CLINICAL STUDY PROTOCOL

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

Investigational Product: ProTmune
Protocol Number: PT-001

Sponsor:
Fate Therapeutics, Inc.
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Version Number: 6.0
Date: 29 March 2019

CLINICAL PROTOCOL APPROVAL FORM

STUDY TITLE:

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

This study protocol was subject to Sponsor review and approval. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational medicinal product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56, 312 and ICH E6(R) and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings related to treatment with the investigational medicinal product.

Name and Title	Signature	Date
Peter Langecker, MD, PhD Executive Medical Director, Oncology		01 APR 2019

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Fate Therapeutics, Inc. (henceforth referred to as Fate) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the investigational product and study procedures. I will let them know that this information is confidential and proprietary to Fate and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Fate, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, IRB/IEC Regulations and International Conference on Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: 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

PHASE: Phase 1/2

INDICATION(S): Reduction of incidence and severity of acute graft-versus-host disease (aGvHD)

OBJECTIVES:

Phase 1 Part of the Study:

Primary Objective:

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.

Secondary Objective:

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 Part of the Study:

Primary Objective:

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.

Secondary Objective:

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.

Exploratory Objectives:

The exploratory objectives for the Phase 2 part 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 aGvHD;

- To assess the incidence of, and time to, CMV viremia, incidence and severity of CMV invasive disease, and incidence of CMV reactivation;
- To assess time to first CMV-specific anti-viral therapy (AVT);
- 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;
- To determine the incidence of non-relapse mortality (NRM);
- To determine survival at one-year and at two-years; and
- To assess immune reconstitution (including B, T, dendritic, and natural killer [NK] cells).

POPULATION:

Inclusion Criteria for Phase 1 Part of the Study and Phase 2 Part of the Study:

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Male and female subjects aged 18 years and older;
2. Subjects must have a hematologic malignancy for which allogeneic hematopoietic peripheral blood cell transplantation is deemed clinically appropriate. Eligible diseases and stages include and are limited to the following:
    - Acute myeloid leukemia in first complete remission (CR) (CR1) or second CR (CR2):
        - CR is defined as ≤5% bone marrow (BM) blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in BM with ≥5% cellularity with normal peripheral blood counts; or
        - Morphologic CR (≤5% BM blasts) with incomplete blood count recovery;
    - Acute lymphoblastic leukemia (ALL), including T lymphoblastic lymphoma with a history of marrow involvement in CR1 or CR2:
        - CR is defined as ≤5% blasts with no morphological characteristics of acute leukemia in a BM with ≥5% cellularity;

- Myelodysplastic syndrome (MDS); or
- Chronic myelogenous leukemia (CML);

3. Availability of a suitable 8/8 human leukocyte antigen (HLA)-A, -B, -C, and -DRB1-matched unrelated mPB donor;
4. Subjects must have an mPB donor collection unit **without** using plerixafor (Mozobil™) that is ≥5 × 10^6 CD34+ cells/kg in Phase 1 and ≥3 × 10^6 CD34+ cells/kg in Phase 2;
5. Adequate performance status, defined as Karnofsky score ≥70%;
6. For female subjects of childbearing potential, all of the following criteria must be met:
   - They are not pregnant (i.e., female subjects must have a negative serum pregnancy test at screening);
   - They are not breastfeeding;
   - They do not plan to become pregnant during the study; and
   - They are using an effective method of contraception from screening to the end of the study, unless their sexual partner is surgically sterile. Effective methods of preventing pregnancy are those contraceptive methods with a Pearl index of <1 used consistently and correctly (including, but not limited to, implantable contraceptives, injectable contraceptives, oral contraceptives, and transdermal contraceptives).

   Women are not considered to be of childbearing potential if they meet 1 of the following 2 criteria, as documented by the Investigator:

   - They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at minimum 1 menstrual cycle prior to signing the informed consent form (ICF); or
   - They are post-menopausal, defined as ≥1 year since their last menstrual period for women ≥55 years of age or ≥1 year since their last menstrual period;
7. For male subjects, agreement to use condoms with spermicide during sexual intercourse from screening to the end of study; and
8. Willingness and ability to sign an Investigational Review Board/Ethics Committee-approved ICF before performance of any study specific procedures or tests and to comply with protocol visits, and study procedures.

Exclusion Criteria for Phase 1 Part of the Study and Phase 2 Part of the Study:

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Phase 1 only: Known bone marrow fibrosis; Phase 2 only: Bone marrow fibrosis grade 3 (severe) or greater;
2. Positive serology for human immunodeficiency virus or human T-cell lymphotropic virus at any time prior to enrollment;
3. Current uncontrolled bacterial, viral, or fungal infection (progression of clinical symptoms despite therapy);
4. Prior autologous or allogeneic HCT;

5. Active malignancy, other than the one for which the allogeneic mPB transplant is being performed, within 12 months of enrollment, excluding superficial basal cell and carcinoma in situ cervical cancer;
6. Pulmonary disease such as symptomatic chronic obstructive lung disease, symptomatic restrictive lung disease, or FVC and FEV1 <50%, or hemoglobin corrected diffusing capacity of the lung of <50% of predicted value;
7. Renal dysfunction defined as a calculated creatinine clearance <40 mL/min (Cockcroft-Gault equation);
8. Hepatic disease defined as total serum bilirubin >2.0 mg/dL (except in the case of Gilbert's syndrome or ongoing hemolytic anemia), or aspartate aminotransferase or alanine aminotransferase >2.0 × the upper limit of normal;
9. Cardiac disease defined as symptomatic congestive heart failure (New York Heart Association [NYHA] Class III/IV) or evidence of left ventricular dysfunction (ejection fraction <45%) as measured by gated radionuclide ventriculogram or echocardiogram (ECHO); active angina pectoris or uncontrolled hypertension; or history of myocardial infarction with depressed ejection fraction;
10. Neurologic disease, defined as symptomatic leukoencephalopathy, active central nervous system malignancy, or other neuropsychiatric abnormalities believed to preclude transplantation;
11. Participation in another clinical trial involving an investigational product within 30 days prior to transplant; or
12. Any condition or therapy, which, in the opinion of the Investigator, might pose a risk to the subject or make participation in the study not in the best interest of the subject (e.g., known allergy to human serum albumin [HSA]).

STUDY DESIGN AND DURATION:

This is a Phase 1, non-randomized, open-label/Phase 2, randomized, blinded, multi-center 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 receive a conditioning regimen comprising 1 of the following 5 preparative regimens: fludarabine and busulfan (FluBu4); busulfan (Bu) and cyclophosphamide (Cy); Cy and ≥12 Gy total body irradiation (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 treat 6 to 10 subjects who have an available 8/8 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 receive 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 treat 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 be randomly assigned in a 1:1 ratio to receive either unmanipulated mPB cells (control arm) or ProTmune *ex vivo* programmed mPB cells (experimental arm) and stratified by the subjects' CMV status (+/-).

At initiation of the Phase 1 part of the study, 3 subjects will be enrolled and treated. At the time a subject engrafts (or fails to engraft by Day +28), a new subject may be treated. If 2 or more subjects fail to engraft by Day +28, or if 2 or more subjects experience secondary graft failure by Day +28, or if 2 of the first 3 or 4 of the first 6 subjects treated have died by ≤Day +28, subject treatment will be stopped until the Independent Data Monitoring Committee (IDMC) has assessed the cases and discussed with the Sponsor. The IDMC will be notified of all subject deaths occurring on study. If the investigational product does not meet release specifications to treat 2 of the first 3 subjects, 3 of the first 6 subjects, or 5 of the first 10 subjects in the Phase 1 part of the study, subject treatment will be stopped.

If after 6 subjects have been dosed and evaluated for up to 28 days and ≤1 subject has not engrafted by Day +28, then enrollment in the Phase 2 portion of the study may proceed following IDMC review.

Both the Phase 1 part of the study and Phase 2 part of the study will include a Screening Period (Day -53 through Day -11), Subject Conditioning Period (Day -10 through Day -1), Study Treatment Administration Day (Day 0; Day of HCT), Post-Transplant Follow-up Period (Day +1 through Day +730, consisting of Post-Transplant Assessment Days and Post-Transplant Weekly Assessments, then intermittent assessments), and an Early Withdrawal Visit (if applicable). The total duration of subject participation will be up to 26 months for each subject in the Phase 1 part of the study and Phase 2 part of the study.

The end of the study is considered as the completion through Day +365. All treated subjects will be followed for survival through Day +730 (i.e., 2 years).

The study will utilize an Endpoint Adjudication Committee (EAC) blinded to treatment. The EAC will be responsible for adjudicating the aGvHD endpoint. Adjudication of the aGvHD endpoint will be in accordance with the EAC charter.

During the Phase 1 part of the study, an 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. During the Phase 2 part of the study, the IDMC will convene according to the guidelines outlined in the IDMC Charter. Additional safety monitoring based on NRM, secondary graft failure, and IDMC input will be applied during the study for the Phase 1 and Phase 2 parts of the study.

With the exception of the stopping rules associated with the failure of ProTmune to meet release specifications, there are no formal stopping rules for the Phase 2 part of the study. Stopping subject treatment may be triggered based on the continued review of subject safety data on study by the Sponsor and IDMC. If the investigational product does not meet release specifications for 2 of the first 3 subjects, 3 of the first 6 subjects, or 5 of the first 10 subjects or 10 of the first 20 subjects, subject treatment in the Phase 2 part of the study will be stopped, pending review by the IDMC.

Screening Period (Day -53 to Day -11) for the Phase 1 and Phase 2 Parts of the Study:

The Screening Period will occur between Day -53 and Day -11 (i.e., up to 6 weeks prior to the Subject Conditioning Period). At Screening, all subjects will review and sign an ICF and eligibility for study participation will be assessed. The Investigator will be required to verify that the subject completed HLA typing. Human leukocyte antigen typing can be completed prior to the Screening

Period. Peripheral blood will be collected during the Screening Period to serve as a baseline sample for immune reconstitution analysis.

The results of the bone marrow aspirate, spirometry, and ECHO or multiple gated acquisition (MUGA) performed prior to consent may be used for subject qualification as long as performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.

As a part of screening, all subjects will be tested for baseline CMV antibody titer and plasma CMV viremia. This baseline testing will be performed by a central laboratory and results will be provided to the clinical site and sponsor before initiation of randomization.

Subject Conditioning Period (Day -10 to Day -1) for the Phase 1 and Phase 2 Parts of the Study:

The Subject Conditioning Period will occur between Day -10 and Day -1. Day 0 is the day of mPB HCT transplant. Conditioning will include one of the following 5 preparative regimens:

- CyTBI, with ≥12 Gy fractionated TBI;
- BuCy where Bu = 16 mg/kg orally (PO) or 12.8 mg/kg intravenous (IV) infusion (alternatively, pharmacokinetic assessment and dose adjustment of busulfan can be based on a test dose or the first dose and will be conducted according to institutional practices);
- FluBu4 with Bu as above;
- TBI and etoposide; or
- FluMel 140

Filgrastim (granulocyte-colony stimulating factor) can be administered at 5 µg/kg/day beginning on Day +12, if ANC<500 cells/µL, until the ANC is >500 cells/µL. At Investigator discretion, filgrastim can be administered longer to support the white blood cells. Similarly, per Investigator discretion, filgrastim may be started before Day +12 if subsequent doses of methotrexate will not be administered due to severe mucositis, other toxicity, or severe infection.

Graft-versus-host disease prophylaxis will be administered to all subjects.

The GvHD prophylaxis regimen:

- Methotrexate (15 mg/m^2 IV infusion on Day +1 after hematopoietic cell infusion and 10 mg/m^2 on Days +3, +6, and +11), and
- Tacrolimus (0.02 mg/kg every 24 hours as an IV infusion or 0.03 mg/kg PO beginning on Day -2, adjusted to target dose level of 5 to 15 ng/mL. Taper starting at Day +100).

The GvHD prophylaxis dose may be reduced based on clinical judgment associated with toxicity.

All chemotherapy administered to subjects will be dosed based on the subject's actual body weight. However, for subjects weighing more than 125% of their ideal body weight, chemotherapy will be dosed based on the adjusted ideal body weight, or by Institutional Standards.

Anti-thymocyte globulin is not permitted during the study.

FDA-approved prophylactic therapies for CMV prevention (e.g., letermovir) will be permitted. Pre-emptive CMV therapy may be provided based upon institutional methodologies, Standard Operating Procedures, and clinical context. An additional blood sample for CMV testing will be collected prior to starting the preemptive therapy and sent for central laboratory testing.

Other procedures for transplant preparation will also be performed at the Subject Conditioning Visit and per Institutional Standard.

Hospital Admission (as per Institution Policy) for the Phase 1 and Phase 2 Parts of the Study:

Subjects will be admitted to the hospital based on institutional policy.

Study Treatment Administration (Day 0; Day of Hematopoietic Cell Transplantation) for the Phase 1 and Phase 2 Parts of the Study:

A 12-lead triplicate electrocardiogram (ECG) (sequential, within 15 minutes total), complete blood count (CBC), and blood chemistry will be obtained on Day 0 prior to HCT. All eligible subjects will receive study treatment on the day of HCT (Day 0). For the Phase 1 part of the study, study treatment will consist of a single unit of ProTmune *ex vivo* programmed mPB cells. For the Phase 2 part of the study, study treatment will consist of either a single unit of ProTmune *ex vivo* programmed mPB cells or a single unit of unmanipulated mPB cells, based upon the subject's randomized treatment allocation. The ProTmune graft will be prepared the same day as administration.

Karnofsky Performance Status will be assessed at Day 0, following transplantation.

Post-Transplant Assessment Days for the Phase 1 and Phase 2 Parts of the Study:

Post-transplant visit windows are as follows: ±3 days for Day +7 through Day +100; ±14 days for Day +180; and ±28 days for Days +270, +365, and +730. Standard post-transplant testing will be performed per institutional guidelines and good clinical practice.

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Post-Transplant Weekly Visits for the Phase 1 and Phase 2 Parts of the Study:

Clinical and laboratory assessments of aGvHD will be performed weekly from Day +1 through Day +100, and on Day +180. Acute GvHD assessments (incidence and maximum severity) of Grades I through IV of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale will be performed.

Chronic GvHD assessments (incidence and maximum severity) of mild, moderate, or severe cGvHD as per National Institutes of Health (NIH) Consensus Criteria for cGvHD must be performed on Days +180, +270, and +365.

Peripheral blood samples will be collected for CMV assessments of deoxyribonucleic acid by quantitative polymerase chain reaction (PCR) weekly from Day +7 through Day +100, and on Days +180, +270, and +365. Assessment of infection will be performed based on the NCI CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) definitions.

Peripheral blood will be collected for safety laboratory panels (hematology and serum chemistry), viral monitoring, immune reconstitution, chimerism, serum immunoglobulins, and GvHD exploratory biomarkers at the pre-specified time points.

A 12-lead triplicate ECG (sequential, within 15 minutes total) will be obtained at Day +100.

Bone marrow aspirate will be sent to pathology and to cytogenetics on Day +21 (only if absolute neutrophil count [ANC] <500/μL), and as clinically indicated (flow cytometry is required on BM aspirate).

Karnofsky Performance Status will be assessed at all subsequent study visits after HCT up through Day +365 (which should include weekly assessments from Day +1 through Day +91, then on Days +100, +180, +270, and +365).

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Unscheduled visits

An unscheduled visit is a visit that occurs in addition to the predefined protocol specific visit calendar. If an unscheduled visit occurs for a given subject, the visit must be documented on the Unscheduled Visit electronic case report form.

Early Withdrawal Visit for the Phase 1 and Phase 2 Parts of the Study:

If a subject is withdrawn from participation in the study prior to Day 0, the subject's mPB will not be processed to a unit of ProTmune *ex vivo* programmed mPB cells, the subject will not be considered evaluable for any study-related endpoint analyses, and a new subject will be added for the Phase 1 portion of the study. If this occurs in the Phase 2 portion of the study, the subject will be replaced and a new subject will be randomized in order to have approximately 80 treated subjects.

