Randomization and Blinding for the Phase 1 Part of the Study

Randomization and blinding for the Phase 1 part of the study are not applicable. The Phase 1 part of the study is non-randomized.

5.1.8.2 Randomization and Blinding for the Phase 2 Part of the Study

For the Phase 2 part of the study, approximately 90 subjects (assuming a dropout rate of approximately 15% prior to treatment) who have an available 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor will have been randomly assigned in a 1:1 ratio to result in approximately 80 treated subjects (40 subjects per treatment group) who received either unmanipulated mPB cells (control arm) or ProTmune ex vivo programmed mPB cells (experimental arm) and will be stratified by the subjects' CMV status (+/-). Randomization will be performed during the subject conditioning period once the central laboratory CMV results are known and must occur no later than Day -7.

Treatment assignment in Phase 2 will be blinded to investigator, subject, and Sponsor, but not Cell Processing Facility (CPF) staff. To blind the investigator and subject, ProTmune and Control mPB units will be prepared by the CPF as described in the cell processing batch records and then sent to the treatment area in the afternoon for administration to the subject. Infusion of the control unit will be held until the afternoon of the subject's Day 0 to mimic the processing time of ProTmune.

The ProTmune unit and control unit will look identical. Both ProTmune and control will be placed in 400 mL blood transfer bags. The volume of each unit may be reduced or increased to achieve a final volume of 250 mL; volume increases will be achieved by addition of PlasmaLyte-A (or equivalent) with 4.2% to 5% HSA, according to the batch production record and site protocol. The blood transfer bags will be labeled with a product label provided by the Sponsor that will maintain the blind to the investigator and subject.

5.1.8.3 Unblinding

Phase 1: Not applicable, as this portion of the study is not blinded.

Phase 2: Phase 2 is double-blinded, but it is unlikely that the blind will need to be broken to the investigator or subject because knowledge of the single-dose treatment assignment would not impact any aspect of a subject's medical management. Should the investigator require information of the treatment assignment, the following unblinding procedure must be followed:

1. Locate the sealed envelope that contains the 6-digit unblinding authorization code provided to your site,
2. Log into the ClinTrak interactive response technology database and select the "Unblind a Patient (Emergency Only)" action, and
3. Select the subject number from the drop-down menu and enter the 6-digit code.

The treatment assignment will be provided by the system, and notification of unblinding will be sent to the study Sponsor and contract research organization.

NOTE: The investigator must print and file the unblinding notification within the subject's source documentation along with a written rationale for the need to unblind the subject. A new sealed envelope with a 6-digit unblinding authorization code will be sent to the site for future use.

At the end of the 1-year completion on study, after all data through Day +365 have been reviewed and cleaned, the blind review has occurred, and subject population assignments have been completed, the database will be declared "ready to lock." After the database has been initially locked for analysis, the study will be unblinded and the final unblinded analyses for the 1 year on study will be produced. The study will remain unblinded from Day +365 through Day +730.

5.1.9 Sample Size Determination

The background cumulative incidence rate of the International Bone Marrow Transplant Registry (IBMTR) Grades B-D aGvHD in this population is assumed to be between 40% and 60% as reported in the literature (Jagasia et al. 2012).

Phase 1: Allowing for a dropout rate of approximately 15%, approximately 8-12 subjects will have been enrolled to include 6-10 evaluable subjects.

Phase 2: When accounting for competing risk factors (death or relapse without aGvHD), a sample size of 80 subjects (40 subjects in each treatment group) allows for approximately 85% power to

detect a reduction in the cumulative incidence rate of CIBMTR Grade II-IV aGvHD through Visit Day +100 from 55% in the control arm to 25% in the ProTmune arm (i.e., a hazard ratio of 0.3464) using a two-sided log-rank test at a 0.05 significance level. This calculation assumes the cumulative incidence rate for competing risk factors is 10% through Visit Day +100. Allowing for a dropout rate of approximately 15%, approximately 90 subjects will have been randomized to include approximately 80 treated subjects in the mITT population. The sample size was calculated using PASS Sample Size Software (2018).

5.2 Analysis of Baseline, Demographic, and Medical History Data

5.2.1 Demographics and Baseline Characteristics

5.2.1.1 Demographics

Demographic characteristics for age, sex, race, and ethnicity at baseline will be summarized by phase, treatment group, Phase 2 total (control and ProTmune), pooled ProTmune group (Phase 1 and Phase 2), and overall totals for the ITT, mITT, PP, and safety populations. In addition, age will be categorized into the following ranges and summarized:

- 18-30 years
- 31-40 years
- 41-50 years
- 51-60 years
- 61-70 years
- >70 years
- <65 years vs. ≥65 years

Descriptive statistics will be presented for age; frequency counts and percentages will be presented for the age groups, sex, race, and ethnicity.

Donor demographic characteristics will also be summarized for the ITT, mITT, and safety populations.

5.2.1.2 Baseline and Disease Characteristics

Summaries for baseline and disease characteristics will be presented by phase, treatment group, Phase 2 total (control and ProTmune), pooled ProTmune group (Phase 1 and Phase 2), and overall totals for the ITT, mITT, PP, and safety populations.

Baseline characteristics will be summarized and will include weight, height, body mass index (BMI), blood type, and Rh factor. Donor baseline characteristics, including blood type and Rh factor, will also be summarized. Descriptive statistics will be presented for weight, height, and BMI; frequency counts and percentages will be presented for the blood type and Rh factor.

Baseline disease characteristics will be summarized for baseline KPS score, KPS score at screening, time from initial diagnosis, primary disease and current diagnosis status, extramedullary involvement, prior therapy for disease, conditioning regimen used, donor-recipient gender disparity, donor CMV status, recipient CMV status, and donor-recipient CMV status. Descriptive statistics will be presented for time from initial diagnosis; frequency counts and percentages will be presented for all other baseline disease characteristics.

The number and percentage of subjects with 8/8 HLA matches (HLA-A, -B, -C, and -DRB1) will be tabulated. The HLA typing of donors and recipients, including HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DP, and HLA-DQ, will be listed.

Duration of hospitalization for transplant from the time of admission for transplant to the first date of discharge will be summarized using descriptive statistics.

5.2.1.3 Medical History

Medical history will be collected at the screening visit. Updated medical history information will be collected at subject conditioning and the hospital admission visit. Summaries and listings of relevant medical history data will use the combination of all medical history data collected for each subject. Summaries using frequency counts and percentages will be presented for the safety population by phase, treatment group, Phase 2 total (control and ProTmune), pooled ProTmune group (Phase 1 and Phase 2), and overall total.

The reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA; see Appendix 1) and will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT), sorted by the overall total by descending frequency of the SOC and by descending frequency of the PT within each SOC.

5.2.1.4 Prior Therapy for Disease

Summaries of prior therapy for disease will be presented for the safety populations by phase, treatment group, Phase 2 total (control and ProTmune), pooled ProTmune group (Phase 1 and Phase 2), and overall total.

Prior therapy includes medications and other therapies that were taken or administered prior to and stopped at least 1 day (Day -1) before the infusion on Study Day 1. Prior therapies will be coded using the World Health Organization (WHO) Drug Dictionary (see Appendix 1). Summaries of prior therapies will be sorted by the overall total by descending frequency of the anatomic therapeutic class (ATC) and by descending frequency of the preferred name within each ATC.