If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected by phone on Days +180, +365, and +730. If a subject withdraws consent, survival outcomes will be assessed via public record search.

If the subject relapses and/or receives a protocol-prohibited therapy, the subject will be withdrawn. However, survival will still be collected at Day +730 by telephone contact unless the subject withdraws consent, in which case survival outcomes will be assessed via public record search.

A peripheral blood sample for safety laboratory panels (hematology and serum chemistry) will be collected.

Karnofsky Performance Status should be assessed, and GvHD assessments must be performed, as applicable.

Adverse Events

Adverse events will be collected during Phase 1 and 2 as per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, AE of infections will use both the CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN, Appendix G) criteria, as follows:

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

Concomitant Medications

All concomitant medications will be recorded starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

ProTmune is a donor-sourced, patient-specific, allogeneic cell therapy product consisting of the cells contained within a human mobilized peripheral blood (mPB) collection that have been programmed through an *ex vivo* programming process using a combination of 2 small molecules, 16,16-dimethyl prostaglandin E2 (FT1050) and dexamethasone (FT4145). The cell populations include hematopoietic cells and other cell types. The final ProTmune product is formulated in Plasmalyte-A (or equivalent) and human serum albumin (HSA).

Mobilized peripheral blood cells will be obtained from a matched-unrelated donor for a given subject. An 8/8 high resolution allelic HLA-match of HLA-A, -B, -C, and -DRB1 with recipient is required. Sites will request that consenting donors be mobilized with filgrastim to achieve a target collected CD34+ dose of $\geq 7 \times 10^6$ CD34+ cells/kg in Phase 1 and $\geq 5 \times 10^6$ CD34+ cells/kg in Phase 2. However, if the donor mPB unit collected for a subject in Phase 1 is not $\geq 5 \times 10^6$ CD34+ cells/kg recipient weight, and in Phase 2 is not $\geq 3 \times 10^6$ CD34+ cells/kg recipient weight, the mPB unit will not be processed for ProTmune manufacturing and the subject will be considered a screen failure.

For subjects enrolled in the Phase 1 part of the study, a reserve dose of 2×10^6 CD34+ cells/kg recipient weight will be maintained during ProTmune manufacturing to serve as a reserve in the event ProTmune manufacturing produces a ProTmune unit that does not meet ProTmune release specifications (e.g., $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable). In this case, the ProTmune unit will be considered "unavailable" and count towards the Phase 1 stopping rules. The reserve unit must be administered; however, the Principal Investigator should follow their Institution's standard operating procedure to determine whether the ProTmune unit should also be

given to the recipient based on the risk-benefit assessment of administering the product with regard to the specification not being met. If the ProTmune unit is not administered, the subject will be withdrawn from study and replaced. If the ProTmune unit is administered, the subject will remain in study but will not be considered in the following assessment - "If after 6 subjects have been dosed and evaluated for up to 28 days and ≤1 subject has not engrafted by Day +28, then enrollment in the Phase 2 portion of the study may proceed following IDMC review". If the reserve unit is not used on Day 0, it will be cryopreserved at the site and can be used in the event of non-engraftment, or delayed engraftment.

For subjects enrolled in the Phase 2 part of the study in the event ProTmune manufacturing produces a ProTmune unit that does not meet ProTmune release specifications (e.g., $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable), the ProTmune unit will be considered "unavailable" and count towards the Phase 2 stopping rules. The Principal Investigator should follow their Institution's standard operating procedure to determine whether the unit should be given to the recipient based on the risk-benefit assessment of administering the product with regard to the specification not being met. If the ProTmune unit is not administered, or a subject is withdrawn from participation in the study prior to Day 0 and the subject's mPB is not processed to a unit of ProTmune, the subject will be replaced and a new subject will be randomized in order to have approximately 80 treated subjects. If the ProTmune unit is administered, the subject will remain in study.

Fate has established specific criteria that will be used to assess the quality of all mPB units collected for *ex vivo* programming.

The Cell Processing Facility (CPF) at each participating site will be qualified and trained by Fate technical staff to manufacture the investigational product on site via the performance of a single ProTmune qualification run. Additionally, Fate technical representative(s) will be on site for the manufacture of each CPF's first or second subject treatments and subsequent subject treatments as necessary by the CPF or Fate.

ProTmune or Control cells will be released immediately by the CPF staff after final processing, including filtration, final packaging, rapid release testing, and labeling.

SAFETY ENDPOINTS:

The safety endpoints for both the Phase 1 and Phase 2 parts of the study include the assessment of adverse events as defined in the NCI CTCAE version 4.0, vital signs, physical examination findings, engraftment, graft failure, chimerism, clinical laboratory assessments, and electrocardiographic data through a 12-lead ECG.

EFFICACY ENDPOINTS:

The primary efficacy endpoint for both the **Phase 1 and Phase 2** parts of the study is the following:

- Cumulative incidence of CIBMTR Grades II-IV aGvHD through Visit Day +100 based on investigator results. Death and relapse without CIBMTR Grades 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 (Appendix E).

The key secondary efficacy endpoint for both the **Phase 1 and Phase 2** parts of the study is the following:

- Proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria at Visit Day +365.

All summaries for acute and chronic GvHD will be based on the investigator assessment unless noted otherwise.

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

- Cumulative incidence through Visit Day +100 and through Visit Day +180 of:
  - CIBMTR Grades III-IV aGvHD;
  - CIBMTR Grades I-II aGvHD;
  - CIBMTR Grades I-IV aGvHD;
  - Maximum CIBMTR Grades II-IV aGvHD;
  - Maximum CIBMTR Grades III-IV aGvHD;
  - Maximum CIBMTR Grades II-IV aGvHD based on EAC adjudicated results;
  - Maximum CIBMTR Grades III-IV aGvHD based on EAC adjudicated results;
- Duration of the Maximum CIBMTR Grade aGvHD through Visit Day +100;
- Duration of CIBMTR Grades II-IV aGvHD through Visit Day +100;
- Duration of CIBMTR Grades III-IV aGvHD through Visit Day +100;
- One-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);
- Time to individual event components for GRFS:
  - Time to CIBMTR Grades III-IV aGvHD;
  - Time to first use of cGvHD-requiring systemic immunosuppressive therapy;
  - Time to relapse;
  - Time to death;
- One-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 Non-relapse mortality (NRM). All deaths in the absence of relapse of the primary malignancy will be considered NRM, where relapse will be considered a competing risk;

- 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;
- 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 anti-viral therapy for CMV;
- Time to first treatment for CMV reactivation;
- Relapse-free survival (RFS);
- One-year survival;
- Two-year survival.

Additional exploratory analyses may be performed as necessary.

STATISTICAL ANALYSES:

All reporting and analyses will be conducted at the end of the study, which is defined as the date when the last subject last visit occurs or the date at which the last data point is collected for the completion of 1-year on study (Day +365), whichever occurs later. Analysis of the 2-year survival follow-up will be conducted upon completion of the Day +730 follow-up. The initial clinical study report will be completed following final analysis of the 1-year data and will be appended to include the 2-year survival data upon completion.

Continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as descriptive statistics. Time-to-event variables will be summarized using Kaplan-Meier methods; competing risk methods will be used in the presence of competing risk factors (e.g., death or relapse without aGvHD for evaluating aGvHD).

Efficacy analyses will be performed based on the mITT Population. Additional sensitivity analyses will be performed based on the PP Population for the primary and key secondary efficacy endpoint for Phase 2. Efficacy data from the Phase 1 part of the study and Phase 2 part of the study will be summarized separately. Summary tables will present results for each phase by treatment group. The safety profile will be based on adverse events, vital signs, physical examinations, clinical laboratory assessments, engraftment, graft failure, chimerism, and ECGs. All safety analysis will be based on the Safety Population.

SAMPLE SIZE DETERMINATION:

The background cumulative incidence rate of 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 be enrolled to include 6-10 evaluable.

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 Grades II-IV aGvHD through Day +100 from 55% to 25% (i.e., a hazard ratio of 0.3464) in the Control versus ProTmune treatment arms 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 be randomized to include approximately 80 treated subjects in the mITT Population. The sample size was calculated using PASS Sample Size Software (PASS 16 Power Analysis and Sample Size Software, 2018).

SITES: Approximately 5 to 10 sites in the United States for the Phase 1 part of the study, and approximately 14 to 20 sites in the United States for the Phase 2 part of the study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
aGvHD	Acute graft-versus-host disease
AIBW	Adjusted ideal body weight
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AVT	Anti-viral therapy
BM	Bone marrow
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
Bu	Busulfan
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
cGvHD	Chronic graft-versus-host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
CPF	Cell Processing Facility
CR	Complete remission
CRA	Clinical research associate
CRFS	Chronic graft-versus-host disease-free, relapse-free survival
CRO	Contract research organization
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	C-X-C chemokine receptor type 4
Cy	Cyclophosphamide
DNA	Deoxyribonucleic acid
EAC	Endpoint Adjudication Committee
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FluBu4	Fludarabine and busulfan
GvHD	Graft-versus-host disease
GRFS	Graft-versus-host disease-free, relapse-free survival

Abbreviation	Definition
GvL	Graft-versus-leukemia
HCT	Hematopoietic stem cells
HHV-6	Human herpes virus 6
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSA	Human serum albumin
HSC	Hematopoietic stem cells
HSV	Herpes simplex virus
HTLV	Human T-cell lymphotropic virus
IB	Investigator's Brochure
IBW	Ideal body weight
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response Services
MAC	Myeloablative conditioning
MDS	Myelodysplastic syndrome
mPB	Mobilized peripheral blood
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	Natural killer
NMDP	National Marrow Donor Program
NRM	Non-relapse mortality
NYHA	New York Heart Association
PCR	Polymerase chain reaction
PO	Orally
RBC	Red blood cell
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDF-1	Stromal derived factor-1
SUSAR	Serious and unexpected suspected adverse reaction
TBI	Total body irradiation

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
VZV	Varicella zoster virus

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Hematologic malignancies encompass a wide range of cancers that involve the bone marrow (BM) and lymph nodes. Rich in growth factors and cytokines, the BM provides an ideal microenvironment for hematologic malignancies that lends itself to progression of leukemogenesis and cancer progression (Raimondo et al. 2015). Malignancies of the BM, such as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), affect all ages (Smith et al. 2011).

Recent advances in survival and treatment options using chemotherapy, transplantation, and radiation have resulted in survival rates around 90% for some hematologic malignancies (McLaughlin 2015). However, patients still incur numerous adverse reactions and systemic toxicities due to such therapies. For patients who do not obtain remission or who relapse, allogeneic hematopoietic cell transplantation (HCT) may be the only remaining treatment option (McLaughlin 2015).

Before receiving allogeneic HCT, a patient must undergo 1 of 2 types of preparative treatment regimens: myeloablative conditioning (MAC) or non-MAC, such as reduced intensity conditioning. The goal of such conditioning regimens is to suppress the recipient's immune system sufficiently to allow adequate engraftment of the donor cells, to reduce the presence of neoplastic cells.

1.2 Hematopoietic Stem Cell Transplants and Potential Complications

For patients with advanced stages of hematologic malignancies, allogeneic HCT is often the only therapeutic option that offers the potential to prolong lifespan or even a curative outcome. While BM has historically been the principal source of hematopoietic stem cells (HSC) in allogeneic HCT, the majority of recent procedures have been conducted with mobilized peripheral blood (mPB) as a cell source, including mPB collected from matched related donors or matched unrelated donors (National Marrow Donor Program [NMDP] 2015). In the United States, approximately 20,000 patients receive autologous or allogeneic HCT each year (Majhail et al. 2015). Only one-third of all patients eligible for allogeneic HCT have a human leukocyte antigen (HLA)-matched related donor in their family and in those cases, transplant from a matched related donor becomes the optimal treatment.

Patients who do not have an HLA-matched relative rely on alternative stem cell sources, which include: matched unrelated donors, haploidentical donors, and umbilical cord blood (Ballen et al. 2012). Approximately 50% to 60% of allogeneic HCTs reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) use unrelated donors (Majhail et al. 2015). Additionally, over the past decade, the number of peripheral blood cell grafts facilitated by the NMDP has grown substantially, such that currently around 75% of unrelated grafts are peripheral blood cells (Woolfrey et al. 2011).

This shift toward the use of mPB over BM was enabled by the relative ease of collection, obviating the need to harvest T-cells from a donor through surgical aspiration of the BM. In addition, mPB results in quicker engraftment kinetics and potentially decreased early morbidity relative to BM (Schmitz et al. 2006; Nagler et al. 2012; Eapen et al. 2007). Specifically, several large, multicenter, randomized studies have collectively demonstrated that time to engraftment/reconstitution is faster

and more robust with mPB than with BM, which may be associated with decreased rates of relapse and infections (Pidala et al. 2009).

Numerous complications may arise from HCT, whether using BM, mPB, or umbilical cord blood. The primary complication that may arise from HCT is graft-versus-host disease (GvHD). The use of mPB is associated with higher rates of GvHD compared to BM, which has limited the universal adoption of this otherwise convenient and highly effective cell source for HCT.

Infections are a second important contributor of morbidity and mortality for patients undergoing HCT. Transplant-related infections are a universal issue that span across the HCT spectrum of stem cell sources, donor graft types and conditioning regimens (Wingard et al. 2010).

For patients undergoing HCT, there is a clear need for new approaches to reduce rates of GvHD without compromising the anti-leukemia and anti-infective properties of the T-cells in the graft.

1.2.1 Graft-Versus-Host Disease

Graft-versus-host disease is the result of an intricate immune response following allogeneic stimuli, when T-cells of the donor recognize the presence of histocompatibility antigens in the host that differ from those of the donor cells. This initial antigen recognition results in T-cell activation and proliferation, which leads to the production and secretion of a variety of cytokines, which are responsible for the inflammatory effects and tissue damage associated with GvHD (Ferrara and Deeg 1991).

Conventionally, GvHD was divided into acute and chronic variants based upon the time of onset, using an arbitrary cutoff of 100 days for acute GvHD (aGvHD). Risk factors for the development of GvHD include degree of HLA disparity (HLA mismatch), donor-recipient gender disparity, increasing age of the host, CMV status of donor and host, intensity of the transplant conditioning regimen, GvHD prophylactic regimen used, source of cell graft, greater pre-transplant comorbidities, and specific HLA haplotypes (Sorror et al. 2014; Hahn et al. 2008).

Between 35% and 60% of patients who undergo allogenic HCT are likely to develop aGvHD (Jacobson and Vogelsang 2007, Choi and Reddy 2014). In 1974, Glucksberg published the first aGVHD classification (Glucksberg et al. 1974), modified by Thomas in 1975. The Glucksberg system remains the most commonly used system. Although this classification has prognostic value, it is complex. In fact, there are 125 possible combinations of organ involvement and severity, where each of 3 organs is staged from 0 to 4, which are then combined to calculate an overall grade. However, in the overall grading system, 62 of the possible 125 combinations are not defined (Cahn et al. 2005). In recognition of the systems limitations, a consensus workshop was held in 1995 and a modified Glucksberg grading system was proposed (Przepiorka et al. 1995) and a severity index published a year later (Rowlings et al. 1997). This modified grading scale is referred to as the CIBMTR grading scale. A revised CIBMTR scale was published in 2012 (CIBMTR Forms Manual 2012) and will be the scale by which aGvHD will be graded in this study.

Acute GvHD is classified based on the degree of severity of the affected organs, skin, liver, and gastrointestinal tract, with involvement of each organ ranging from mild to severe based on the International Blood and Marrow Transplant Research Index (Majhail et al. 2015; Rowlings et al. 1997). Acute GvHD is then given an overall grade based a 4-grade scale, with Grade A (I) considered mild, Grade B (II) moderate, Grade C (III) severe, and Grade D (IV) life-threatening. The survival of patients at Day +100 post-transplant is reduced with increasingly severe aGvHD,

with survival in less than 45% of patients with severe aGvHD (Weisdorf et al. 1990; Nash et al. 1992).