5.3 Analysis of Disposition, Protocol Deviations, and Exposure Data

5.3.1 Summary of Subject Disposition

Subject disposition will be summarized for all screened subjects. The following subject disposition categories will be summarized using frequency counts by phase (Phase 1, Phase 2), pooled ProTmune group (Phase 1 and Phase 2), and overall total:

- Subjects screened
- Subjects who were screen failures (applicable to Phase 1 ProTmune, Phase 2 total, and overall total)
  - Prior to randomization
  - After randomization
- Subjects who were randomized
  - NOTE: For Phase 1, this includes subjects who signed the informed consent form and met all eligibility criteria.
- Subjects who received IP

Subsequent subject disposition information will be summarized using frequency counts and percentages by phase, treatment group, Phase 2 total, pooled ProTmune group (Phase 1 and Phase 2), and overall total for the ITT and mITT populations for the following disposition categories:

- Subjects in the analysis populations: ITT, mITT, PP, and safety
- Subjects in each of the visit categories completed (e.g., Visit Day +28, Visit Day +100, Visit Day +180, Visit Day +270, Visit Day +365, and Visit Day +730)
- Subjects' most recent/last study visits, with categories of the nominal visit/study day
- Subjects who did not complete the first year of the study, with reason for withdrawal
  - Primary reason for withdrawal was related to COVID-19
- Subjects who did not complete the 2-year follow-up of the study, with reason for withdrawal
  - Primary reason for withdrawal was related to COVID-19

Follow-up time since transplantation in days through the 2-year follow-up will be summarized using descriptive statistics.

Percentages will be based on the number of subjects in the ITT and mITT populations.

The distribution of subjects at each study center and country will be summarized in a separate table for subjects in the ITT population.

Subject disposition will be presented at the 1-year completion for the primary analysis and at the completion of the 2-year follow-up for the final analysis. For the primary analysis at the 1-year completion, summaries for Day +730 and follow-up time since transplantation through the 2-year follow-up will be based on available data at the time of the database lock.

5.3.2 Protocol Deviations

Protocol deviations are tracked throughout the conduct of the study and documented by the clinical research associates in a separate Clinical Trials Management System. In addition, protocol deviations regarding study visits (missed visit, altered or partially completed visit, or out of window visit) impacted by COVID-19 will be captured on the electronic Case Report Form (eCRF). Protocol deviations are categorized as CSR reportable and CSR non-reportable per the Protocol Deviation Plan.

A list of protocol deviations for all subjects will be reviewed during the blind data review meeting, which will occur prior to the database lock at the completion of the 1 year on study (Day +365).

All CSR-reportable protocol deviations will be categorized per the Protocol Deviation Plan and summarized by phase and treatment group for the mITT population. All CSR-reportable protocol deviations will be presented in a data listing.

All COVID-19-related protocol deviations will be summarized by phase and treatment group for the mITT population and will be listed by subject.

5.3.3 Study Treatments and Extent of Exposure

5.3.3.1 Treatment Duration

Subjects will be administered a single infusion of either ProTmune or Control mPB units. The duration of the infusion will be derived from the start of the infusion to the end of the infusion. The duration of the infusion (in minutes) will be summarized by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) for the safety population.

5.3.3.2 Exposure to Investigational Product

IP is defined as either ProTmune or Control mPB units. The cumulative dose of IP (CD34+ total and CD34+/kg) will be summarized by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) as a continuous variable using descriptive statistics for the safety population.

In addition, CXCR4 expression on CD34+ cells (measured as mean fluorescence intensity [MFI] and as a percentage of cells) will be summarized by phase and treatment group as a continuous variable using descriptive statistics for the safety population.

5.3.3.3 Dose Modifications – Interruption or Reserved Cell-Dose Utilization

A summary of subjects with the entire infusion administered and subjects requiring infusion modifications, including infusion interruption with reason for infusion interruption, will be presented by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) for the safety population. Likewise, a summary of subjects requiring utilization of the reserved cell dose in Phase 1 will be presented.

5.4 Analysis of Safety Data

All analyses of safety data will be conducted using the safety population, unless otherwise specified. Safety summaries will be provided by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2). No formal hypothesis will be tested for safety data. Categorical endpoints will be summarized using number and percentage of subjects within each category. Continuous endpoints will be summarized descriptively with summary statistics (n, mean, standard deviation, standard error, median, first quartile [Q1], third quartile [Q3], minimum, and maximum).

5.4.1 Adverse Events

AEs will be coded per MedDRA (see Appendix 1). Subjects with multiple events reported for the same PT will be counted only once per SOC level and PT level. When reporting AEs by severity, events will be included within the highest severity recorded in each study period (e.g., Conditioning Period vs. Treatment Period).

The severity of AEs will be graded per NCI CTCAE, v4.03 (see Appendix 1), where applicable. If an AE is not graded per CTCAE, severity will be assessed according to the following scale: mild, moderate, severe, life-threatening, or death. The incidence of AEs will be summarized by severity for the following categories: Grade 1/Mild, Grade 2/Moderate, Grade 3/Severe, Grade 4/Life-threatening, or Grade 5/Death. AEs of infections will use both the CTCAE and the Bone and Marrow Transplant Clinical Trials Network (BMT CTN) criteria. AEs with a missing severity assessment will be presented in the summary table as a severity category of "Missing."

AEs will be recorded on the eCRF as follows:

- All serious adverse events (SAEs) will be recorded from Day -10, the start of conditioning regimen dosing, through Day +365, and only SAEs related to infused cells (ProTmune ex vivo modulated mPB cells or unmodulated mPB cells) from Day +366 through Day +730
- From the start of conditioning regimen dosing (Day -10) through Day +100: AEs associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5) and all other AEs (Grades 2 through 5). Laboratory abnormalities will only be recorded as AEs if deemed clinically significant by the investigator.
- From Day +100 through Day +365: Only AEs associated with GvHD, infections, or secondary engraftment failure (Grades 1 through 5)

5.4.1.1 Adverse Events During the Conditioning Period

AEs during the conditioning period are defined as AEs with a start date and time on or after the start of conditioning-regimen dosing and prior to the administration of IP.

5.4.1.2 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs with a start date and time on or after the administration of IP. If the start time of the AE is unknown but is on the same day as the first administration of IP, the AE will be deemed a TEAE.

5.4.1.3 GvHD-Related Adverse Events

AEs that the investigator indicates are related to GvHD are considered signs and symptoms of GvHD. GvHD-specific details are also collected on separate eCRFs to assess efficacy.

5.4.1.4 Summaries of Adverse Events and Treatment-Emergent Adverse Events

An overview of AEs during the study will be provided that summarizes subject incidence of the following information:

AEs starting during the conditioning period:

- All AEs
- Conditioning-regimen-related AEs
- GvHD-prophylaxis-related AEs
- SAEs

TEAEs:

- All TEAEs, IP-related TEAEs, conditioning-regimen-related TEAEs, GvHD-prophylaxis-related TEAEs, GvHD-related TEAEs, and CMV-related TEAEs
- Grade 3 or higher TEAEs, IP-related Grade 3 or higher TEAEs, conditioning-regimen-related Grade 3 or higher TEAEs, GvHD-prophylaxis-related Grade 3 or higher TEAEs, GvHD-related Grade 3 or higher TEAEs, and CMV-related Grade 3 or higher TEAEs
- Treatment-emergent SAEs (TESAEs), IP-related TESAEs, conditioning-regimen-related TESAEs, GvHD-prophylaxis-related TESAEs, GvHD-related TESAEs, and CMV-related TESAEs
- Discontinuation from the study due to TEAEs and discontinuation from the study due to IP-related TEAEs, conditioning-regimen-related TEAEs, GvHD-prophylaxis-related TEAEs, GvHD-related TEAEs, and CMV-related TEAEs
- TEAEs leading to deaths: All TEAEs, IP-related TEAEs, conditioning-regimen-related TEAEs, GvHD-prophylaxis-related TEAEs, GvHD-related TEAEs, and CMV-related TEAEs

Incidence of TEAEs and TESAEs will be summarized for each treatment group by SOC and PT and will also be repeated by study period (overall, Study Day 1 for infusion reactions, Study Days 2-29, Study Days 30-101, Study Days 102-181, Study Days 182-366, and Study Days >366).