Despite the accepted role of allogeneic T-cells in GvHD, the overall pathophysiology is still poorly understood. The development of predictive biomarkers to better assess the balance between GvHD and graft-versus-leukemia (GvL), as well as response to therapy, may provide better insights into disease prognosis and treatment optimization. A number of biomarkers have been previously proposed and summarized (Rozmus and Shultz 2011). Human leukocyte antigen disparity between donor and recipient has been linked to incidence and severity of chronic GvHD (cGvHD), however while HLA-A/-B disparity increases risk of cGvHD, HLA-DR or -DQ does not. The role of minor histocompatibility antigens in promoting GvHD has been debated as has the role of non-HLA polymorphisms. Non-HLA polymorphisms associated with susceptibility or severity of GvHD include heparinase, poly-ADP-ribose polymerase 1, madCAM-1, haptoglobin, HMGB-1 CCR9, and a range of classical Th1 and Th2 cytokines, including interleukin (IL)-10, tumor necrosis factor-α, IL-6, IL-1α, and interferon (IFN)-ɣ. Increased numbers of CD8/CD4 T-cells, TH-17 T-cells, and monocytes can be observed in tissues affected by GvHD. Where practical, investigating the expression and distribution of putative biomarkers may provide additional insights into the safety and efficacy of novel approaches to treat or prevent GvHD.

1.2.2 Current Strategies to Prevent and/or Treat Graft-versus-Host Disease

In the mid-1980s, calcineurin-inhibitor-based regimens were first used for GvHD prevention and treatment (Choi and Reddy 2014). While there have been several new insights regarding the pathophysiology of GvHD, there has been little progress in GvHD prevention and treatment. Despite better HLA-matching between donor and recipient and GvHD prophylaxis methods, aGvHD. Graft-versus-host disease still develops in approximately 40% to 60% of recipients (Choi and Reddy 2014). Additional preventative and therapeutic measures used for GvHD include non-specific immunosuppressive drugs, such as corticosteroids and methotrexate, as well as more specific T-cell immunosuppressive drugs, such as cyclosporine and tacrolimus (FK506). Corticosteroids remain the most widely used "front-line" therapy for the treatment of clinical GvHD, commonly administered in combination with therapeutic doses of cyclosporine or tacrolimus. Long-term use of corticosteroids may result in numerous adverse reactions, including Cushingoid features, hyperglycemia, psychosis, dyslipidemia, myopathy, osteoporosis, cataract formation, osteonecrosis, and immunosuppression (Liu et al. 2013). In addition, corticosteroids have been linked with a variety of drug-drug interactions, including those that share critical metabolic steps mediated by cytochrome P450 enzymes, resulting in clearance of concomitantly administered corticosteroids (Feldweg and Leddy 1999). Given the number and severity of the side effects associated with existing treatment options, there is a clear need for new approaches to treat GvHD.

1.2.3 Infections in the Hematopoietic Cell Transplant Setting

Despite significant improvements in the supportive care of HCT patients and modifications to the guidelines for infection prevention, infections remain the primary cause of death for 17% to 20% of patients who undergo allogeneic HCT (Tomblyn et al. 2009). As such, there remains an unmet medical need for the prevention and pre-emptive therapy of infections in the HCT setting.

Cytomegalovirus is an important pathogen in patients who undergo an allogeneic HCT, since CMV can affect almost any organ, and can result in pneumonia, gastrointestinal ulcers, and

retinitis. Without prophylaxis, CMV infection after allogeneic HCT affects approximately 80% of CMV-seropositive patients (Ljungman et al. 2011). Although current strategies have resulted in the decreased incidence of CMV disease, CMV prophylaxis and pre-emptive therapy are not without risk. Ganciclovir, a synthetic guanine derivative active against CMV, is one of several drugs utilized for both prophylaxis and pre-emptive therapy in patients receiving allogeneic HCT (Tomblyn et al. 2009). Those patients who do not tolerate standard doses of ganciclovir typically receive foscarnet, with lower doses in those with renal impairment (Tomblyn et al. 2009).

The use of ganciclovir has an important toxicity profile as noted by its current black box warning for granulocytopenia, anemia, and thrombocytopenia diaphoresis (Ganciclovir [Systemic]: Drug Information 2015). In animal studies, ganciclovir was found to be carcinogenic, teratogenic, and caused aspermatogenesis (Ganciclovir [Systemic]: Drug Information 2015). Significant adverse reactions (>10%) of fever, diarrhea, anorexia, vomiting, cytopenias, retinal detachment, increased serum creatinine, sepsis, and diaphoresis are associated with ganciclovir (Ganciclovir [Systemic]: Drug Information 2015). When given at engraftment, ganciclovir can be deleterious to the graft due to prolonged neutropenia, and can result in more invasive bacterial and fungal infections (Boeckh et al. 1996; Goodrich et al. 1993; Salzberger et al. 1997).

As use of pre-emptive anti-CMV therapy has increased, late CMV infection and disease (after Day +100) has become more significant following allogeneic HCT and is associated with non-relapse mortality (NRM) (Ozdemir et al. 2007). To minimize the toxicity from antiviral agents, most prefer a pre-emptive approach for CMV in HCT recipients rather than prophylaxis. The drawback of pre-emptive therapy, in addition to drug toxicity, is that the outcome is limited by the frequency and duration of monitoring (Tomblyn et al. 2009). The outcome of pre-emptive therapy is largely dependent on timely detection of CMV in the blood before the onset of disease and the early detection of CMV. Disease may occur due to missed surveillance tests or tests that are spaced too far apart. If a patient progresses to disease, treatment is not always effective; CMV pneumonia is the most detrimental complication of CMV in HCT recipients due to its high mortality rate, despite treatment (Reed et al. 1988).

The opportunistic bacterial, viral, fungal, and parasitic pathogens that occur in allogeneic HCT recipients result in numerous clinical syndromes, including, but not limited to CNS and ocular manifestations, sinusitis and mucositis, pneumonia, esophagitis, diarrhea and colitis, hepatitis, hemorrhagic cystitis, nephritis, skin lesions, bone marrow suppression, blood stream infection, shock (including septic shock) and fever (Tomblyn et al. 2009). Among the current strategies for prophylaxis or pre-emptive therapy are fluoroquinolones (e.g., levofloxacin) and immune globulin intravenous (IV) for bacterial infections; acyclovir for HSV infections; fluconazole for fungal diseases; and trimethoprim sulfamethoxazole for parasitic infections (Tomblyn et al. 2009). The adverse reactions and toxicities from such drugs include, but are not limited to, anaphylaxis, QT prolongation; hepatoxicity and hematologic toxicity; central nervous system and dermatologic adverse reactions; pulmonary edema (e.g., transfusion-related acute lung injury); tendinitis and tendon rupture; exacerbation of muscle weakness; fatal reactions to agranulocytosis, aplastic anemia, and other blood dyscrasias; fatal renal failure; and fatal reactions to Stevens-Johnson syndrome and toxic epidermal necrolysis (Acyclovir [Systemic]: Drug Information 2015; Fluconazole: Drug Information. Lexicomp. 2015; Immune Globulin: Drug Information 2015; Levofloxacin [Systemic]: Drug Information 2015; Trimethoprim-Sulfamethoxazole [co-trimoxazole]: Drug Information 2015).

In summary, infectious diseases are still a common cause of morbidity and mortality in patients undergoing HCT. Even in the setting of enhanced infectious disease surveillance, the therapies used in the prophylaxis and pre-emptive settings have limitations due to potentially severe or life-threatening toxicities, as well as possibly being deleterious to the graft. Therefore, there continues to be an unmet medical need for the prevention or treatment of infectious complications in patients who undergo an HCT transplant.

1.3 ProTmune

ProTmune is a donor-sourced, patient-specific, allogeneic cell therapy product consisting of the cells contained within a human mobilized peripheral blood (mPB) collection that have been programmed through an *ex vivo* programming process using a combination of 2 small molecules, 16,16-dimethyl prostaglandin E2 (FT1050) and dexamethasone (FT4145). The cell populations include hematopoietic cells and other cell types.

The objective of ProTmune is to prevent aGvHD and CMV infection. ProTmune products are manufactured by *ex vivo* programming of cells in donor mPB units with a combination of 16, 16-dimethyl prostaglandin E2 (dmPGE2, also referred to as FT1050) and a glucocorticoid (dexamethasone, also referred to as FT4145). ProTmune is intended for adults who will undergo HCT with cells contained in donor mPB units. Based on nonclinical data, ProTmune has the potential to reduce aGvHD while retaining GvL activity through programming a number of key biological pathways in both HSC and T-cells contained in mPB. Three processes are thought to be responsible for the development of aGvHD: cytokine storm following tissue injury caused by the conditioning regimen given prior to HCT, alloactivation of donor T-cells (activation, proliferation, and differentiation), and organ damage caused by direct cytotoxic activity or through the production of inflammatory cytokines (Hill and Ferrara 2000; Bouchlaka et al. 2010).

1.3.1 Effects of FT1050 and FT4145 on T-cells

In the nonclinical setting, ProTmune was found to have a significantly reduced allogeneic response in a mixed lymphocyte reaction. The reduced proliferation in response to an allogeneic target was accompanied by a significant reduction in IFN-ɣ cytokine response and concomitant induction of an immunomodulatory IL-4 response, suggesting that these cells have been programmed into a less responsive state. Consistent with this finding, *ex vivo* programming also served to upregulate expression of IL-10 by T-cells, a well-known potent and anti-inflammatory cytokine. This reduced proliferation response was also accompanied by decreased expression levels of the T-cell activation markers ICOS and 41BB. This phenotype may improve patient outcomes by preventing the unwanted cytokine-driven expansion of alloreactive T-cells in the first days and weeks following HCT. In addition, *in vivo* experiments demonstrated that programmed donor T-cells led to reduced rates of aGvHD without compromising the GvL response. Nonclinical studies are further summarized in Section 1.4.1.

1.3.2 Effects of F1050 and FT4145 on Hematopoietic Stem Cells

FT1050 specifically interacts with HSC by binding the G protein-coupled prostaglandin receptors, EP2 and EP4, which activates adenylate cyclase and increases the intracellular levels of the secondary messenger molecule, cyclic adenosine monophosphate (cAMP). This increase in intracellular cAMP initiates a signaling cascade that activates cAMP response element-binding protein and other transcription factors in the nucleus inducing a number of gene expression

changes in human CD34+ cells involved in cell cycle, anti-apoptosis and survival, and improved HSC function (North et al. 2007 and Hoggatt et al. 2009). Glucocorticoids were identified in a combinatorial small molecule screen performed at Fate. Dexamethasone (FT4145) was found to synergize with FT1050 to further enhance the homing and engraftment properties of HSC.

1.3.3 Role of FT1050 and FT4145 in Hematopoietic Stem Cell Biology

Approximately 30% of patients receive a suboptimal dose of HSC due to poor mobilization and collection, which can result in delayed neutrophil recovery and increased susceptibility to life-threatening infections (To et al. 2011). Approaches to improve HSC engraftment have previously focused on increasing numbers of donor HSCs using multi-week expansion strategies (Wagner et al. 2015); however, more recent approaches involve simple *ex vivo* programming strategies designed to enhance the homing efficiencies of HSCs to the BM niche (Hogatt et al. 2009; Greim et al. 2014).

Several factors play a role in the engraftment of HSC into BM. Bone marrow niche sites represent specific microenvironments that promote the proliferation and differentiation of HSC into mature blood cells. An important phase of engraftment of HSC involves the homing of these cells to the appropriate sites within the BM. A key component of this homing mechanism is the interaction between stromal derived factor-1 (SDF-1), which is displayed on cells within the BM niche, and C-X-C chemokine receptor type 4 (CXCR4), which is expressed on the cell surface of HSC. The ligand-receptor interaction between SDF-1 and CXCR4 promotes the localization and retention of HSC in the BM niche. *Ex vivo* programming of mPB derived HSCs with FT1050 and FT4145 leads to significant upregulation of CXCR4 and enhanced migration *in vitro* to gradients of SDF-1 in transwell assays; see ProTmune Investigator's Brochure (IB). The mechanism of action for the 2 modulators, FT1050 and FT4145 is derived by a "cross-talk" that occurs via downstream intracellular signaling events which directly leads to the synergistic increase in CXCR4 gene and protein expression.

1.4 Risk/Benefit

1.4.1 Summary of Nonclinical Studies

1.4.1.1 *In vitro* characterization studies of hematopoietic stem cells

Homing is an important first step in the engraftment process in which circulating HSC actively cross the blood/BM endothelium barrier and lodge in BM niches. These niche sites represent specific microenvironments that promote the expansion and differentiation of HSC into progenitors and mature lineages. The receptor CXCR4 is one of the key surface receptors involved in stem cell homing, activation of this receptor by ligand binding promotes the migration of these stem cells towards the high levels of SDF-1α. Additionally, SDF-1α is the natural ligand for CXCR4 found in high levels in post-cytoablated BM (Hogatt et al. 2009). FT1050 and FT4145-programmed HSC exhibited dramatic upregulation of CXCR4 at both the messenger ribonucleic acid level (~60-fold, $p \leq 0.0001$; paired t-test; see ProTmune IB) and the surface protein level ($p \leq 0.0005$; paired t-test; see ProTmune IB). Hematopoietic stem cells programmed with FT1050 and FT4145 also displayed increased migration rates to a gradient of SDF-1 in an *in vitro* transwell migration assay relative to vehicle controls ($p=0.0001$; paired t-test). This increased directional migration demonstrates an increased SDF-1α homing ability in the programmed cells.

1.4.1.2 *In vivo* repopulating ability (engraftment)

Increased CXCR4 levels on HSC may lead to an increased ability of these cells to migrate *in vivo* into BM stem cell niches and accelerate engraftment, thereby improving immune reconstitution. Using an immunodeficient mouse model, Fate evaluated the ability of *ex vivo* programming of mPB CD34+ cells with FT1050 and FT4145 to improve engraftment. Compared to untreated control cells, significantly enhanced engraftment (engraftment defined >0.5% human CD45 in the marrow, p=0.01; unpaired t-test) of human CD34+ treated with FT1050 and FT4145 was observed in several independent experiments with 3 different donors, with an average overall human hematopoietic cell engraftment of 8% at 8 weeks post infusion compared to 2.9% in the control group; see ProTmune IB.

Human chimerism was tracked in the peripheral blood of human mPB CD34+ treated with vehicle, FT1050, or FT1050 and FT4145 for all 3 donors over time. This study demonstrated that *ex vivo* programming significantly improved long-term engraftment outcomes of human mPB CD34+ cells.

Using *ex vivo* programming to enhance immune reconstitution minimizes the risks of infections and relapse. In multiple *in vitro* assays and *in vivo* models, HSC modulated with FT1050 and FT4145 demonstrated improved homing, migration and enhanced long-term engraftment.

1.4.1.3 T-cell characterization studies

As highlighted earlier, one of the major complications associated with allogenic HCT is aGvHD mediated by allogenic activated donor T-cells. Fate has conducted several nonclinical studies to characterize how the T-cell compartment of mPB is affected by *ex vivo* programming with FT1050 and FT4145. T-cells programmed with FT1050 and FT4145 were characterized using both *in vitro* assays (e.g., mixed lymphocyte reactions) and *in vivo* models (e.g., GvHD and GvL). Programmed T-cells (both CD4 and CD8) had lower proliferation rates relative to vehicle-treated cells in a 5-day co-culture with mismatched peripheral blood mononuclear cells from a different donor. In the mouse GvHD model, T-cells programmed with FT1050 and FT4145 had reduced levels of inflammatory cytokines, reduced GvHD scores and enhanced survival relative to the vehicle treated cells; see ProTmune IB. Lastly, in mouse GvL models, T-cells programmed with FT1050 and FT4145 retained GvL activity against the A20 lymphoma cells; see ProTmune IB.

ProTmune utilizes a small molecular modulator, referred to as FT4145, which synergizes with FT1050 to promote the supra-physiologic activation of genes implicated in the cell cycle, immune tolerance, and anti-viral properties of T-cells. Nonclinical *in vitro* and animal studies have demonstrated that mPB treated with FT1050 and FT4145 result in reduced allogeneic GvHD while maintaining GvL response, suggesting that ProTmune may provide a clinical benefit in terms of GvHD reduction. These data also suggest that programmed cell populations in mPB treated with FT1050 and FT4145 have further potential to prevent viral (CMV) reactivation though the same modulation of T-cells.

Combined, these studies demonstrated that pharmacologic programming mPB cells with FT1050 + FT4145 prior to allogenic HCT may offer an innovative therapeutic approach to reduce rates of GvHD without compromising the GvL response.

1.4.1.4 Summary of nonclinical findings

Predictive *in vitro* assays and *in vivo* models have demonstrated the potential safety and efficacy of ProTmune. Results of the currently available *in vitro* and *in vivo* nonclinical studies have demonstrated that *ex vivo* programming of mPB cells with FT1050 and FT4145 can enhance engraftment of HSC and reduce GvHD through programming a number of key biological pathways in mPB T-cells. Reduced expression levels of phenotypic markers of activation is suggestive of a reduced activation capacity in the programmed T-cells that could, in concert with the cytokine data, lead to a lower potential for transplanted cells to promote GvHD in patients. Furthermore, mouse models demonstrated that treatment with FT1050 and FT4145 led to reduced GvHD scores, enhanced survival, reduced levels of pro-inflammatory cytokines without compromising the GvL activity of the T-cells. Taken together, these nonclinical studies demonstrate the safety and potential efficacy of ProTmune.

1.4.2 Summary of Clinical Studies

This study is the first time ProTmune programmed mPB will be administered to humans. Based on current nonclinical data, ProTmune programming of mPB is anticipated to be safe and well tolerated. In conjunction with continual safety monitoring for all subjects enrolled in the study, various clinical and biomarker endpoints will be monitored in this first-in-human trial.

Refer to the ProTmune Investigator Brochure for additional information on the safety of ProTmune.

1.5 Rationale

1.5.1 Proof-of-Concept Clinical Data

Recent results from Fate's Phase 2 PUMA clinical trial of ProHema (FT1050-programmed umbilical cord blood) provide compelling proof-of-concept data that *ex vivo* programming of donor grafts can enhance the therapeutic properties of donor-derived T-cells in the setting of HCT. Interim data from the PUMA study showed that subjects administered ProHema experienced a 46% reduction in severe viral infection-related adverse events following HCT. Specifically, 9 of 28 subjects administered ProHema, or 32%, experienced 1 or more severe viral infection-related adverse events (Grades 3 through 5) following HCT, as compared to 9 of 15 control subjects, or 60%. Immunophenotyping analysis of subject blood samples from the PUMA study taken at different time points post-HCT (30, 60, 100, and 180 days) showed that, in subjects administered ProHema, T-cells had improved persistence compared to T-cells of control subjects. These observations are consistent with a 2014 publication by Fate's collaborators that investigated the T-cell compartment of subjects administered ProHema in Fate's Phase 1b clinical trial of ProHema (Li et al. 2014). The collaborator's immunophenotyping analysis showed that the T-cell compartment of subjects administered ProHema exhibited a higher percentage of T-cells with a stem/memory phenotype compared to samples from historical control subjects (N = 53). The data from the PUMA study, including both the reduction in severe viral infection-related adverse events and the phenotypic changes to the T-cell compartment, provides supporting evidence for the ability to efficiently program donor immune cells.

Infections are a major cause of morbidity and mortality for patients undergoing HCT procedures. During the first 100 days following HCT, graft-derived T lymphocytes provide the first wave of the immune protection against viral infections. The second wave of T-cells comes from de novo

thymopoiesis, which typically requires 6 to 12 months to fully restore the T-cell compartment. Viral infections, including those from CMV, are particularly prevalent in the immediate post-transplant period, where it has been reported that over 90% of CMV infections occur within the first 100 days following HCT (Jain et al. 2014).

The protection afforded by the graft-derived T-cells is limited during the initial period following HCT for several reasons. One of the factors that limits the effectiveness of the donor-derived T-cells in fighting viral infections results directly from the HCT conditioning regimen. In the days following HCT, high levels of inflammatory cytokines are present in patients' blood, which can drive the rapid expansion and exhaustion of the adoptively-transferred CD4+ and CD8+ T-cells. This response results in a depleted and functionally-impaired T-cell compartment, limiting the ability of these cells to provide immune protection.

1.5.2 Nonclinical Data Supporting ProTmune's Ability to Reduce Viral Infections

Fate has been advancing the nonclinical development of ProTmune, an mPB unit programmed with 2 small molecules, FT1050, which is the small molecule Fate uses for the production of ProHema, and FT4145. This development effort has been driven by Fate's specific intent of enhancing the therapeutic properties of donor T-cells in in the setting of HCT. Nonclinical studies demonstrate that *ex vivo* programming mPB with the combination of FT1050 and FT4145 renders the immune cells in mPB less responsive to the high levels of activating cytokines, which reduces the expansion and exhaustion of donor T-cells. *In vitro* assays designed to mimic the high levels of inflammatory cytokines found in patients following HCT show that programmed T-cells have reduced proliferation rates and reduced expression levels of key T-cell activation markers compared to vehicle treated cells; see ProTmune IB. Importantly, these assays show that the viability of the programmed T-cells is not negatively impacted; see ProTmune IB. Preliminary data suggests that preventing the rapid expansion and exhaustion of T-cells during the first week post-HCT has the potential to preserve a diverse T-cell repertoire over the first critical weeks and months following HCT, and that the programming of donor-derived T-cells has the potential to reduce the incidence of life-threatening viral infections.

1.6 Rationale for ProTmune Clinical Study in Matched Unrelated Donors

Many patients with hematologic malignancies advance to a stage where allogeneic HCT becomes the only remaining therapeutic option that offers the potential to prolong lifespan or even a curative outcome. Approximately 50% to 60% of allogeneic HCTs reported to the CIBMTR use unrelated donors (Majhail et al. 2015). Over the past decade, the number of peripheral blood cell grafts facilitated by the NMDP has grown substantially, such that currently around 75% of HCT procedures that utilize unrelated grafts employ peripheral blood cells (Woolfrey et al. 2011).

Several large, multicenter, randomized studies have collectively demonstrated that time to engraftment/reconstitution is faster and more robust with mPB than with BM (Pidala et al. 2009). However, mPB is also associated with higher rates of both acute and cGvHD (as compared to the use of BM or umbilical cord blood), which has limited the universal adoption of this otherwise convenient and highly effective cell source for HCT. This is attributed in part to the large number of T-cells infused with mPB as compared to other cell sources (Anasetti et al. 2012). Since no therapy has yet been approved for the prevention of GvHD, current treatments for GvHD include drugs prescribed off-label and can thus be ineffective. For patients undergoing HCT, there is a

clear need for new approaches to reduce rates of GvHD without compromising the anti-leukemia and anti-infective properties of the T-cells in the graft.

ProTmune has the potential to reduce aGvHD while retaining GvL activity through programming a number of key biological pathways in both HSC and T-cells in mPB. Additionally, previous clinical experience with one of the ProTmune programming agents (FT1050) suggests the potential of ProTmune to reduce viral infections following HCT. The nonclinical studies summarized previously demonstrate the safety and potential efficacy of ProTmune.

Taken together, patients undergoing HCT who receive mPB that has been programmed using FT1050 and FT4145 are expected to have improved outcomes. The primary goal of this Phase 1/2 study is to assess the safety, tolerability, and potential efficacy of ProTmune for reduction of incidence and severity of aGvHD in adult subjects who have undergone a matched, unrelated HCT for hematologic malignancies.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

2.1.1 Primary Objective for the Phase 1 Part of the Study

The primary objective of the Phase 1 part of the study is to evaluate the safety and tolerability of ProTmune *ex vivo* programmed mPB cells for HCT in adult subjects with hematologic malignancies.

2.1.2 Primary Objective for the Phase 2 Part of the Study

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

2.2.1 Secondary Objective for the Phase 1 Study

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.

2.2.2 Secondary Objective for the Phase 2 Study

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

2.3.1 Exploratory Objectives for the Phase 2 Part of the Study

The exploratory objectives for the Phase 2 part 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 aGvHD;
- To assess the incidence of, and time to, CMV viremia, incidence and severity of CMV invasive disease, and incidence of CMV reactivation;
- To assess time to first CMV-specific anti-viral therapy (AVT);
- 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 cGvHD;
- To assess cumulative incidence of primary and secondary graft failure;
- To assess neutrophil and T-cell chimerism;
- To determine relapse-free survival;
- To determine the incidence of NRM;
- To determine the survival at one-year and at two-years; and
- To assess immune reconstitution (including B, T, dendritic, and natural killer [NK] cells).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 1, non-randomized, open-label/Phase 2, randomized, blinded, multi-center study of ProTmune *ex vivo* programmed mPB versus non-programmed mPB cells for allogeneic HCT in adult subjects with hematologic malignancies in the United States. All subjects in Phases 1 and 2 will receive a conditioning regimen comprising 1 of the following 5 preparative regimens: fludarabine and busulfan (FluBu4); busulfan (Bu) and cyclophosphamide (Cy); Cy and ≥12 Gy total body irraditiation (TBI); TBI and etoposide; or fludarabine and melphalan (FluMel 140). Refer to Section 3.4 for a detailed description of the regimens required per the protocol.

It is anticipated that the majority of subjects will be recruited from referrals for transplantation at the study sites. Potential study subjects can be pre-screened for study eligibility (evaluation of inclusion and exclusion criteria) based on the standard of care assessments that were completed prior to obtaining an informed consent, only with previously obtained Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of such pre-screening procedures. Data will be requested from study centers in order to track screening and recruitment activity.

Both the Phase 1 part of the study and Phase 2 part of the study will include a Screening Period (Day -53 through Day -11), Subject Conditioning Period (Day -10 through Day -1), Study Treatment Administration Day (Day 0; Day of HCT), Post-Transplant Follow-up Period (Day +1 through Day +730, consisting of Post-Transplant Assessment Days and Post-Transplant Weekly Assessments, then intermittent assessments), and an Early Withdrawal Visit (if applicable). Refer to Appendix A for a summary of the Study Procedures for the Phase 1 and 2 parts of the study. The total duration of subject participation will be up to 26 months for each subject in the Phase 1 part of the study and Phase 2 part of the study.

The end of the study is considered as the completion through Day +365. All treated subjects will be followed for survival through Day +730 (i.e., 2 years).

The study will utilize an Endpoint Adjudication Committee (EAC) blinded to treatment. The EAC will be responsible for adjudicating the aGvHD endpoint in accordance with the EAC charter.

3.1.1 Study Design for the Phase 1 Part of the Study

The Phase 1 part of the study is a non-randomized, open-label, single-arm study that will enroll 6 to 10 subjects who have an available 8/8 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 receive 1 unit of ProTmune *ex vivo* programmed mPB cells as the cell source for the HCT procedure. For a study design schematic for the Phase 1 part of the study, refer to Appendix B.

At initiation of the Phase 1 part of the study, 3 subjects will be enrolled and treated. At the time a subject engrafts (or fails to engraft by Day +28), a new subject may be treated.

The study will utilize an EAC blinded to treatment who will be responsible for adjudicating the aGvHD endpoint in accordance with the EAC charter.

Early stopping rules for the Phase 1 part of the study will be in place from the start of the study throughout the duration of the study and, if applicable, triggered prior to assessments by the Independent Data Monitoring Committee (IDMC). Refer to Section 3.1.3.1 for a description of the early stopping rules for the Phase 1 part of the study.

An 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.

The Phase 1 part of the study will consist of approximately 5 to 10 sites in the United States.

For a flow schematic for the Phase 1 part of the study, refer to Appendix C.

A summary of the study visits for the Phase 1 part of the study are described below. For further detail regarding study procedures at each study visit, refer to Appendix A.

Screening Period for the Phase 1 Part of the Study (Day -53 to Day -11)

The Screening Period will occur between Day -53 and Day -11 (i.e., up to 6 weeks prior to the Subject Conditioning Period). At Screening, all subjects will review and sign an informed consent form (ICF) and eligibility for study participation will be assessed. The Investigator will be required to verify that the subject completed HLA typing, which can be completed prior to the Screening Period. Peripheral blood will be collected during the Screening Period to serve as a baseline sample for immune reconstitution analysis.

The results of the bone marrow aspirate, spirometry, and ECHO or multiple gated acquisition (MUGA) performed prior to consent may be used for subject qualification as long as performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.

As a part of screening, all subjects will be tested for baseline CMV antibody titer and plasma CMV viremia. This baseline testing will be performed by a central laboratory and results will be provided to the clinical site and sponsor before initiation of randomization.

All concomitant medications will be recorded starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.

Subject Conditioning Period for the Phase 1 Part of the Study (Day -10 to Day -1)

The Subject Conditioning Period will occur between Day -10 and Day -1. Day 0 is the day of mPB HCT transplant. Subject conditioning will be administered as the conditioning regimen per the protocol (refer to Section 3.4). Graft-versus-host disease prophylaxis will be administered to subjects.

Anti-thymocyte globulin is not permitted during the study.

FDA-approved prophylactic therapies for CMV prevention (e.g., letermovir) will be permitted. Refer to Section 3.5 for a description of pre-emptive therapy for infection. Pre-emptive CMV therapy will be provided based upon institutional methodologies, Standard Operating Procedures, and clinical context. An additional blood sample for CMV testing will be taken for central laboratory testing prior to starting the preemptive therapy.

Other procedures for transplant preparation will also be performed at the Subject Conditioning Visit and per Institutional Standard.

Adverse events will be collected during Phase 1 and 2 as per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, AE of infections will use both the CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN, Appendix G) criteria, as follows:

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

Hospital Admission for the Phase 1 Part of the Study

Subjects will be admitted to the hospital based on institutional policy.

Study Treatment Administration for the Phase 1 Part of the Study (Day 0; Day of Hematopoietic Cell Transplant)

A 12-lead triplicate electrocardiogram (ECG) (sequential, within 15 minutes total), complete blood count (CBC), and blood chemistry will be obtained on Day 0 prior to HCT. All eligible subjects will receive study treatment on the day of HCT (Day 0). For the Phase 1 part of the study, study treatment will consist of a single unit of ProTmune *ex vivo* programmed mPB cells. The ProTmune graft will be prepared the same day as administration. Refer to the ProTmune IB for a description of release testing criteria. Refer to Section 3.6 for a description of the algorithm for reserve HSC.

Karnofsky Performance Status will be assessed at Day 0, following transplantation (refer to Appendix D for a description of Karnofsky Performance Status). For a description of transfusion and support guidelines, refer to Section 3.7.

Post-Transplant Assessment Days for the Phase 1 Part of the Study

Post-transplant visit windows are as follows: ±3 days for Day +7 through Day +100; ±14 days for Day +180; and ±28 days for Days +270, +365, and +730. Standard post-transplant testing will be performed per institutional guidelines and good clinical practice.

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Post-Transplant Weekly Visits for the Phase 1 Part of the Study

Clinical and laboratory assessments of aGvHD will be performed weekly from Day +1 through Day +100, and on Day +180. Acute GvHD assessments (incidence and maximum severity) of Grades I through IV of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale will be performed. For a description of the CIBMTR aGvHD Grading Scale, refer to Appendix E.

Chronic GvHD assessments (incidence and maximum severity) of mild, moderate, or severe cGvHD as per National Institutes of Health (NIH) Consensus Criteria for cGvHD will be

performed on Days +180, +270, and +365. For a description of the NIH Consensus Criteria for cGvHD, refer to Appendix F.