Additional summaries for TEAEs where (1) the difference in incidence between the Phase 2 ProTmune and control groups is by at least 2 subjects and (2) the incidence in the Phase 2 ProTmune group is greater than or equal to 10% will be presented by SOC and PT, and by PT only for each treatment group.

IP-related TEAEs and TESAEs, Grade 3 or higher TEAEs and TESAEs, GvHD-prophylaxis-related TEAEs, and TEAEs leading to withdrawal from the study will be summarized by SOC and PT for each treatment group.

Summaries will also be provided by the highest NCI CTCAE grade for subjects with TEAEs by SOC and PT. TESAEs and IP-related TEAEs will also be summarized in the same manner. For these summaries, subjects with multiple AEs will be counted only once by the highest NCI CTCAE grade within an SOC and by PT.

TEAEs and TESAEs for infections and Grade 3 or higher TEAEs and TESAEs for infections will be summarized by the highest BMT CTN grade for subjects with infections by SOC and PT. For these summaries, subjects with multiple AEs for infections will be counted only once by the highest BMT CTN grade within an SOC and by PT.

AEs, conditioning-regimen-related AEs, GvHD-prophylaxis-related AEs, and SAEs starting during the conditioning period will be summarized separately by SOC and PT.

Additional summaries will be presented for TEAEs, IP-related TEAEs, TESAEs, IP-related TESAEs, Grade 3 or higher TEAEs, and IP-related Grade 3 or higher TEAEs by PT only for each treatment group.

5.4.1.5 Deaths and Other Serious Adverse Events

All deaths, SAEs, and AEs leading to discontinuation of the study will be listed by phase, treatment, and subject. Subject data listings will be updated based on the completion of the 2-year follow-up.

5.4.1.6 Hospitalizations for Serious Adverse Events

The total number of days in the hospital for SAEs through Day +365 will be summarized using descriptive statistics.

5.4.1.7 Febrile Neutropenia

Febrile neutropenia, as collected on the eCRF, is based on NCI CTCAE, v4.03. The number of subjects with febrile neutropenia, as part of the TEAEs, will be summarized using frequency counts and percentages and will be presented by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) for the safety population.

5.4.2 Clinical Laboratory Evaluations

Clinical laboratory data (chemistry and hematology) will be presented by phase and treatment group for the safety population. Both scheduled and unscheduled visits will be considered when evaluating the worst, maximum, minimum, or last clinical laboratory value for all analyses.

Chemistry and hematology (excluding differentials in %) results at each timepoint, including the maximum value on study, minimum value on study, and last value on study, will be summarized using descriptive statistics.

All chemistry values will be categorized as low, normal, or high relative to the normal range. Shift tables from baseline to worst post-baseline value, and from screening to Visit Day +100, will be summarized using frequency counts and percentages for the following categories: low, normal, high, and missing.

Abnormal laboratory results will be graded according to NCI CTCAE, v4.03, if applicable. Shift tables from baseline to the worst post-baseline value according to the NCI CTCAE grade will be provided for selected chemistry parameters (ALT, AST, total bilirubin, alkaline phosphatase, and creatinine). NCI CTCAE grade shift tables will also be repeated from screening to Visit Day +100.

The number and percentage of subjects with the following potentially clinically significant abnormal liver function tests will be summarized by phase and treatment group:

- ALT ≥3 × upper limit of normal (ULN), ≥5 × ULN, and ≥10 × ULN
- AST ≥3 × ULN, ≥5 × ULN, and ≥10 × ULN
- ALT and AST ≥3 × ULN, ≥5 × ULN, and ≥10 × ULN
- Total bilirubin >2 × ULN
- Potential Hy's Law cases: ALT or AST >3 × ULN, total bilirubin ≥2 × ULN, and ALP <2 × ULN

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot with a log/log display of correlation between peak total bilirubin versus ALT or AST post-baseline will be presented by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2). A data listing of subjects that are considered potential Hy's Law cases will be presented and will include the ULN values identified in the eDISH plot.

Line plots will be provided for the mean value over time for all chemistry parameters and hematology parameters (excluding differentials in %) by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2).

All laboratory data will be listed by subject. Values outside the normal ranges will be flagged. In addition, NCI CTCAE grades will be included, where applicable.

5.4.3 Engraftment, Graft Failure, and Chimerism

Summaries for engraftment and chimerism endpoints will be presented by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) using the safety population.

5.4.3.1 Neutrophil Engraftment

Neutrophil engraftment per CIBMTR is defined as the first date of 3 consecutive laboratory values of an ANC $\geq 0.5 \times 10^9$/L obtained on different days.

Neutrophil engraftment per CIBMTR will be summarized for the number of subjects with engraftment at any time, including a subcategory for subjects that engraft through Visit Day +28, the number of subjects that never have an ANC value below 0.5×10^9/L, and the number of subjects that did not engraft.

Time to neutrophil engraftment per CIBMTR will be calculated as the number of days from the date of transplantation to the first date of neutrophil engraftment for subjects who achieved neutrophil engraftment post-transplant and will be summarized descriptively.

5.4.3.2 Platelet Engraftment

Platelet engraftment per CIBMTR is defined as the first date of 3 consecutive laboratory values of platelets $\geq 20 \times 10^9$/L obtained on different days on or after Study Day 7 without platelet transfusions within the preceding 7 days.

Platelet engraftment per CIBMTR will be summarized for the number of subjects with engraftment at any time, including a subcategory for subjects that engraft through Visit Day +100, the number of subjects that never have a platelet value below 20×10^9/L, and for the number of subjects that did not engraft.

Time to platelet engraftment per CIBMTR will be calculated as the number of days from the date of transplantation to the first date of platelet engraftment for subjects who achieved platelet engraftment post-transplant and will be summarized descriptively.

5.4.3.3 Primary and Secondary Graft Failure

Primary graft failure is defined as the subject not ever meeting the definition of neutrophil engraftment or any use of the reserve hematopoietic cell product (in Phase 1). If donor engraftment is not present through Visit Day +28 bone marrow examination and the subject's disease is not present, the subject is also considered as a primary graft failure (in the absence of relapsed disease).

Secondary graft failure is defined as a graft failure occurring after initial engraftment (ANC $\geq 0.5 \times 10^9$/L), including the presence of >95% recipient CD3+ cells, re-infusion of donor cells because of permanent loss of neutrophils (ANC $< 0.5 \times 10^9$/L) and/or platelets $< 30 \times 10^9$/L, or >50% recipient CD3+ cells and treatment with donor lymphocyte infusion.

The number of subjects with primary graft failure and the number of subjects with secondary graft failure will be summarized using frequency counts and percentages.

5.4.3.4 Chimerism

Donor chimerism will be assessed on peripheral blood samples collected on Visit Days +28, +100, +180, and +365. Donor chimerism may be reported as total chimerism (from unseparated blood) or as fractional chimerism (myeloid [neutrophil] or lymphoid [T cell] from separated cell populations). Chimerism will be measured by polymerase chain reaction (PCR) amplification of DNA sequences from recipient- and donor-derived cells, which may include single nucleotide polymorphism, fragment length polymorphism, and/or DNA microsatellite (short tandem repeats) analyses consistent with institutional standards and according to local laboratory practices. If there is no evidence of donor engraftment by Day +21 then chimerism studies will be performed on both bone marrow and peripheral blood at approximately that timepoint. Subjects who never have >5% total chimerism in the peripheral blood or bone marrow in the absence of relapsed disease are considered to have primary graft failure.

At any time post-transplant:

- Complete chimerism is defined as ≥95% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available).
- Mixed chimerism is defined as ≥10 to <95% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available).
- Chimerism <10% is defined as <10% donor cells detected in T cells or in the total unseparated sample (if fractionated results for T cells are not available).

The following summaries will be performed at Visit Days +28, +100, +180, and +365, and at any time through Day +365 using descriptive statistics categorically (e.g., ≥95% to 100%, 50% to <95%, 10 to <50%, and <10%) to assess chimerism:

- Total (unfractionated) donor chimerism, assessed as the percentage of donor cells in an unseparated blood sample
- T-cell chimerism, assessed as the percentage of donor cells in the lymphoid fraction of the peripheral blood

Additional summaries include:

- Proportion of subjects with complete chimerism, mixed chimerism, and chimerism <10% at Visit Days +28, +100, +180, and +365, and at any time through Day +365

5.4.4 Vital Sign Measurements

Vital sign data will be presented in a by-subject data listing.

5.4.5 Physical Examination

Physical examination findings will be presented in a by-subject data listing.

5.4.6 Prior and Concomitant Therapy/Procedures

Prior and concomitant therapy/procedures will be summarized. Prior and concomitant therapy/procedures include medications and other therapies/procedures that were taken or administered either prior to transplantation (Study Day 1) and continued to or after Study Day 1 or medications and other therapies starting on or after Study Day 1. Prior and concomitant therapies will be coded using the WHO Drug Dictionary (see Appendix 1).

Summaries of prior and concomitant therapies will be sorted by descending frequency of the ATC and descending frequency of the preferred name and will be presented by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2).

5.4.7 Electrocardiograms

Summaries of ECG interval actual values and change from baseline by timepoint and by phase, treatment group, and pooled ProTmune group (Phase 1 and Phase 2) will be presented.

The incidence of notable ECG changes in maximum absolute QT and QTcF intervals (>450, >480, and >500 msec) over all post-treatment evaluations, as well as in QT and QTcF maximum changes from baseline (>30 and >60 msec) over all post-treatment evaluations, will be summarized.

All triplicate ECG measurements at a particular timepoint will be averaged prior to analysis and summarization.

All ECG measurements and the investigator interpretation of findings, including details of any abnormalities, will be listed by subject.

5.5 Analysis of Efficacy Data

Based on the timing from randomization to infusion of IP, a post-randomization screen failure may occur if the mPB donor collection unit fails to meet the requirements for ProTmune or control processing (see Section 4.4 of the protocol). As such, the ITT population will only be used to summarize subject disposition.

Efficacy analyses will be performed based on the mITT population. Sensitivity analyses will be performed on the primary and key secondary efficacy endpoints for Phase 2 based on the PP population. The relationship of the following covariates to the primary and key secondary efficacy endpoints in the models will also be explored using the mITT population:

- Age (continuous)
- Sex (female, male)
- Conditioning regimen (with TBI, without TBI)
- Baseline KPS score (continuous)
- Primary indication for transplant (acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia)
- Time from diagnosis of disease to HCT (continuous)
- Donor-recipient gender (matched, unmatched)
- Donor age (continuous)

Efficacy data from Phase 1 and Phase 2 will be summarized separately. Summary tables will present results for each phase by treatment group. All efficacy data will be summarized using the 1-year data for the primary analysis. For the survival follow-up analyses at 2 years, NRM, RFS, and survival will be summarized for the final analysis. Subject data listings will be updated based on the completion of the 2-year follow-up.

No formal hypothesis tests will be performed for Phase 1. Formal statistical tests will be performed for the primary and key secondary efficacy endpoints of Phase 2 each at a two-sided 0.05 significance level.

5.5.1 Analysis of Primary Efficacy Endpoint: Cumulative Incidence of CIBMTR Grade II-IV aGvHD Through Visit Day +100

The primary efficacy endpoint is the cumulative incidence of CIBMTR Grade II through IV aGvHD through Visit Day +100, based on investigator results in the mITT population; death and relapse without Grade II-IV aGvHD will be considered competing risks. Subjects who are alive with no occurrence of Grade II-IV aGvHD through Visit Day +100 will be censored at their last assessment for aGvHD on or prior to Visit Day +100.

Acute GvHD clinical and laboratory assessments will be performed weekly from Visit Day +1 through Visit Day +100 per the CIBMTR aGvHD Scoring System for Individual Organs (see Appendix 4). Each study site will determine the presence or absence of aGvHD by assigning the clinical stage for the target organs (skin, liver, and gut) along with assigning an overall grade based on the minimum degree of organ involvement required to confer that grade.

Phase 1: A cumulative incidence curve will be constructed for the primary efficacy endpoint along with curves for death and relapse without Grade II-IV aGvHD as competing risks. The first day of Grade II-IV aGvHD will be used to estimate the cumulative incidence curve. The estimate of the cumulative incidence rate of Grade II-IV aGvHD by Visit Day +100 (i.e., Target Study Day 101 post-HCT) and the associated two-sided 95% confidence intervals will be estimated based on the cumulative incidence function with variance estimated using the Delta method.

Phase 2: The null and alternative hypotheses for the primary efficacy endpoint in Phase 2 are as follows:

- H_0 (null hypothesis): There is no difference in the cumulative incidence of CIBMTR Grade II-IV aGvHD (with death or relapse without CIBMTR Grade II-IV aGvHD as competing events) through Visit Day +100 between the ProTmune and control groups.
- H_1 (alternative hypothesis): There is a difference in the cumulative incidence of CIBMTR Grade II-IV aGvHD (with death or relapse without CIBMTR Grade II-IV aGvHD as competing events) through Visit Day +100 between the ProTmune and control groups.

The cumulative incidence functions for CIBMTR Grade II-IV aGvHD by Visit Day +100 between the two treatment groups will be compared using Gray's test (Gray 1988) at a two-sided 0.05 significance level. The corresponding hazard ratio of the treatment effect along with the 95% confidence interval will be calculated using the Fine and Gray's subdistribution hazard model (Fine and Gray 1999) with treatment as an explanatory variable. The cumulative incidence curves for each treatment group and estimates of the cumulative incidence rate by Visit Day +100 (i.e., Target Study Day 101 post-HCT) along with the associated two-sided 95% confidence intervals will be presented in the same manner as described in Phase 1.

5.5.2 Analysis of the First Key Secondary Efficacy Endpoint

The first key secondary efficacy endpoint is the 1-year GRFS in the mITT population. GRFS per BMT CTN is a composite endpoint in which events include Grade III-IV aGvHD, cGvHD requiring systemic immunosuppressive therapy, relapse, or death from any cause (Holtan et al. 2015). GRFS is defined as the time from the date of transplantation to the earlier of the dates of the first documented CIBMTR Grade III-IV aGvHD, first use of systemic immunosuppressive therapy for cGvHD, first documented relapse of the underlying malignancy, or death from any cause. Subjects who are alive with no documented events for Grade III-IV aGvHD, use of systemic immunosuppressive therapy for cGvHD, relapse, or death at the data cutoff will be censored at their last visit date or follow-up on or prior to the date of one-year study completion/early discontinuation. The number of subjects with an event failure along with counts for the earliest

contributing event and the number of subjects censored will be summarized by phase and treatment group.