Peripheral blood samples will be collected for CMV assessments of deoxyribonucleic acid (DNA) by quantitative polymerase chain reaction (PCR) weekly from Days +7 through Day +100, and on Days +180, +270 and +365. Assessment of infection will be performed based on the NCI CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) definitions. Study sites will monitor CMV viremia using local assays and frequencies as determined by local practices for in-patient and out-patient care. Therefore, if a blood sample is being drawn for a CMV PCR at a local virology laboratory, a sample must also be drawn at the same time and sent to the central virology laboratory for a CMV PCR result. See Appendix G.

Peripheral blood will be collected for safety laboratory panels (hematology and serum chemistry), viral monitoring, immune reconstitution, chimerism, serum immunoglobulins, and GvHD exploratory biomarkers at the time points specified in Appendix A.

A 12-lead triplicate ECG (sequential, within 15 minutes total) will be obtained at Day +100.

Bone marrow aspirate will be sent to pathology and to cytogenetics on Day +21 (only if absolute neutrophil count [ANC] <500/µL), and as clinically indicated (flow cytometry is required on BM aspirate).

Karnofsky Performance Status (Appendix D) will be assessed at all subsequent study visits after HCT up through Day +365 (which should include weekly assessments from Day +1 through Day +91, then on Days +100, +180, +270, and +365).

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Unscheduled visits

An unscheduled visit is a visit that occurs in addition to the predefined protocol specific visit calendar. If an unscheduled visit occurs for a given subject, the visit must be documented on the Unscheduled Visit CRF.

Early Withdrawal Visit for the Phase 1 Part of the Study

If a subject is withdrawn from participation in the study prior to Day 0, the subject's mPB will not be processed to a unit of ProTmune *ex vivo* programmed mPB cells, the subject will not be considered evaluable for any study-related endpoint analyses, and the subject will be replaced.

If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected by phone on Days +180, +365, and +730. If a subject withdraws consent, survival outcomes will be assessed via public record search.

If the subject relapses and/or receives a protocol-prohibited therapy, the subject will be withdrawn from the study. However, survival will still be collected at Day +730 by telephone contact unless the subject withdraws consent, in which case survival outcomes will be assessed via public record search.

A peripheral blood sample for safety laboratory panels (hematology and serum chemistry) will be collected.

Karnofsky Performance Status should be assessed (Appendix D), and GvHD assessments (incidence and maximum severity) (Appendix E and Appendix F) must be performed.

In instances where donors require plerixafor for mobilization of peripheral blood, the subject will be off-study and replaced.

3.1.2 Study Design for the Phase 2 Part of the Study

The Phase 2 part of the study may begin after 6-10 subjects have completed Phase 1 and the safety data has been reviewed by the IDMC. If after 6 subjects have been dosed and evaluated in Phase 1 for up to 28 days and ≤1 subject has not engrafted by Day +28, then enrollment in the Phase 2 portion of the study may proceed following IDMC review.

The Phase 2 part of the study is a randomized, blinded, 2-arm study that will treat 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 be randomly assigned in a 1:1 ratio to receive either unmanipulated mPB cells (control arm) or ProTmune *ex vivo* programmed mPB cells (experimental arm) and stratified by the subjects' CMV status). For a study design schematic of the Phase 2 part of the study, refer to Appendix H.

The study will utilize an Endpoint Adjudication Committee (EAC) blinded to treatment. The EAC will be responsible for adjudicating the aGvHD endpoint in accordance with the EAC charter.

Early stopping rules for the Phase 2 part of the study will be in place from the start of the study throughout the duration of the study and, if applicable, triggered prior to assessments by the IDMC. With the exception of the stopping rules associated with the failure of ProTmune to meet release specifications, there are no formal stopping rules for the Phase 2 part of the study. Stopping subject treatment may be triggered based on the continued review of subject safety data on study by the Sponsor and IDMC. If the investigational product does not meet release specifications to treat 2 of the first 3 subjects, 3 of the first 6 subjects, or 5 of the first 10 subjects or 10 of the first 20 subjects, subject treatment in the Phase 2 part of the study will be stopped. Refer to Section 3.1.3.2 for a description of the early stopping rules for the Phase 2 part of the study.

During the Phase 2 part of the study, the IDMC will convene according to the guidelines outlined in the IDMC Charter. Additional safety monitoring based on NRM, secondary graft failure, and IDMC input will be applied during the study for the Phase 1 and Phase 2 parts of the study.

The Phase 2 part of the study will comprise approximately 14 to 20 sites in the United States.

For a flow schematic for the Phase 2 part of the study, refer to Appendix I.

A summary of the study visits for the Phase 2 part of the study are described below. For further detail regarding study procedures at each study visit, refer to Appendix A.

Screening Period for the Phase 2 Part of the Study (Day -53 to Day -11)

The Screening Period will occur between Day -53 and Day -11 (i.e., up to 6 weeks prior to the Subject Conditioning Period). At Screening, all subjects will review and sign an ICF and eligibility for study participation will be assessed. The Investigator will be required to verify that the subject completed HLA typing. HLA typing can be completed prior to the Screening Period. Peripheral blood will be collected during the Screening Period for baseline immune reconstitution analysis. After meeting eligibility, subjects will be randomly assigned in a 1:1 ratio to receive either

unmanipulated mPB cells (control arm) or ProTmune *ex vivo* programmed mPB cells (experimental arm) and stratified by the subjects' CMV status.

The results of the bone marrow aspirate, spirometry, and ECHO or multiple gated acquisition (MUGA) performed prior to consent may be used for subject qualification as long as performed within 6 weeks prior to the Subject Conditioning, from Day -53 to Day -11.

As a part of screening, all subjects will be tested for baseline CMV antibody titer and plasma CMV viremia. This baseline testing will be performed by a central laboratory and results will be provided to the clinical site and sponsor before initiation of randomization.

All concomitant medications will be recorded starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.

Subject Conditioning Period for the Phase 2 Part of the Study (Day -10 to Day -1)

The Subject Conditioning Period will occur between Days -10 and Day -1 (i.e., up to 9 days prior to Hospital Admission). Subject conditioning will be administered as the conditioning regimen, as required per the protocol (refer to Section 3.4). Graft-versus-host disease prophylaxis will be administered.

Anti-thymocyte globulin is not permitted during the study.

FDA-approved prophylactic therapies for CMV prevention (e.g., letermovir) will be permitted. Refer to Section 3.5 for a description of pre-emptive therapy for infection. Pre-emptive CMV therapy may be provided based upon institutional methodologies, Standard Operating Procedures, and clinical context. An additional blood sample for CMV testing will be taken for central laboratory testing prior to starting the preemptive therapy.

Other procedures for transplant preparation will also be performed at the Subject Conditioning Visit and per Institutional Standard.

Adverse events will be collected during Phase 1 and 2 as per the CTCAE version 4.0, AE of infections will use both the CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN, Appendix G) criteria, as follows:

- All SAEs will be recorded from Day -10 through Day +365, and only SAEs related to infused cells (ProTmune mPB cells or Control mPB cells) from Day +366 through Day +730;
- Start of conditioning regimen (Day -10) through Day +100: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator;
- From Day +100 through Day +365: Only adverse events associated with GvHD, infections, or secondary engraftment failure (Grades 1 through 5).

Hospital Admission for the Phase 2 Part of the Study

Subjects will be admitted to the hospital based on institutional policy.

Study Treatment Administration for the Phase 2 Part of the Study (Day 0; Day of Hematopoietic Cell Transplant)

A 12-lead triplicate ECG (sequential, within 15 minutes total), CBC, and blood chemistry will be obtained on Day 0 prior to HCT. All eligible subjects will receive study treatment on the day of HCT (Day 0). For the Phase 2 part of the study, study treatment will consist of either a single unit of ProTmune *ex vivo* programmed mPB cells or a single unit of unmanipulated mPB cells, based upon the subject's randomized treatment allocation. The ProTmune graft will be prepared the same day as administration. Refer to the ProTmune IB for a description of release testing criteria.

Karnofsky Performance Status (Appendix D) will be assessed at Day 0, following transplantation. For a description of transfusion and support guidelines, refer to Section 3.7.

Post-Transplant Assessment Days for the Phase 2 Part of the Study

Post-transplant visit windows are as follows: ±3 days for Day +7 through Day +100; ±14 days for Day +180; and ±28 days for Days +270, +365, and +730. Standard post-transplant testing will be performed per institutional guidelines and good clinical practice.

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Post-Transplant Weekly Visits for the Phase 2 Part of the Study

Clinical and laboratory assessments of aGvHD will be performed weekly from Day +1 through Day +100, and at Day +180. Acute GvHD assessments (incidence and maximum severity) of Grades I through IV aGvHD of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale. For a description of the CIBMTR cGvHD Grading Scale, refer to Appendix E.

Chronic GvHD assessments (incidence and maximum severity) of mild, moderate, or severe cGvHD as per NIH Consensus Criteria for cGvHD must be performed on Days +180, +270 and +365. For a description of the NIH Consensus Criteria for cGvHD, refer to Appendix F.

Peripheral blood samples will be collected for CMV assessments of DNA by quantitative PCR weekly from Days +7 through Day +100, and at Days +180, +270 and +365. Assessment of infection will be performed based on the NCI CTCAE and the BMT CTN Definitions. Study sites will monitor CMV viremia using local assays and frequencies as determined by local practices for in-patient and out-patient care. Therefore, if a blood sample is being drawn for a CMV PCR at a local virology laboratory, a sample must also be drawn at the same time and sent to the central virology laboratory for a CMV PCR result. See Appendix G.

Peripheral blood will be collected for safety laboratory panels (hematology and serum chemistry), viral monitoring, immune reconstitution, chimerism, serum immunoglobulins, and GvHD exploratory biomarkers at the time points specified in Appendix A.

A 12-lead triplicate ECG (sequential, within 15 minutes total) will be obtained at Day +100.

Bone marrow aspirate will be sent to pathology and to cytogenetics on Day +21 (only if ANC <500/µL), and as clinically indicated (flow cytometry is required on BM aspirate).

Karnofsky Performance Status (Appendix D) will be assessed at all subsequent study visits after HCT up through Day +365 (which should include weekly assessments from Day +1 through Day +91, then on Days +100, +180, +270, and +365).

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

Unscheduled visits

An unscheduled visit is a visit that occurs in addition to the predefined protocol specific visit calendar. If an unscheduled visit occurs for a given subject, the visit must be documented on the Unscheduled Visit CRF.

Early Withdrawal Visit for the Phase 2 Part of the Study

If a subject is withdrawn from participation in the study prior to Day 0, the subject's mPB will not be processed to a unit of ProTmune *ex vivo* programmed mPB cells, the subject will not be considered evaluable for any study-related endpoint analyses, and the subject will be replaced. If this occurs in the Phase 2 portion of the study and the subject was already randomized, the subject will be replaced and a new subject will be randomized in order to have approximately 80 treated subjects.

If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected by phone on Days +180, +365, and +730. If a subject withdraws consent, survival outcomes will be assessed via public record search.

If the subject relapses and/or receives a protocol-prohibited therapy, the subject will be withdrawn. However, survival will still be collected unless the subject withdraws consent, in which case survival outcomes will be assessed via public record search. A peripheral blood sample for safety laboratory panels (hematology and serum chemistry) will be collected.

Karnofsky Performance Status should be assessed (Appendix D), and GvHD assessments must be performed, as applicable.

In instances where donors require plerixafor for mobilization of peripheral blood, the subject will be off-study and replaced.

3.1.3 Early Stopping Rules for the Study

3.1.3.1 Early stopping rules for the Phase 1 part of the study

At initiation of the Phase 1 part of the study, 3 subjects will be enrolled and treated. At the time a subject engrafts (or fails to engraft by Day +28), a new subject may be treated. If 2 or more subjects fail to engraft by Day +28, or if 2 or more subjects experience secondary graft failure by Day +28, or if 2 of the first 3 or 4 of the first 6 subjects treated have died by ≤Day +28, subject treatment will be stopped until the IDMC has assessed the cases and discussed with the Sponsor. The IDMC will be notified of all subject deaths occurring on study. If the investigational product does not meet release specifications to treat 2 of the first 3 subjects, 3 of the first 6 subjects, or 5 of the first 10 subjects, subject treatment will be stopped pending review by the IDMC.

3.1.3.2 Early stopping rules for the Phase 2 part of the study

With the exception of the stopping rules associated with the failure of ProTmune to meet release specifications, there are no formal stopping rules for the Phase 2 part of the study. Stopping subject treatment may be triggered based on the continued review of subject safety data on study by the Sponsor and IDMC. If the investigational product does not meet release specifications to treat 2 of the first 3 subjects, 3 of the first 6 subjects, or 5 of the first 10 subjects or 10 of the first 20 subjects, subject treatment in the Phase 2 part of the study will be stopped, pending review by the IDMC.

3.2 Independent Data Monitoring Committee

During the Phase 1 part of the study, an 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 the Phase 2 part of the study, the IDMC will convene according to the guidelines outlined in the IDMC Charter. Additional safety monitoring based on NRM, secondary graft failure, and IDMC input will be applied during the study for the Phase 1 and Phase 2 parts of the study.

3.2.1 Endpoint Adjudication Committee

The study will utilize an Endpoint Adjudication Committee (EAC) blinded to treatment assignment. The EAC will be responsible for adjudicating the aGvHD endpoint in accordance with the EAC charter.

3.3 Study Indication(s)

For the Phase 1 and Phase 2 part of the study, ProTmune will be evaluated for the reduction of incidence and severity of acute GvHD in adult subjects with hematologic malignancies.

3.4 Conditioning and Graft-versus-Host Disease Prophylaxis Regimens

All eligible subjects in the Phase 1 part of the study and Phase 2 part of the study will receive 1 of the following 5 preparative regimens:

- CyTBI, with ≥12 Gy fractionated TBI;
- BuCy where Bu = 16 mg/kg orally (PO) or 12.8 mg/kg IV infusion (alternatively, pharmacokinetic assessment and dose adjustment of Bu can be based on a test dose or the first dose and will be conducted according to institutional practices);
- FluBu4 with Bu as above;
- TBI and etoposide; or
- FluMel 140

Graft-versus host disease prophylaxis will be administered to all subjects.

The GvHD prophylaxis regimen:

- Methotrexate (15 mg/m^2 IV infusion on Day +1 after hematopoietic cell infusion and 10 mg/m^2 on Days +3, +6, and +11), and
- Tacrolimus (0.02 mg/kg every 24 hours as an IV infusion or 0.03 mg/kg PO beginning on Day -2, adjusted to target dose level of 5 to 15 ng/mL. Taper starting at Day +100).

The GvHD prophylaxis may be dose reduced based on clinical judgment and associated with toxicity.

All chemotherapy administered to subjects will be dosed based on the subject's actual body weight. However, for subjects weighing more than 125% of their ideal body weight (IBW), chemotherapy will be dosed based on the adjusted ideal body weight (AIBW), or by Institutional Standards (Hicks et al. 2012).

Ideal Body Weight Formula:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) × (Actual Body Weight - IBW)]

3.5 Prophylactic and Pre-emptive Therapy for CMV Infection

For the study, prophylactic and pre-emptive therapy for viral infection for the Phase 1 part of the study and Phase 2 part of the study comprise the following:

- FDA-approved prophylactic therapies for CMV prevention (e.g., letermovir) will be permitted;
- Two peripheral blood samples at each testing time point (1 blood sample to be utilized locally at the site for subject management and 1 blood sample for central laboratory testing) will be collected for viral assessments of DNA by quantitative PCR for Epstein Barr Virus (EBV), CMV, human herpes virus 6 (HHV-6), and BK virus weekly from Days +7 through Day +100, and at Days +180, +270 and +365;
- Pre-emptive CMV therapy may be initiated based upon institutional policies and procedures, Standard Operating Procedures, and clinical context. An additional blood sample for CMV testing will be obtained for central laboratory testing and prior to starting the preemptive therapy. and
- If clinical site viral testing is positive, subjects will receive pre-emptive therapy with an anti-viral therapy (i.e., ganciclovir, foscarnet, etc.) per Institutional Standard.