Phase 1: Kaplan-Meier estimates of GRFS will be summarized by phase and treatment group. The quartiles, including the median GRFS and their respective two-sided 95% confidence intervals, will be presented. The estimated GRFS rate at Visit Day +365 (i.e., Target Study Day 366 post-HCT) will be presented along with the 95% confidence intervals. The Kaplan-Meier curves will also be presented.

Phase 2: The null and alternative hypotheses for the first key secondary efficacy endpoint in Phase 2 are as follows:

- H_0 (null hypothesis): There is no difference in the 1-year GRFS between the ProTmune and control groups.
- H_1 (alternative hypothesis): There is a difference in the 1-year GRFS between the ProTmune and control groups.

Phase 2: Kaplan-Meier estimates and curves for GRFS will be presented in the same manner as described in Phase 1. A two-sided log-rank test will be used to compare GRFS between the two treatment groups. In addition, the hazard ratio of the treatment effect on GRFS along with the 95% confidence interval will be calculated using a Cox proportional hazards model with treatment as an explanatory variable.

The estimate of the GRFS rate at Visit Day +180 (i.e., Target Study Day 181 post-HCT) will be provided along with the 95% confidence intervals.

5.5.3 Analysis of the Second Key Secondary Efficacy Endpoint

The second key secondary efficacy endpoint is the proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria for the global severity score at Visit Day +365 in the mITT population. Subjects meeting these criteria will be considered responders. Subjects who discontinued early from the study or subjects who had relapse, moderate or severe cGvHD, or death prior to or at Visit Day +365 will be considered non-responders.

Phase 1: The number of subjects that are alive without relapse and without moderate or severe cGvHD at Visit Day +365 will be summarized using counts and percentages. The 95% exact binomial confidence intervals for the percentage will also be presented. Summaries will also include the number of subjects that are considered non-responders.

Phase 2: The null and alternative hypotheses for the second key secondary efficacy endpoint in Phase 2 are as follows:

- H_0 (null hypothesis): There is no difference in the proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria at Visit Day +365 between the ProTmune and control groups.

- H_1 (alternative hypothesis): There is a difference in the proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria at Visit Day +365 between the ProTmune and control groups.

Statistical comparison between treatment groups will be performed using a logistic regression model with treatment as a covariate. The odds ratio between the two treatments will be estimated along with the 95% confidence interval. The same summaries described in Phase 1 will be presented for each treatment group.

5.5.4 Sensitivity Analyses

Sensitivity analyses of the primary and key secondary efficacy endpoints will be performed based on the PP population to assess the robustness of the primary analyses.

5.5.5 Analysis of Exploratory Efficacy Endpoints

Exploratory endpoints will be summarized descriptively by phase and treatment groups using the mITT population, unless otherwise noted. For Phase 2, nominal two-sided p-values (without adjustment for multiple comparisons) will be reported as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

5.5.5.1 Exploratory Analyses Using Cumulative Incidence Function

Chronic GvHD assessments for each organ system and global severity will be scored based on the NIH Consensus Criteria (Filipovich, et al. 2005; see Appendix 4). Chronic GvHD assessments of mild, moderate, or severe cGvHD per NIH Consensus Criteria for cGvHD must be performed on Days +180, +270, and +365.

Analyses of the cumulative incidence of aGvHD and cGvHD, and analysis of NRM, will be performed using the cumulative incidence function for the mITT population in the same manner as the primary efficacy endpoint (see Section 5.5.1):

- Cumulative incidence through Visit Day +100 and through Visit Day +180:
  - CIBMTR Grade III-IV aGvHD
  - Maximum CIBMTR Grade II-IV aGvHD
  - Maximum CIBMTR Grade III-IV aGvHD
  - Maximum CIBMTR Grade II-IV aGvHD based on EAC-adjudicated results
  - Maximum CIBMTR Grade III-IV aGvHD based on EAC-adjudicated results
  - CIBMTR Grade II-IV aGvHD without skin involvement
  - CIBMTR Grade III-IV aGvHD without skin involvement

  For these analyses, death and relapse without the specified grades of aGvHD will be considered competing risks. Subjects who are alive with no occurrence of the specified grades of aGvHD

through Visit Day +100 or Visit Day +180 will be censored at their last assessment for aGvHD on or prior to Visit Day +100 or Visit Day +180.

The concordance rate between the investigator assessment and the EAC-adjudicated assessment for the maximum CIBMTR Grade II-IV aGvHD and the maximum CIBMTR Grade III-IV aGvHD results through Day +100 and through Day +180 will be evaluated.

- Cumulative incidence of NRM. All deaths in the absence of relapse of the primary malignancy will be considered NRM, where relapse will be considered a competing risk; subjects that are alive at the data cutoff without relapse will be censored at their last assessment date the subject is known to be alive. NRM will be assessed at 1 and 2 years (i.e., Target Study Days 366 and 731 post-HCT, respectively).
- Cumulative incidence of moderate or severe cGvHD per NIH Consensus Criteria for the global severity score cGvHD through Visit Day +365. Death and relapse without moderate or severe cGvHD will be considered competing risks; subjects who are alive with no occurrence of moderate or severe cGvHD per NIH Consensus Criteria through Visit Day +365 will be censored at their last assessment date for cGvHD. Subjects without any assessments for cGvHD per NIH Consensus Criteria will be censored on the date of infusion of IP (i.e., Study Day 1).

5.5.5.2 Exploratory Efficacy Analyses Using Kaplan-Meier Methods

The following time-to-event exploratory efficacy endpoints will be summarized by phase and treatment group using Kaplan-Meier methods in the same manner as described above for the key secondary efficacy endpoint of 1-year GRFS analysis:

- **1-year CRFS**, a composite endpoint in which events include any cGvHD requiring systemic immunosuppressive therapy, relapse, or death from any cause (Pasquini et al. 2018) through 1 year; subjects who are alive with no documented events for cGvHD requiring systemic immunosuppressive therapy, relapse, or death will be censored at their last visit date or follow-up on or prior to the date of one-year study completion/early discontinuation.
- **RFS**, defined as the time from the date of transplantation to the earlier of the dates of the first documented relapse of the underlying malignancy or death due to any cause. Subjects who are alive with no documented relapse will be censored at their last assessment date the subject is known to be alive. RFS will be assessed at 1 and 2 years (i.e., Target Study Days 366 and 731 post-HCT, respectively).
- **OS**, defined as the time from the date of transplantation to death due to any cause. Subjects who are still alive at the data cutoff will be censored at the last date the subject is known to be alive. OS will be assessed at 1 and 2 years (i.e., Target Study Days 366 and 731 post-HCT, respectively).

The Kaplan-Meier estimates along with the 95% confidence intervals will be presented for the time-to-event variables.

5.5.5.3 Other Exploratory Efficacy Analyses

All other exploratory efficacy endpoints will be summarized descriptively by phase and treatment group using the mITT population.

- Proportion of subjects with steroid-refractory aGvHD, defined as subjects who have started a new systemic immunosuppressive therapy after initial systemic steroid use for the treatment of aGvHD
- Cumulative dose of systemic steroid for GvHD, converted to cumulative systemic prednisone equivalent dose in mg (refer to Appendix 2 for conversions)

In addition to the analyses described above, the highest stage for each organ system and the maximum overall grade per the CIBMTR aGvHD Grading Scale will be summarized through Visit Day +100, Visit Day +180, and through the last study visit.

Chronic GvHD assessments for each organ system and the global severity score will be summarized at each visit using descriptive statistics. In addition, the highest organ system scores and the maximum global severity score will also be summarized.

5.5.6 Analysis of Exploratory GvHD Biomarker Data and Immune Reconstitution Data

Select exploratory GvHD biomarkers will be summarized at each assessment (Visit Days +7, +14, +21, +28, +35, +42, and +100) using descriptive statistics by phase and treatment group for the mITT population.

Immune reconstitution will be evaluated with B cells, T cells, and NK cells. Each lymphocyte subset (NK cells, T cells, CD4+ T cells, CD8+ T cells, Treg, and B cells) will be described from the Visit Day +91 and Visit Day +365 using descriptive statistics by phase and treatment group for the mITT population. Immune reconstitution results will be presented in a data listing.

6 CHANGES TO PROTOCOL-PLANNED ANALYSES

The purpose of this section is to document changes from the planned analyses specified in Protocol PT-001 (Version 6.0, 29 March 2019) as noted below.

The following changes were made from the protocol-planned efficacy analyses:

Protocol Section 7: Efficacy Assessments

- 1-year GRFS was moved from an exploratory endpoint to a key secondary endpoint and will also be assessed at Day +180
- The following exploratory efficacy endpoints have been removed:
  - Cumulative incidence through Visit Day +100 and through Visit Day +180 of:

    CIBMTR Grade I-II aGvHD

    CIBMTR Grade I-IV aGvHD

- Duration of the maximum CIBMTR Grade aGvHD through Visit Day +100
- Duration of CIBMTR Grade II-IV aGvHD through Visit Day +100
- Duration of CIBMTR Grade III-IV aGvHD through Visit Day +100
- Time to individual event components for GRFS:

  Time to CIBMTR Grade III-IV aGvHD

  Time to first use of cGvHD requiring systemic immunosuppressive therapy

  Time to relapse

  Time to death
- Proportion of subjects with systemic steroid use for aGvHD
- Time to first use of systemic steroids for aGvHD
- Total number of days of systemic steroid use for aGvHD
- Proportion of subjects with second-line therapies for treatment of aGvHD
- Time to first use of second-line therapies for treatment of aGvHD
- Proportion of subjects who are CMV-positive at baseline with subsequent CMV reactivation. CMV reactivation is defined as subjects who have initiated antiviral therapy for CMV.
- Time to first treatment for CMV reactivation

- The endpoint of the proportion of subjects with second-line therapies for treatment of aGvHD as the proportion of subjects with steroid-refractory aGvHD, defined as subjects who have started a new systemic immunosuppressive therapy after initial systemic steroid use for the treatment of aGvHD, was revised and clarified.
- Cumulative dose of systemic steroid for GvHD, converted to cumulative systemic prednisone equivalent dose in mg, was added as an exploratory endpoint.

The overall rationale for these changes was to focus on established clinically relevant endpoints in the setting of allogenic transplant and treating hematologic disease.

The rationale for moving the endpoint of GRFS from an exploratory endpoint to a key secondary endpoint was that GRFS is a more clinically meaningful and relevant endpoint because it provides additional context to the clinical benefit of being free from severe disease.

Protocol Section 9.2.1: Analysis of Efficacy

Age will not be included in the model for the primary and key secondary efficacy analyses. Instead, the covariates listed in Section 5.5 will be included in the models to explore the relationship to the primary and key secondary efficacy endpoints.

The key secondary efficacy endpoint for the proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria for the global severity score at Visit Day +365 will be evaluated for all subjects instead of observed cases for the primary analysis. Subjects meeting these criteria will be considered responders. Subjects who discontinued early from the study or subjects who had relapse, moderate or severe cGvHD, or death prior to or at Visit Day +365 will be considered non-responders.

Protocol Section 9.2.2: Analysis of Safety

All TEAEs will be included in the AE analyses; non-serious GvHD-related AEs will no longer be excluded and summarized separately in order to provide a more complete safety profile.

A separate summary for non-CMV infections will not be performed as there is no clinical relevance for excluding CMV infections.

Given the heterogeneity and imprecision regarding vital sign collection that confounds interpretation of trends across subject groups, vital sign data will not be summarized using descriptive statistics and will be presented in a by-subject data listing.

7 SUPPORTING DOCUMENTATION

This section includes the following supporting documentation:

- Appendix 1: Reporting Conventions
- Appendix 2: Technical Appendix for Statistical Methodology
- Appendix 3: Conventions Related to Dates
- Appendix 4: Additional Relevant Appendices from the Protocol
- Appendix 5: Table, Figure, and Listing Shells
- Appendix 6: List of Abbreviations

Appendix 1 Reporting Conventions

1 TABLE, FIGURE, AND LISTING STANDARDS

General Considerations

Summary statistics will consist of the number (n) and percentage (%) in each category for categorical variables and n, mean, standard deviation (SD), standard error (SE), minimum, first quartile (Q1), median, third quartile (Q3) and maximum for continuous variables. The total group sample size (n) will also be presented in column headers of data tabulations.

Data from all study centers and geographical regions will be combined for overall analyses. Randomization stratification factors will be included as factors in statistical tests and models, as appropriate.

All data presented in tables will be listed, with appropriate cross-referencing from the table to the associated listing. Data listings will cross-reference the source dataset used in the production of the listing. Figures will cross-reference tables, as appropriate.

Number of Decimal Places and Rounding Rules Used in Reporting Numeric Results

The following will be used as the standard for reporting number of decimal places for numeric results:

Summary Statistic	Number of Decimal Places
n	0
Mean	Number in observed value + 1, up to a maximum of 3
Standard deviation/standard error	Number in observed value + 2, up to a maximum of 3
Quartiles (including median)	Number in observed value + 1, up to a maximum of 3
Percentage	1
Proportion	3
p-value [a]	4
Confidence interval – mean, standard deviation, or variance	Match number of decimal places in margin of error to number of decimal places in standard deviation
Confidence interval – proportion	3

[a] p-values that round to 0.0000 will be presented as <0.0001, and p-values that round to 1.0000 will be presented as >0.9999.

Format for Tables, Figures, and Listings

All tables, figures, and listings (TFLs) specified in this Statistical Analysis Plan will be provided as appendices in the Clinical Study Report. TFL numbering will follow International Council on Harmonisation E3 Structure and Content of Clinical Study Reports as follows:

Topic	Table and Figure Section Number Prefix	Listing Number Prefix
Demographics and baseline characteristics	14.1	16.2.1
Efficacy	14.2	16.2.2
Safety	14.3	16.2.3
Statistical documentation	N/A	16.1.9

2 DATA INTEGRATION AND STANDARDIZATION CONSIDERATIONS

Data from this study may be combined with data from other studies for integrated analyses. The below information is provided for consideration of consistency in data format and applicable standards should data from this study be integrated with other studies.