3.6 Reserve Hematopoietic Stem Cells

For subjects enrolled in the Phase 1 part of the study, a reserve dose of 2×10^6 CD34+ cells/kg recipient weight will be maintained during ProTmune manufacturing to serve as a reserve in the event ProTmune manufacturing produces a ProTmune unit that does not meet ProTmune release specifications (e.g., $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable). In this case, the ProTmune unit will be considered "unavailable" and count towards the Phase 1 stopping rules. The reserve unit must be administered; however, the Principal Investigator should follow their Institution's standard operating procedure to determine whether the ProTmune unit should also be given to the recipient based on the risk-benefit assessment of administering the product with regard to the specification not being met. If the ProTmune unit is not administered, the subject will be withdrawn from study and replaced. If the ProTmune unit is administered, the subject will remain in study but will not be considered in the following assessment- "If after 6 subjects have been dosed and evaluated for up to 28 days and ≤1 subject has not engrafted by Day +28, then enrollment in the Phase 2 portion of the study may proceed following IDMC review". If the reserve

unit is not used on Day 0, it will be cryopreserved at the site and can be used in the event of non-engraftment, or delayed engraftment. If unused, the reserve dose may be disposed of in accordance with institutional practices.

3.7 Transfusion and Support Guidelines

The following guidelines for platelet and red blood cell (RBC) transfusions will be followed starting on Day 0:

- Platelet and RBC transfusion technical support will be dictated by Institutional guidelines including product irradiation and CMV status of transfused product;
- Platelet threshold transfusion guidelines:
  - A threshold of 10×10^9/L for prophylactic platelet transfusion;
  - A threshold of 20×10^9/L for fever, sepsis, splenomegaly, and other well-established causes of increased platelet consumption;
  - A threshold of $>50 \times 10^9$/L if an invasive procedure is planned;
  - Single donor platelets should be used in preference to random donor platelets, if feasible; and
  - HLA-matched platelets should be used in subjects with allo-immunization;
- Red blood cell transfusion guidelines:
  - An attempt should be made to maintain the hematocrit ≥24% and hemoglobin >8 g/dL, or higher in cases of symptomatic management of anemia or other medically indicated indications; and
- Filgrastim (granulocyte-colony stimulating factor) can be administered at 5 µg/kg/day beginning on Day +12, if engraftment has not occurred, until the ANC is >500 cells/µL. At Investigator discretion, filgrastim can be administered longer to support the white blood cells. Similarly, per Investigator discretion, filgrastim may be started before Day +12 if subsequent doses of methotrexate will not be administered due to severe mucositis, other toxicity, or severe infection.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria for the Phase 1 Part of the Study and the Phase 2 Part of the Study

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Male and female subjects aged 18 years and older;
2. Subjects must have a hematologic malignancy for which allogeneic hematopoietic peripheral blood cell transplantation is deemed clinically appropriate. Eligible diseases and stages include and are limited to the following:
    - Acute myeloid leukemia in first complete remission (CR) (CR1) or second CR (CR2):
        - CR is defined as ≤5% BM blasts with no morphological characteristics of acute leukemia (e.g., Auer Rods) in BM with ≥5% cellularity with normal peripheral blood counts; or
        - Morphologic CR (≤5% BM blasts) with incomplete blood count recovery;
    - Acute lymphoblastic leukemia (ALL), including T lymphoblastic lymphoma with a history of marrow involvement in CR1 or CR2:
        - CR is defined as ≤5% blasts with no morphological characteristics of acute leukemia in a BM with ≥5% cellularity;
    - Myelodysplastic syndrome (MDS); or
    - Chronic myelogenous leukemia (CML);
3. Availability of a suitable 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated mPB donor;
4. Subjects must have an mPB donor collection unit **without** using plerixafor (Mozobil™) that is ≥5 × 10^6 CD34+ cells/kg in Phase 1 and ≥3 × 10^6 CD34+ cells/kg in Phase 2;
5. Adequate performance status, defined as Karnofsky score ≥70%;
6. For female subjects of childbearing potential, all of the following criteria must be met:
    - They are not pregnant (i.e., female subjects must have a negative serum pregnancy test at screening);
    - They are not breastfeeding;
    - They do not plan to become pregnant during the study; and
    - They are using an effective method of contraception from screening to the end of the study, unless their sexual partner is surgically sterile. Effective methods of preventing pregnancy are those contraceptive methods with a Pearl index of <1 used consistently and correctly (including, but not limited to, implantable contraceptives, injectable contraceptives, oral contraceptives, and transdermal contraceptives);

Women are not considered to be of childbearing potential if they meet 1 of the following 2 criteria, as documented by the Investigator:

- They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at minimum 1 menstrual cycle prior to signing the ICF; or
- They are post-menopausal, defined as ≥1 year since their last menstrual period for women ≥55 years of age or ≥1 year since their last menstrual period; and

7. For male subjects, agreement to use condoms with spermicide during sexual intercourse from screening to the end of study; and
8. Willingness and ability to sign an IRB/IEC-approved ICF before performance of any study specific procedures or tests and to comply with protocol visits, and study procedures.

4.2 Exclusion Criteria for the Phase 1 Part of the Study and the Phase 2 Part of the Study

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Phase 1 only: Known bone marrow fibrosis; Phase 2 only: Bone marrow fibrosis grade 3 (severe) or greater;
2. Positive serology for human immunodeficiency virus (HIV) or human T-cell lymphotropic virus (HTLV) at any time prior to enrollment;
3. Current uncontrolled bacterial, viral, or fungal infection (progression of clinical symptoms despite therapy);
4. Prior autologous or allogeneic HCT;
5. Active malignancy, other than the one for which the allogeneic mPB transplant is being performed, within 12 months of enrollment, excluding superficial basal cell and carcinoma in situ cervical cancer;
6. Pulmonary disease such as symptomatic chronic obstructive lung disease, symptomatic restrictive lung disease, or FVC and FEV1 <50%, or hemoglobin corrected diffusing capacity of the lung of <50% of predicted value;
7. Renal dysfunction defined as a calculated creatinine clearance <40 mL/min (Cockroft-Gault equation);
8. Hepatic disease defined as total serum bilirubin >2.0 mg/dL (except in the case of Gilbert's syndrome or ongoing hemolytic anemia), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.0 × the upper limit of normal;
9. Cardiac disease defined as symptomatic congestive heart failure (New York Heart Association [NYHA] Class III/IV) or evidence of left ventricular dysfunction (ejection fraction <45%) as measured by gated radionuclide ventriculogram or echocardiogram (ECHO); active angina pectoris or uncontrolled hypertension; or history of myocardial infarction with depressed ejection fraction;
10. Neurologic disease, defined as symptomatic leukoencephalopathy, active central nervous system malignancy, or other neuropsychiatric abnormalities believed to preclude transplantation;

11. Participation in another clinical trial involving an investigational product within 30 days prior to transplant; or
12. Any condition or therapy, which, in the opinion of the Investigator, might pose a risk to the subject or make participation in the study not in the best interest of the subject (e.g., known allergy to human serum albumin [HSA]).

4.3 Withdrawal Criteria

A subject may voluntarily withdraw from the study at any time and without prejudice to his or her future medical care by the Investigator or at the institution. The Investigator, at his or her discretion, may withdraw a subject from participating in the study.

Participation of a subject in this clinical study can be discontinued for any of the following reasons:

1. The subject withdraws consent or requests discontinuation from the study for any reason;
2. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
3. Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
4. Pregnancy;
5. Requirement of prohibited concomitant medication;
6. Subject failure to comply with protocol requirements or study-related procedures, including lost to follow-up;
7. Other safety or ethical reasons; or
8. Discontinuation of the study by the Sponsor or the regulatory authority.

If a subject withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Withdrawal Visit. The date and reason for subject withdrawal from the study must be documented in the electronic Case Report Form (eCRF).

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected on Days +180, +365, and +730 by phone.

If the subject relapses and/or receives non-protocol therapy, the subject will be withdrawn. However, survival will still be collected unless the subject withdraws consent, in which case survival outcomes will be obtained via public record search.

If the Sponsor discontinues the study, the Investigator should notify the IRB/IEC in writing of the study's completion or discontinuation and send a copy of the notification to the Sponsor.

4.4 Screen Failures and Subject Replacement

A screen failure is any subject who signs consent but fails to meet at least one of the eligibility requirements during screening and whose donor cells are not processed as ProTmune or Control. This may occur for many reasons, such as:

- The donor unit does not meet requirements for ProTmune (or Control) processing, such as CD34+ count of the mPB unit is lower than specified in the protocol or cannot be processed prior to the expiration of the unit,
- The donor requires plerixafor for mobilization of peripheral blood.

In all cases, the subject will be considered a screen-failure, will not continue in study and will be replaced. If this occurs after randomization in the Phase 2 portion of the study, a new subject will be randomized.

In the event ProTmune/Control manufacturing produces a ProTmune/Control unit that does not meet release specifications (e.g. for ProTmune, $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable) and the ProTmune/Control unit is not administered, the subject will be withdrawn from the study and a new subject will be added for the Phase 1 portion of the study. If this occurs in the Phase 2 portion of the study, the subject will be replaced and a new subject will be randomized in order to have approximately 80 treated subjects.

5 STUDY TREATMENTS

5.1 Treatment Groups

5.1.1 Study Treatment Groups for the Phase 1 Part of the Study

For the Phase 1 part of the study, 6 to 10 subjects will receive a single unit of ProTmune *ex vivo* programmed mPB cells as the cell source for the HCT procedure at Day 0.

5.1.2 Study Treatment Groups for the Phase 2 Part of the Study

For the Phase 2 part of the study of the study, all eligible subjects will receive either a single unit of ProTmune *ex vivo* programmed mPB cells or a single unit of unmanipulated mPB cells, based upon the subject's randomized treatment allocation.

5.2 Rationale for Dosing

According to the American Society of Blood & Marrow Transplant, the absolute cell threshold to guarantee engraftment is not specifically known. The minimally accepted cells dose is 2×10^6 CD34+ cells/kg. The literature reports successful engraftment can occur at doses as low as 0.75×10^6 CD34+ cells/kg. However, higher doses are associated with faster engraftment, reduced rates of infection, and NRM. Therefore, the Sponsor has selected a target minimum treatment dose of $\geq 2 \times 10^6$ CD34+ cells/kg.

5.3 Randomization and Blinding

5.3.1 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 nonrandomized and open-label.

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

For the Phase 2 part of the study, approximately 90 subjects who have an available 8/8 HLA-A, -B, -C, and -DRB1-matched unrelated peripheral blood cell donor will be randomly assigned in a 1:1 ratio to result in approximately 80 treated subjects (40 subjects per treatment group) to receive either unmanipulated mPB cells (control arm) or ProTmune *ex vivo* programmed mPB cells (experimental arm) and stratified by the subjects' CMV status. Randomization will be performed during the Subject Conditioning Period once the central lab 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 similar. 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% - 5% HSA according to the Batch Production record and site protocol. The

blood transfer bags will be labeled with a Fate-provided product label that will maintain the blind to investigator and subject.

5.4 Breaking the Blind

The Phase 1 part of the study is not blinded, and although the Phase 2 part of the study is blinded, it is likely not necessary to break the blind to the Investigator or subject as knowledge of the single-dose treatment assignment would not impact any aspects of subject management. Should the Investigator require 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 (IRT) database and select the "Unblind a Patient (Emergency Only)" action,
3. Select the subject number from the drop-down menu and enter the 6-digit code,
4. The treatment assignment will be provided by the system and a notification of unblinding will be sent to the study Sponsor and CRO.

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

5.5 Drug Supplies

5.5.1 Formulation and Packaging

ProTmune is a donor-sourced, patient-specific, allogeneic cell therapy product consisting of the cells contained within a human mobilized peripheral blood (mPB) collection that have been programmed through an *ex vivo* programming process using a combination of 2 small molecules, 16,16-dimethyl prostaglandin E2 (FT1050) and dexamethasone (FT4145). The cell populations include hematopoietic cells and other cell types. The final ProTmune product is formulated in Plasmalyte-A (or equivalent) and HSA. Refer to the ProTmune IB for specific details regarding the manufacture and release testing of the investigational product.

Control cells will be comprised of an unmanipulated mPB unit that is visually indistinguishable from ProTmune. 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% - 5% HSA according to the Batch Production record and the site protocol. The blood transfer bags will be labeled with a Fate-provided product label that will maintain the blind to investigator and subject.

Fate has established specific criteria that will be used to assess the suitability of all mPB units collected for *ex vivo* programming or Control.

The CPF at each participating site will be qualified and trained by Fate technical staff to manufacture the investigational product on site via the performance of a single ProTmune qualification run. Additionally, Fate technical representative(s) will be on site for the manufacture

of each CPF's first or second subject treatments and subsequent subject treatments as necessary by the CPF or Fate.

ProTmune *ex vivo* programmed mPB cells (or Control) will be released immediately by the CPF staff after final processing, including filtration, final packaging, and rapid release testing, and labeling. If the product does not meet Fate's pre-defined rapid release acceptance criteria, the CPF will immediately contact Fate Manufacturing and the Investigator to make a prompt decision on use of the investigational product. Exceptional use of investigational product when specification is not met will be documented by the CPF with signature approval documented by the Investigator. Refer to the ProTmune IB for a description of release testing criteria.

The final container of the investigational product will be labeled by the CPF using a Fate-approved label. A photocopy of the investigational product label will be retained by the CPF. If additional labeling is required by the clinical site or CPF, this labeling must be distinct from the Fate product label.

5.5.2 Study Drug Preparation and Dispensing

Mobilized peripheral blood cells will be obtained from a matched-unrelated donor for a given subject. An 8/8 high resolution allelic HLA-match of HLA-A, -B, -C, and -DRB1 with recipient is required. Sites will request that consenting donors be mobilized with filgrastim to achieve a target collected CD34+ dose of $\geq 7 \times 10^6$ CD34+ cells/kg in Phase 1 and $\geq 5 \times 10^6$ CD34+ cells/kg in Phase 2. However, if the donor mPB unit collected for a subject in Phase 1 is not $\geq 5 \times 10^6$ CD34+ cells/kg recipient weight, and in Phase 2 is not $\geq 3 \times 10^6$ CD34+ cells/kg recipient weight, the mPB unit will not be processed for ProTmune manufacturing and the subject will be considered a screen failure.

For subjects enrolled in the Phase 1 part of the study, a reserve dose of 2×10^6 CD34+ cells/kg recipient weight will be maintained during ProTmune manufacturing to serve as a reserve in the event ProTmune manufacturing produces a ProTmune unit that does not meet ProTmune release specifications (e.g., $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable). In this case, the ProTmune unit will be considered "unavailable" and count towards the Phase 1 stopping rules. The reserve unit must be administered; however, the Principal Investigator should follow their Institution's standard operating procedure to determine whether the ProTmune unit should also be given to the recipient based on the risk-benefit assessment of administering the product with regard to the specification not being met. If the ProTmune unit is not administered, the subject will be withdrawn from study and replaced. If the ProTmune unit is administered, the subject will remain in study but will not be considered in the following assessment. If after 6 subjects have been dosed and evaluated for up to 28 days and ≤1 subject has not engrafted by Day +28, then enrollment in the Phase 2 portion of the study may proceed following IDMC review. If the reserve unit is not used on Day 0, it will be cryopreserved at the site and can be used in the event of non-engraftment, or delayed engraftment.