Standard	Version
ADaM	Version 2.1
ADaM Implementation Guide	Version 1.1
CDISC Controlled Terminology	2017-06-30
MedDRA	Version 18.1
NCI CTCAE	Version 4.03
SAS	9.3, 9.4
SDTM	Version 1.4
SDTM Implementation Guide	Version 3.2
WHODrug	Version March 2016E B2

ADaM = Analysis Data Model; CDISC = Clinical Data Interchange Standards Consortium; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SDTM = Standard Data Tabulation Model; WHO = World Health Organization

Appendix 2 Technical Appendix for Statistical Methodology

1 STUDY VISIT MAPPING AND WINDOWING FOR ANALYSIS

In order to align study visit names from the protocol with conventional reporting methods required under Clinical Data Interchange Standards Consortium (CDISC), protocol visit names will be mapped to study days for analysis and reporting for select data. The table below describes the methods for mapping study visit names to study day. Protocol-allowed visit windows converted to study days is provided for clarity on mapping of data from unscheduled and early termination visits. Unscheduled and early termination assessments that occur outside of the protocol visit window will not be mapped to a protocol-specified visit. Data recorded on the electronic Case Report Form corresponding to the protocol visit name will be used wherever possible for by-visit summaries except in the cases of time-to-event endpoints (e.g., acute graft-versus-host disease [aGvHD], chronic GvHD, neutrophil and platelet engraftment) in which the earliest event is used. If a scheduled visit is not available, the unscheduled or early termination visits within the visit window that is closest in time to the scheduled study day will be utilized. The latest time will be used in case of ties.

Mapping and Windowing for Protocol Visit Names to Study Days

Protocol Visit Name	Study Day	Protocol Visit Window (Study Days)
Screening Period	Day -53 to Day -12	N/A
Conditioning Period	Day -11 to Day -1	N/A
Day 0	Day 1	N/A
Day +1	Day 2	N/A
Day +7	Day 8	Day 5 to Day 11
Day +14	Day 15	Day 12 to Day 18
Day +21	Day 22	Day 19 to Day 25
Day +28	Day 29	Day 26 to Day 32
Day +35	Day 36	Day 33 to Day 39
Day +42	Day 43	Day 40 to Day 46
Day +49	Day 50	Day 47 to Day 53
Day +56	Day 57	Day 54 to Day 60
Day +63	Day 64	Day 61 to Day 67
Day +70	Day 71	Day 68 to Day 74
Day +77	Day 78	Day 75 to Day 81
Day +84	Day 85	Day 82 to Day 88
Day +91	Day 92	Day 89 to Day 95
Day +100	Day 101	Day 98 to Day 104
Day +180	Day 181	Day 167 to Day 195
Day +270	Day 271	Day 243 to Day 299
Day +365	Day 366	Day 338 to Day 394
Day +730	Day 731	Day 703 to Day 759

Using aGvHD as an example for censoring purposes, a subject without aGvHD and without either of the two competing events through Visit Day +100 (Study Day 101) would be censored at his or her date of last assessment on or prior to Visit Day +100. If their last assessment occurred at Visit Day +100 (Study Day 101), the actual study day could range from Day 98 to Day 104 per the protocol visit window; this censored data point could extend beyond the targeted study day of 101 (Visit Day +100) to 104 days. Similarly, if their last assessment occurred at Visit Day +84 (Study Day 85), the study day could range from Day 82 to Day 88.

2 SYSTEMIC PREDNISONE EQUIVALENT DOSE CONVERSION

Systemic prednisone equivalent dose conversions in mg are presented in the table below in order to evaluate systemic steroid use for GvHD.

Systemic Prednisone Equivalent Dose Conversion in mg

Medication	Route	Equivalent Dose (mg)	Prednisone Equivalent Conversion Factor
Betamethasone	IV	0.75	6.7
Cortisone	PO	25	0.2
Dexamethasone	IV or PO	0.75	6.7
Hydrocortisone	IV or PO	20	0.25
Methylprednisolone	IV or PO	4	1.25
Prednisolone	PO	5	1
Prednisone	PO	5	1
Triamcinolone	IV	4	1.25

Source: https://www.mdcalc.com/steroid-conversion-calculator
NOTES:
1. Prednisone equivalent conversion factor is calculated by dividing the equivalent dose for prednisone by the equivalent dose for each medication.
2. Systemic prednisone equivalent dose is calculated by multiplying the dose by the prednisone equivalent conversion factor.

Appendix 3 Conventions Related to Dates

1 HANDLING OF DATES

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

Procedure dates are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for protocol-specified procedures are present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.

Log dates are dates recorded in electronic Case Report Form (eCRF) data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as ongoing in the database. Otherwise, incomplete log dates will be imputed according to the rules in Section 2 of this appendix; however, in listings, log dates will be shown as recorded without imputation.

Milestone dates are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.

Outcome dates are dates corresponding to study endpoints such as survival, progression, etc. In most cases, they are derived either from a milestone (e.g., the survival date is derived from the death date) or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject- to endpoint-specific censoring rules if the outcome did not occur but are not otherwise subject to imputation.

Special dates cannot be classified in any of the above categories, and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

2 IMPUTATION OF PARTIAL DATES

If only a partial date is available and is required for a calculation, the following standards will be applied:

Diagnosis Date of Primary Disease

a. For missing day only: Day will be imputed as the first day of the month (i.e., 01).

b. For missing day and month: Day and month will be imputed as the first day of the year (i.e., 01 January).

Start Dates (e.g., adverse event [AE] onset date or start date of concomitant medication)

a. For missing onset/start day only: Day will be imputed as the first day of the month (i.e., 01) with the following exception: if the partial date falls in the same month and year as the date of infusion of Investigational Product (IP) then the partial date will be imputed to equal the date of infusion of IP.

b. For missing onset/start day and month: Day and month will be imputed as the first day of the year (i.e., 01 January) with the following exception: if the partial date falls in the same year as the date of infusion of IP then the partial date will be imputed to equal the date of infusion of IP.

c. Imputed start dates must be prior to the stop date.

Stop Dates (e.g., AE resolution date or stop date of concomitant medication)

a. For missing resolution/stop day only: Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).

b. For missing stop day and month: Day and month will be imputed as the last day of the year (i.e., 31 December).

c. Imputed resolution/stop dates should not exceed beyond the end of 1-year completion on study.

d. Imputed resolution/stop dates must be on or after the onset/start date.

3 CALCULATIONS USING DATES

Calculations using dates (e.g., subject's age or relative day after the infusion of IP) will adhere to the conventions described below.

Study days after the start day of IP will be calculated as the difference between the date of interest and the date of infusion of IP plus 1 day. The generalized calculation algorithm for relative day is the following:

If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE − DSTART) + 1

Or else use STUDY DAY = TARGET DATE − DSTART

Study Day 1 is the infusion of IP. Negative study days are reflective of observations obtained during the baseline/screening period.

Age (expressed in days) is calculated as:

AGE = CONSENT − DATE of BIRTH + 1

In practice, age will be transformed to years by dividing the difference by 365.25 days then rounding down to the closest integer.

- The preference is to use calculated age from the clinical database. When not available, calculated age from the eCRF or the Interactive Voice Response System may be used.
- Partial birth date: Impute the missing day as the 15th of the month; impute the missing month as July; set the missing age for the missing year.

Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

WEEKS = DAYS/7

Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

MONTHS = DAYS/30.4

Appendix 4 Additional Relevant Appendices from the Protocol

1 ACUTE GVHD SCORING SYSTEM FOR INDIVIDUAL ORGANS: CIBMTR SCALE

Stage	Skin	Liver	Gut
1	Rash on <25% of skin[a]	Bilirubin 2-3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash on 25%-50% of skin	Bilirubin 3-6 mg/dL	Diarrhea >1000 mL/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	--	Stage 2-3 or	Stages 2-4
IV[f]	Stage 4	Stage 4	--

Source: CIBMTR Forms Manual: Post-TED (Form2450); A00425 version 2.0 (8/01/2012).