For subjects enrolled in the Phase 2 part of the study in the event ProTmune manufacturing produces a ProTmune unit that does not meet ProTmune release specifications (e.g., $<2 \times 10^6$ CD34+ cells/kg recipient weight, <70% viable), the ProTmune unit will be considered "unavailable" and count towards the Phase 2 stopping rules. The Principal Investigator should follow their Institution's standard operating procedure to determine whether the unit should be given to the recipient based on the risk-benefit assessment of administering the product with regard

to the specification not being met. If the ProTmune or Control unit is not administered, or a subject is withdrawn from participation in the study prior to Day 0, the subject will be replaced and a new subject will be randomized in order to have approximately 60 treated subjects. If the ProTmune or Control unit is administered, the subject will remain in study.

5.5.3 Study Drug Administration

Prior to infusion of ProTmune or Control, the subject will be pre-medicated 30 to 60 minutes before the administration of ProTmune or Control based upon institutional standards (e.g., acetaminophen, diphenhydramine, or H2 blockers).

Upon receipt of the infusion of ProTmune or Control, the chain of custody documentation should be completed to confirm that the specified unit of ProTmune is the correct product for the subject by checking both the product label and the subject's identity, and the product should be inspected for any irregularities such as visible particulates or leakage from the container. Any irregularities noted should be immediately discussed with the CPF and with the Sponsor that issued the product for infusion to determine whether the product is safe for infusion.

ProTmune cells have already been filtered by the CPF and therefore should NOT be filtered during administration. If the investigational product meets release criteria, it should be administered by IV infusion via gravity. The investigational product should not be administered in the same tubing concurrently with products or solutions other than 0.9% Sodium Chloride, Injection (USP). The ProTmune investigational product should be infused at approximately 5 mL to 15 mL per minute, for a total infusion time of approximately 15 to 50 minutes. If the infusion of investigational product is not complete by 30 minutes, the contents of the bag should be mixed by gently massaging the bag once 30 minutes after start of infusion. The infusion rate should be reduced if the fluid load is not tolerated. Diuretics may be used to prevent volume overload. The infusion should be held if the subject develops a clinically significant infusion reaction that requires intervention. The infusion can be restarted if the reaction resolves, based upon the Investigator's medical judgment.

5.5.4 Treatment Compliance

Only qualified members of the study team should administer the study treatment to eligible subjects.

The conditioning regimen, GvHD prophylaxis, GvHD treatments and any other immunosuppression should be documented in the eCRF for each subject. The start and stop dates and start and stop times of the conditioning regimen (including dosages of chemotherapy and TBI), GvHD prophylaxis and GvHD treatments should be documented in the eCRF for each subject.

The CD34+ cell dose administered will be documented in the eCRF.

If the reserve cell dose was used, this must be documented in the eCRF.

The start and stop date and start and stop times of the HCT, including whether the HCT was completed, should be documented in the eCRF for each subject.

5.5.5 Storage and Accountability

The Sponsor will supply all reagents and manufacturing supplies that are necessary for ProTmune preparation to all study sites.

It is the responsibility of the Investigator to supervise accurate monitoring of the receipt, storage, dispensing, and accounting of all supplies. Sites must retain accurate, original site records of study supplies, inventory, and copies of all invoices of study supplies, shipments, and records of investigational product disposition.

Supplies accountability forms will be provided for tracking study supplies such as FT1050 and FT4145.

Each site must keep all unused study supplies until the Site Monitor either arranges return to the Sponsor or gives instructions pertaining to its disposition.

During Phase 1 each site will label, cryopreserve and store the frozen reserve unit for each subject, if unused the reserve dose may be disposed in accordance with institutional practices.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Prohibited Medications and/or Procedures for the Phase 1 Part of the Study and Phase 2 Part of the Study

Subjects may not receive the following concurrent medications or procedures unless otherwise noted:

- Treatment with non-protocol mandated cytotoxic/myelosuppressive or investigational therapy from Day -30 onwards,

  EXCEPTIONS:

  - The use of tyrosine kinase inhibitors (TKIs) against Bcr-Abl & FLT3, for maintenance therapy in eligible subjects are permitted prior to Day -14 and then again after neutrophil engraftment.
  - Following transplant, enrollment into acute GvHD-treatment studies will be allowed for subjects with steroid-refractory GvHD.
- Non-protocol induction radiation therapy,
  - EXCEPTION: palliative radiation therapy is allowed.
- Anti-thymocyte globulin,
- GvHD prophylaxis not specified per the protocol, or
- mPB units from donors that required plerixafor for mobilization.

5.6.2 Documentation of Prior and Concomitant Medication Use for the Phase 1 Part of the Study and Phase 2 Part of the Study

All concomitant medications will be recorded starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.

All medications taken up to 30 days prior to Day 0 and throughout the study will be captured in the eCRFs. Examples include the following:

- Conditioning and immunosuppressive agents and medications,

- Premedications for ProTmune or Control unit infusion,
- Transfusions,
- GvHD prophylaxis and treatment, and
- Medications taken for a reportable adverse event.

Pre-emptive CMV therapy may be provided based upon institutional methodologies, Standard Operating Procedures, and clinical context. An additional blood sample for CMV testing will be collected prior to starting the preemptive therapy and sent for central laboratory testing and prior to starting the preemptive therapy.

Filgrastim can be administered at 5 μg/kg/day beginning on Day +12, if ANC <500 cells/μL, until the ANC is >500 cells/μL. At Investigator discretion, filgrastim can be administered longer to support the white blood cells. Similarly, per Investigator discretion, filgrastim can be started before Day +12 if subsequent doses of methotrexate will not be administered due to severe mucositis, other toxicity, or severe infection.

6 STUDY PROCEDURES

For a study visit schedule in tabular format for the Phase 1 part of the study and Phase 2 part of the study, refer to Appendix A.

6.1 Informed Consent

6.1.1 Informed Consent for the Phase 1 Part of the Study and Phase 2 Part of the Study

Prior to any study-related activities that are not standard of care (e.g., before administration of the study treatment) the subject or subject's legal representative must review, sign, and date an IRB/IEC-approved ICF. The format and content of the subject ICF must be agreed upon by the Investigators, the appropriate IRB/IEC, and the Sponsor.

The original signed ICFs (together with any subsequent IRB/IEC-approved amended versions) must be retained by the Investigator in the subject's study file. A copy of the original signed and dated ICF must be given to the subject.

6.2 Screening Period (Day -53 to Day -11)

6.2.1 Screening Period (Day -53 to Day -11) for the Phase 1 Part of the Study and Phase 2 Part of the Study

For the Phase 1 part of the study and Phase 2 part of the study, all subjects will undergo screening procedures once they have given their written, informed consent to participate in the study. Screening procedures must be completed within 6 weeks prior to initiation of conditioning regimen.

Upon completion of all screening procedures and determination of eligibility, subjects will be scheduled for administration of conditioning regimen and admission for transplant, per institutional procedures. A screening log will be maintained to record the reasons for exclusion from study for all subjects who sign the informed consent and undergo screening.

There may be situations in which a subject is not able to begin the conditioning within 6 weeks of the study screening. In these instances, the subject may need to be re-screened. This will involve repeating select or all screening procedures, as advised by the Medical Monitor.

The following procedures and assessments will be performed during the Screening Period (Day -53 to Day -11) for the Phase 1 part of the study and Phase 2 part of the study (refer to Appendix A for details):

- Informed Consent will be obtained from all subjects prior to the initiation of any study procedures or tests;
- Inclusion and Exclusion Criteria will be reviewed and completed for subject registration;
- Investigator is required to verify that the subject completed HLA typing (HLA typing can be completed prior to the Screening Period);
- ECHO or multiple gated acquisition (MUGA) scan (to assess left ventricular ejection fraction or shortening fraction) will be obtained if not completed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11;

- Demographics and medical history, including prior treatment history information for hematological malignancy, will be reviewed and recorded;
- Qualification of mPB unit by Fate representative;
- Karnofsky Performance Status (Appendix D) will be assessed;
- Bone marrow aspirate will be performed and sent to pathology and cytogenetics;
- All subjects will be tested for baseline CMV antibody titer (immunoglobulin [Ig]G/IgM) and plasma CMV viremia. This baseline testing will be performed by a central laboratory and results will be provided to the clinical site prior to the initiation of randomization;
- A complete physical examination will be performed;
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) will be obtained;
- 12-lead triplicate ECG will be obtained;
- All concomitant medications will be recorded starting at Day -30 (through Day +100);
- Pulmonary function tests will be performed; and
- Peripheral blood sample(s) will be collected for the following:
  - Blood typing and RBC antibody screen,
  - Safety laboratory tests (hematology [CBC and when possible per Institutional practice to include a differential (automated or manual)] and serum chemistry panels),
  - Infectious disease titers,
  - Immune reconstitution assays, and
  - Serum pregnancy testing for females of child-bearing potential.

For the Phase 2 part of the study only: after meeting eligibility and results of the central lab CMV antibody titer are available, subjects will be randomized to either the control arm or ProTmune arm no later than Day -7.

6.3 Subject Conditioning (Day -10 to Day -1)

6.3.1 Subject Conditioning (Day -10 to Day -1) for the Phase 1 Part of the Study and Phase 2 Part of the Study

For the Phase 1 part of the study and Phase 2 part of the study, the following procedures will be performed for subjects who are enrolled, meet the eligibility criteria, and randomized, in preparation for the subject's transplant:

- Medical history will be updated prior to start of conditioning regimen;
- All SAEs will be recorded;

- Starting on Day -10, adverse events will be collected as per CTCAE 4.0, AE of infections will use both the CTCAE and the BMTN CT criteria as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator;
- A complete physical examination will be performed;
- Vital signs will be collected and recorded;
- Concomitant medications will be reviewed and recorded;
- For pre-emptive CMV therapy, 2 peripheral blood samples (1 blood sample to be utilized locally at the site for subject management and 1 blood sample for central laboratory testing) will be collected for CMV assessments of DNA by quantitative PCR prior to starting the preemptive therapy;
- Subject conditioning will include 1 of the following 5 preparative regimens:
  - CyTBI, with ≥12 Gy fractionated TBI;
  - BuCy where Bu = 16 mg/kg PO or 12.8 mg/kg IV infusion (Pharmacokinetic assessment and dose adjustment of Bu can be based on a test dose or the first dose and will be conducted according to institutional practices);
  - FluBu4 with Bu as above;
  - TBI with etoposide; or
  - FluMel 140; and
- GvHD prophylaxis will be initiated (see Section 3.4); and
- Randomization of subject within Interactive Web Response Services (IWRS) will be performed once the central lab screening CMV results are known and must occur no later than Day -7.

6.4 Hospital Admission (Institution Policy)

6.4.1 Hospital Admission (Institution Policy) for the Phase 1 Part of the Study and Phase 2 Part of the Study

The following procedures will be performed at the time of Hospital Admission:

- Subject will be admitted to the hospital unit;
- Medical history will be updated;
- All SAEs will be recorded;
- Adverse events will be collected as per CTCAE 4.0, AE of infections will use both the CTCAE and the BMTN CT criteria as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator;

- A complete physical examination will be performed;
- Vital signs will be collected and recorded;
- All concomitant medications will be reviewed and recorded; and
- Peripheral blood samples will be collected for safety laboratory tests (hematology [CBC and when possible per Institutional practice to include a differential (automated or manual)] and serum chemistry panels).

6.5 Study Treatment Administration: Day of Hematopoietic Stem Cell Transplant (Day 0)

6.5.1 Study Treatment Administration: Day of Hematopoietic Stem Cell Transplant (Day 0) for the Phase 1 Part of the Study and Phase 2 Part of the Study

The following assessments and procedures will be performed on Day 0:

- A subset of follow-up physical examination assessments will be performed prior to HCT;
- Vital signs will be obtained prior to infusion of investigational product, and at 15, 30, 45, and 60 minutes after the start of infusion of investigational product (Note: these are targeted collection times; protocol deviations will only be documented when a collection is missed);
- A 12-lead triplicate ECG will be obtained prior to HCT;
- All concomitant medications will be reviewed and recorded;
- Peripheral blood samples will be collected for safety laboratory tests (hematology [CBC and when possible per Institutional practice to include a differential (automated or manual)] and serum chemistry panels) prior to HCT;
- Investigational product will be prepared;
- Subject will receive transplant;
- Karnofsky Performance Status (Appendix D) will be assessed after HCT; and
- All SAEs will be recorded;
- Adverse events will be collected as per CTCAE 4.0, AE of infections will use both the CTCAE and BMTN CT criteria as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator.

6.6 Post-Transplant Assessment Days

6.6.1 Post-Transplant Assessment Days for the Phase 1 Part of the Study and Phase 2 Part of the Study

Post-transplant visit windows are as follows: ±3 days for Day +7 through Day +100; ±14 days for Day +180; and ±28 days for Days +270, +365, and +730.

The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.

The following procedures will be performed at the time points as described in Appendix A:

- A subset of follow-up physical examination assessments (with the exception of height) will be performed weekly from Day +1 through Day +28;
- Vital signs will be obtained weekly from Day +1 through Day +28;
- All concomitant medications will be recorded (starting at Day -30) through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded;
- Karnofsky Performance Status (Appendix D) will be assessed at all subsequent study visits after HCT up through Day +365 (which should include weekly assessments from Day +1 through Day +28);
- A peripheral blood sample for hematology (CBC and when possible per Institutional practice to include a differential (automated or manual)) will be collected daily from Day +1 through Day +28 (or until the subject achieves neutrophil engraftment, whichever event occurs first; following engraftment, blood for hematology is to be collected per institutional policy);
- A 12-lead triplicate ECG will be obtained at Day +100;
- All SAEs will be recorded;
- Through Day +100, adverse events will be collected as per CTCAE 4.0, AE of infections will use both CTCAE and BMTN CT criteria as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator; and
- From Day +100 through Day +365: Only adverse events associated with GvHD, infections, or secondary engraftment failure (Grades 1 through 5).

6.7 Post-Transplant Weekly Assessments

6.7.1 Post-Transplant Weekly Visits for the Phase 1 Part of the Study and Phase 2 Part of the Study

Post-transplant visit windows are as follows: ±3 days for Day +7 through Day +100; ±14 days for Day +180; and ±28 days for Days +270, +365, and +730.

Standard post-transplant testing will be performed per institutional guidelines and good clinical practice.

The following assessments will be performed at the time points as described in Appendix A:

- A subset of follow-up physical examination assessments (with the exception of height) will be performed weekly from Day +35 through Day +91, then on Days +100, +180, +270, and +365;
- The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting;

- Vital signs will be obtained weekly from Day +35 through Day +91, then on Days +100, +180, +270, and +365;
- All concomitant medications will be recorded (starting at Day -30) through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded;
- Bone marrow aspirate will be sent to pathology and to cytogenetics on Day +21 (only if ANC <500/µL), and as clinically indicated (flow cytometry is required on BM aspirate);
- Karnofsky Performance Status (Appendix D) will be assessed at all subsequent study visits after HCT up through Day +365 (which should include weekly assessments from Day +1 through Day +91, then on Days +100, +180, +270, and +365);
- A peripheral blood sample for hematology (CBC and when possible per Institutional practice to include a differential (automated or manual)) will be collected on Days +35, +42, +49, +56, +63, +70, +77, +84, +100, +180, and +365;
- A peripheral blood sample for serum chemistry panels will be collected weekly from Day +1 through Day +100, then at Day +180;
- Two peripheral blood samples at each testing time point (1 blood sample to be utilized locally, per institutional policy as required, at the site for subject management and 1 blood sample for central laboratory testing) will be collected for viral assessments of DNA by quantitative PCR for EBV, CMV, HHV-6, and BK virus weekly from Day +7 through Day +100, and at Days +180, +270, and +365;
- Peripheral blood samples for immune reconstitution assays will be collected at Days +7, +14, +28, +56, +91, +180, +270, and +365. The peripheral blood sample will be sent to a central laboratory for analysis;
- All SAEs will be recorded;
- Through Day +100, adverse events will be collected as per CTCAE 4.0, AE of infections will use both the CTCAE and BMTN CT criteria as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator;
- From Day +100 through Day +365: Only adverse events associated with GvHD, infections, or secondary engraftment failure (Grades 1 through 5);
- Clinical and laboratory assessments of aGvHD will be performed weekly from Day +1 through Day +100, and on Day +180. Acute GvHD assessments (incidence and maximum severity) of Grades I through IV of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale (Appendix E) will be performed;
- Chronic GvHD assessments (incidence and maximum severity) of mild, moderate, or severe cGvHD as per NIH Consensus Criteria for cGvHD (Appendix F) will be performed on Days +180, +270, and +365;

- Peripheral blood samples will be collected for CMV assessments of DNA by quantitative PCR weekly from Days +7 through Day +100, and at Days +180, +270, and +365. Assessment of infection will be performed based on the NCI CTCAE and the BMT CTN Definitions;
- Neutrophil and T-cell chimerism will be assessed on the third consecutive day of ANC >500 cells/μL (neutrophil only) and on Days +28, +100, +180, and +365 (both neutrophil and T-cell):
  - When feasible, fractional chimerism (total, myeloid, lymphoid) will be performed from peripheral blood samples;
  - If there is no evidence for donor engraftment by Day +21, then the subject will undergo BM and peripheral blood chimerism studies; and
  - If donor engraftment is not present by Day +28 BM examination, and the subject's disease is not present, the subject should be considered a primary graft failure (in the absence of relapsed disease);
- Serum IgG, IgM, and IgA will be collected by a peripheral blood sample at Days +100, +180, and +365; and
- Peripheral blood samples for GvHD exploratory biomarkers will be obtained once weekly from Days +7 through Day +42, then on Day +100. Samples will be banked.