[a] Use "Rule of Nines" or burn chart to determine extent of rash.

[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[c] Volume of diarrhea applies to adults. For pediatric subjects, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[d] Persistent nausea with histologic evidence of GvHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV may also include lesser organ involvement with an extreme decrease in Performance Status.

CIBMTR = Center for International Blood and Marrow Transplant Research; GvHD = Graft-versus-host disease

2 NIH CONSENSUS CRITERIA FOR CHRONIC GVHD

Performance Score:	SCORE 0	SCORE 1	SCORE 2	SCORE 3
KPS, ECOG LPS	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%).	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80%-90%).	Symptomatic, ambulatory, capable of selfcare, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60%-70%).	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%).
Skin Clinical features: • Maculopapular rash • Lichen planus-like features • Papulosquamous lesions or ichthyosis • Hyperpigmentation • Hypopigmentation • Keratosis pilaris • Erythema • Erythroderma • Poikiloderma • Sclerotic features • Pruritus • Hair involvement • Nail involvement	No symptoms.	<18% BSA with disease signs but **NO** sclerotic features.	19%-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pitch).	>50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration, or severe pruritus.
Mouth	No symptoms.	Mild symptoms with disease signs but not limiting oral intake significantly.	Moderate symptoms with disease signs **with** partial limitation of oral intake.	Severe symptoms with disease signs on examination **with** major limitation of oral

(Continued)

Performance Score:	SCORE 0	SCORE 1	SCORE 2	SCORE 3
(Continued)				
Eyes Mean tear test (mm): • >10 • 6-10 • ≤5 **Not done**	No symptoms.	Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤3 × per day) **OR** asymptomatic signs of keratoconjunctivitis sicca.	Moderate dry eye symptoms partially affecting ADL (requiring drops >3 × per day or punctal plugs), **WITHOUT** vision impairment.	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca.
Gastrointestinal Tract	No symptoms.	Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain, or diarrhea without significant weight loss (<5%).	Symptoms associated with mild to moderate weight loss (5%-15%).	Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation.
Liver	Normal LFT.	Elevated bilirubin, AP[a], AST, or ALT.	Bilirubin >3 mg/dL or bilirubin, enzymes 2-5 × ULN.	Bilirubin or enzymes >5 × ULN.
Lungs[b] **FEV1** **DLCO**	No symptoms. • FEV1 >80% **OR** LFS = 2	Mild symptoms (shortness of breath after climbing 1 flight of steps). • FEV1 60%-79% **OR** LFS 3-5	Moderate symptoms (shortness of breath after walking on flat ground). • FEV1 40%-59% **OR** LFS 6-9	Severe symptoms (shortness of breath at rest; requiring 0_2). • FEV1 ≤39% **OR** LFS 10-12
Joints and Fascia	No symptoms.	Mild tightness of arms or legs, normal or mild decreased ROM **AND** not affecting ADL.	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM, **AND** mild to moderate limitation of ADL.	Contractures **WITH** significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
(Continued)				

Performance Score:	SCORE 0	SCORE 1	SCORE 2	SCORE 3
(Continued)				
Genital Tract	No symptoms.	Symptomatic with mild signs on examination **AND** no effect on coitus and minimal discomfort with gynecologic exam.	Symptomatic with moderate signs on examination **AND** with mild dyspareunia or discomfort with gynecologic exam.	Symptomatic **WITH** advanced signs (stricture, labial agglutination, or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum.
Other indicators, clinical manifestations or complications related to chronic GvHD (check all that apply and assign a score to its severity [0-3] based on its functional impact where applicable [none – 0, mild – 1, moderate – 2, severe – 3]):				
• Esophageal stricture or web • Ascites (serositis) • Myasthenia gravis • Polymyositis • Platelets <100,000/µL • Pericardial effusion • Nephrotic syndrome • Cardiomyopathy • Cardiac conduction defects • Progressive onset • Pleural effusion(s) • Peripheral neuropathy • Eosinophilia >500/µL • Coronary artery involvement				

Source: Filipovich et al. 2005.

[a] AP may be elevated in growing children, and not reflective of liver dysfunction.

[b] Pulmonary scoring should be performed using both the symptom and PFT scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the LFS is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70%-79% = 2; 60%-69% = 3; 50%-59% = 4; 40%-49% = 5; <40% = 6. The LFS = FEV1 score = DLCO score, with a possible range of 2-12.

ADL = Activities of daily living; ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase; BSA = Body surface area; DLCO = Diffusing capacity of the lung; ECOG = Eastern Cooperative Oncology Group; FEV1 = Forced expiratory volume in the first second; GvHD = Graft-versus-host disease; KPS = Karnofsky Performance Status; LFS = Lung Function Score; LFT = Liver function test; LPS = Lansky Performance Status; NIH = National Institutes of Health; PFT = Pulmonary function testing; ROM = Range of motion; ULN = Upper limit of normal

Global Severity Scoring of Chronic GvHD (Filipovich et al. 2005)

Elements included in the proposed global scoring system include both the number of organs or sites involved and the severity within each affected organ (note that Performance Status scoring is not incorporated into the global scoring system). The global descriptions of mild, moderate, and severe were chosen to reflect the degree of organ impact and functional impairment due to chronic GvHD (cGvHD). Although scoring is often used at the time of initial diagnosis, evaluating the clinical score periodically during the course of cGvHD may revise prognostic expectations and better describe the current severity of cGvHD. Note that the global scoring system can be applied only after the diagnosis of cGvHD is confirmed by either (1) the presence of a diagnostic feature or, if a diagnostic feature is not present, (2) at least 1 distinctive manifestation of cGvHD with the diagnosis supported by histologic, radiologic, or laboratory evidence of GvHD from any site.

Mild cGvHD involves only 1 or 2 organs or sites (except the lung, see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites). Moderate cGvHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate cGvHD. Severe cGvHD indicates major disability caused by cGvHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe cGvHD.

Appendix 5 Table, Figure, and Listing Shells

Table, figure, and listing shells will be defined in a separate document.

Appendix 6 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
aGvHD	Acute graft-versus-host disease
ATC	Anatomic therapeutic class
BMI	Body mass index
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BuCy	Busulfan and cyclophosphamide
CDISC	Clinical Data Interchange Standards Consortium
cGvHD	Chronic graft-versus-host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CPF	Cell Processing Facility
CRFS	cGvHD-free, relapse-free survival
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Cy	Cyclophosphamide
Cy-TBI	Cyclophosphamide and total body irradiation
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
FluBu4	Fludarabine and busulfan
FluMel 140	Fludarabine and melphalan 140 mg/m^2
GRFS	GvHD-free, relapse-free survival
GvHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HCT	Hematopoietic cell transplantation
IBMTR	International Bone Marrow Transplant Registry
IDMC	Independent Data Monitoring Committee

(Continued)

Abbreviation	Definition
	(Continued)
IP	Investigational Product
ITT	Intent-to-treat (population)
KPS	Karnofsky Performance Status
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
mITT	Modified intent-to-treat (population)
mPB	Mobilized peripheral blood
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	Natural killer (cell)
NRM	Non-relapse mortality
OS	Overall survival
PCR	Polymerase chain reaction
PP	Per-protocol (population)
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, figures, and listings
ULN	Upper limit of normal
WHO	World Health Organization

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