6.8 Unscheduled visits

An unscheduled visit is a visit that occurs in addition to the predefined protocol specific visit calendar. If an unscheduled visit occurs for a given subject, the visit must be documented on the Unscheduled Visit CRF.

6.9 Early Withdrawal Visit and Study Withdrawal Procedures

If a subject withdraws or is withdrawn from the study prior to Day 0, the subject's mPB will not be processed to a unit of ProTmune or Control cells, and the subject will not be considered evaluable for any study-related endpoint analyses. If this occurs in the Phase 2 portion of the study and the subject was already randomized, the subject will be replaced and a new subject will be randomized in order to have approximately 80 treated subjects.

If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected on Days +180, +365, and +730 by phone.

If the subject relapses and/or receives a protocol-prohibited therapy, the subject will be withdrawn. However, survival will still be collected unless the subject withdraws consent, in which case survival outcomes will be assessed via public record search.

A subject will have completed the study when he or she completes the Day +365 study visit. For subjects who are withdrawn from the study prior to completion, all assessments as described in Appendix A for the Early Withdrawal Visit should be completed. Procedures include the following:

- Applicable concomitant medications will be reviewed and recorded as per Section 8.12;

- A subset of follow-up physical examination assessments (with the exception of height) will be performed;
- Vital signs will be obtained;
- Karnofsky Performance Status (Appendix D) will be assessed;
- Peripheral blood samples will be collected for the following:
  - Safety laboratory tests (hematology [CBC and when possible per Institutional practice to include a differential (automated or manual)] and serum chemistry panels),
  - Viral assessments, and
  - CMV assessments of DNA by quantitative PCR. Assessment of infection will be performed based on the NCI CTCAE and the BMT CTN Definitions; and
- Acute GvHD or cGvHD assessments (Appendix E and Appendix F) must be performed, as applicable.

If a subject withdraws or is withdrawn from the study at any time following the study treatment administration, the Investigator should make every effort to follow the subject and collect the information as specified for the Early Withdrawal Visit in Appendix A. If a subject is withdrawn for safety reasons, additional safety assessments and follow-up could be required. Refer to Section 8.1 and Section 8.3 for a description of the follow-up of adverse events and SAEs.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint for both the **Phase 1 and Phase 2** parts of the study is the following:

- Cumulative incidence of CIBMTR Grades II-IV aGvHD through Visit Day +100 based on investigator results. Death and relapse without CIBMTR Grades 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 (Appendix E).

The key secondary efficacy endpoint for both the **Phase 1 and Phase 2** parts of the study is the following:

- Proportion of subjects alive without relapse and without moderate or severe cGvHD per NIH Consensus Criteria at Visit Day +365.

All summaries for acute and chronic GvHD will be based on the investigator assessment unless noted otherwise.

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

- Cumulative incidence through Visit Day +100 and through Visit Day +180 of:
    - CIBMTR Grades III-IV aGvHD
    - CIBMTR Grades I-II aGvHD;
    - CIBMTR Grades I-IV aGvHD;
    - Maximum CIBMTR Grades II-IV aGvHD;
    - Maximum CIBMTR Grades III-IV aGvHD;
    - Maximum CIBMTR Grades II-IV aGvHD based on EAC adjudicated results;
    - Maximum CIBMTR Grades III-IV aGvHD based on EAC adjudicated results;
- Duration of the Maximum CIBMTR Grade aGvHD through Visit Day +100;
- Duration of CIBMTR Grades II-IV aGvHD through Visit Day +100;
- Duration of CIBMTR Grades III-IV aGvHD through Visit Day +100;
- One-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);
- Time to individual event components for GRFS:
    - Time to CIBMTR Grades III-IV aGvHD;
    - Time to first use of cGvHD-requiring systemic immunosuppressive therapy;
    - Time to relapse;
    - Time to death;

- One-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 Non-relapse mortality (NRM). All deaths in the absence of relapse of the primary malignancy will be considered NRM, where relapse will be considered a competing risk;
- 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;
- 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 anti-viral therapy for CMV;
- Time to first treatment for CMV reactivation;
- Relapse-free survival (RFS);
- One-year survival;
- Two-year survival.

Additional exploratory analyses may be performed as necessary.

7.1 Acute Graft-versus-Host Disease Assessment

Acute GvHD assessments of the overall Grades I through IV aGvHD of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale must be performed weekly from Day +1 through Day +100 and on Day +180. Assessments must be made consistently for each subject by the Investigator. For a detailed description of the CIBMTR aGvHD Grading Scale, refer to Appendix E.

The data for the GvHD target organs should be recorded on the GvHD eCRF, and must include the percentage of skin rash involvement, volume of stool output, and level of weekly maximum reported bilirubin level. Differential diagnoses should be recorded (e.g., investigational product reaction, conditioning regimen, total parenteral nutrition, infection, or veno-occlusive disease) each week for the specified organ involved.

7.2 Chronic Graft-versus-Host Disease Assessment

Chronic GvHD assessments of mild, moderate, or severe cGvHD as per NIH Consensus Criteria for cGvHD must be performed on Days +180, +270, and +365. Assessments must be made consistently for each subject by the Investigator. For a detailed description of the NIH Consensus Criteria for cGvHD, refer to Appendix F.

The data for the GvHD target organs should be recorded on the GvHD eCRF.

7.3 Viral Monitoring

Two peripheral blood samples at each testing time point (1 blood sample to be utilized locally at the site for subject management and 1 blood sample for central laboratory testing) will be collected for viral assessments of DNA by quantitative PCR for EBV, CMV, HHV-6, and BK virus weekly from Days +7 through Day +100 and at Days +180, +270, and +365.

7.4 Infectious Disease Titers

Infectious diseases screen during the Screening Period by peripheral blood sample will include titers for EBV, CMV, hepatitis panel (hepatitis A antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody), BK virus, herpes simplex virus (HSV), HHV-6, HIV, HTLV types I/II antibody, syphilis, and varicella zoster virus (VZV). Additionally, testing for CMV viremia via PCR will be performed. Titer and CMV viremia testing will be done by central laboratory testing during the Screening Period.

7.5 Karnofsky Performance Status

The Karnofsky Performance Status (Appendix D) will be assessed as part of the study eligibility assessment, and will be assessed during the Screening Period, at Day 0 after HCT, all subsequent study visits up through Day +365 (which should include, but are not limited to, weekly from Day +1 through Day +91, then on Days +100, +180, +270, and +365), and the Early Withdrawal Visit, if applicable.

7.6 Relapse of Malignancy

The definition of relapse is based on the disease under study and should be sourced from the National Comprehensive Cancer Network guidelines. For AML and ALL, relapse following CR is defined as reappearance of leukemic blasts in the peripheral blood or the finding of >5% blasts in the BM, not attributable to another cause or extramedullary relapse.

Evidence of minimal residual disease will not be sufficient to meet the definition of disease recurrence in the context of this study.

7.7 Immune Reconstitution

Peripheral blood samples for immune reconstitution assays will be collected at baseline (during the Screening Period), and at Days +7, +14, +28, +56, +91, +180, +270, and +365. The peripheral blood sample will be sent to a central laboratory for analysis.

7.8 Serum Immunoglobulin

Serum IgG, IgM, and IgA will be collected by a peripheral blood sample at Days +100, +180, and +365.

7.9 Bone Marrow Aspirate

Bone marrow aspirate will be sent to pathology and to cytogenetics during the Screening Period, on Day +21 in those subjects whose ANC is <500/µL, and as clinically indicated. Flow cytometry is required on BM aspirate.

7.10 GvHD Biomarkers

Peripheral blood samples for GvHD exploratory biomarkers will be obtained once weekly from Days +7 through Day +42, then on Day +100. Samples will be banked.

7.11 Radiologic Tumor Staging

If appropriate, radiologic tumor staging will be completed by the Investigator during the Screening Period.

8 SAFETY ASSESSMENTS

The safety endpoints for both the Phase 1 and Phase 2 parts of the study include the assessment of adverse events, vital signs, physical examination findings, engraftment, graft failure, chimerism, clinical laboratory assessments, and electrocardiographic data through a 12-lead ECG.

8.1 Adverse Events

Any adverse event experienced between signing the ICF and prior to administration of the study conditioning regimen will be recorded in the medical history.

Adverse events will be collected during Phase 1 and 2, as follows:

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

The details of each event will be recorded in the appropriate eCRF.

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinically significant laboratory test results, will be monitored and documented. Subjects should be instructed to report any adverse event that they experience to the Investigator. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

The following information about each adverse event should be recorded in the source documentation and in the eCRF:

- Onset and cessation dates of adverse events or SAEs,
- Severity,
- SAE (yes or no),
- Relationship to the cell product, (ProTmune *ex vivo* programmed mPB cells or Control mPB cells). For SAEs only, relationship to conditioning regimen medications, and GvHD prophylaxis medications (tacrolimus and methotrexate) is also required.
- Action taken in response to the event.

The Investigator will make assessments of adverse event or SAE severity and of the possible relationship to study medication(s).

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening or randomization should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at screening or randomization and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

If a clinically significant abnormal laboratory finding meets the definition of an adverse event, a diagnosis or any clinical signs and symptoms rather than the abnormal laboratory finding should be recorded if possible.

All adverse events must be followed until resolution, until the condition stabilizes, until the event is otherwise explained or is judged by the Investigator to be no longer clinically significant, or until the subject is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations necessary to elucidate as completely as practical the nature and/or causality of the adverse event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations of an adverse event. If a subject dies during participation in the study or during a recognized follow-up period, then Sponsor should be provided with a copy of any post-mortem findings, including histopathology, as required.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to the study medication(s) should be considered an adverse drug reaction. “Responses” to the infused cells means that a causal relationship between the study medication(s) and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

8.1.3 An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.
Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to the infused cells using the categories of yes or no.

The severity of all adverse events should be graded according to the NCI CTCAE version 4.0. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse events not listed in the NCI CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities;
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable;
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms that cause considerable interference with the subject's daily activities, unacceptable;
- Life-threatening (CTCAE Grade 4): Life threatening or disabling adverse event; and
- Death (CTCAE Grade 5): Death-related adverse event.

AEs of infections will use both the CTCAE and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN, Appendix G) criteria.

Causality Assessment:

For this study, the Investigator should evaluate the relatedness of all adverse events to investigational study medications (ProTmune *ex vivo* programmed mPB cells or Control mPB cells). Relatedness to non-investigational study medications (conditioning medications and GvHD prophylaxis medications) is only required for SAEs. Safety monitoring for adverse events for this study begins as of the start of the conditioning regimen and will be reported as per the requirements outlined in Section 8.1.

The relationship of an adverse event to the study medication(s) is (are) to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of the study medication(s) and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of the study medication(s) and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study medication(s). This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from the study medication(s) administration:

  The event should occur during or after the study medication(s) is administered. The length of time from the administration of the study medication(s) to the event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases:

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug:

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for study medication(s) administration:

  Clinical and/or nonclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses:

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

NOTE: Any hospital admission with at least 1 overnight stay will be considered an in-patient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered in-patient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the start of the conditioning regimen (Day -10) until Day +365, and only SAEs related to infused cells (ProTmune *ex vivo* programmed mPB cells or Control mPB cells) from Day +366 through Day +730, must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAE forms must list the subject identification number and a comprehensive narrative that includes a chronological description and assessment of the event.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Facsimile: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

Expedited reporting will only be conducted for SUSARs related to ProTmune.

The current ProTmune IB will be used to assess for expectedness for the purposes of serious and unexpected suspected adverse reaction (SUSAR) reporting. The ProTmune IB will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.6 Engraftment, Graft Failure, and Chimerism

8.6.1 Neutrophil and platelet engraftment per CIBMTR

ANC and platelets from the clinical laboratory assessments will be used to evaluate engraftment.

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

8.6.2 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 graft failure occurring after initial engraftment (ANC ≥500 cells/µL), including the presence of >95% recipient CD3+ or myeloid cells, re-infusion of donor cells because of permanent loss of neutrophils (<0.5 × 10^9/L) and/or platelets <30 × 10^9/L, or >50% recipient CD3+ cells and treatment with donor lymphocyte infusion.

8.6.3 Chimerism

Neutrophil and T-cell chimerism will be assessed on the third consecutive day of ANC >500 cells/µL (neutrophil only) and on Days +28, +100, +180, and +365 (both neutrophil and T-cell). Chimerism will be measured by PCR amplification of recipient-and-donor-derived cells; which may include single nucleotide polymorphism and/or DNA microsatellites (short tandem repeats) analyses consistent with Institutional Standards. Chimerism will be measured by restriction fragment length polymorphism or microsatellite. Chimerism studies will be performed by short tandem repeats and/or flow cytometry according to local laboratory practices. When feasible, fractional chimerism (total, myeloid, lymphoid) will be performed from peripheral blood samples. If there is no evidence for donor engraftment by Day +21, then the subject will undergo BM and peripheral blood chimerism studies. If donor engraftment is not present by Day +28 BM examination, and the subject's disease is not present, the subject should be considered a primary graft failure (in the absence of relapsed disease).

8.7 Clinical Laboratory Evaluations

Safety laboratory tests will include hematology and serum chemistry panels. Peripheral blood samples will be collected and forwarded to either local laboratories or central laboratories for testing as described in Appendix A.

The following clinical laboratory tests will be performed (the analyses of which are the minimum):

- Hematology (CBC and when possible per Institutional practice to include a differential (automated or manual)): RBCs, hemoglobin, hematocrit, platelets, total white blood cell, neutrophils, bands, lymphocytes, eosinophils, and monocytes. Manual differential will include blasts if present and ANC calculation; and
- Serum chemistry: includes creatinine, ALT, AST, alkaline phosphatase, blood urea nitrogen, lactate dehydrogenase, sodium, potassium, calcium, phosphorus, chloride, CO_2, albumin, bilirubin (total and direct), and magnesium.

Clinical laboratory test results should be within normal limits or for certain clinical laboratory tests, within an "acceptable" range based on disease characteristics.

The results will be forwarded to the Investigator for review. Any abnormalities deemed clinically significant by the Investigator will be reported as adverse events and recorded in the subject's eCRF if they meet adverse event reporting criteria (refer to Section 8.1). Any clinically significant abnormal laboratory values that persist should be followed by the Investigator. Such events should be followed until they have resolved (within normal limits or return to baseline) or the Investigator assesses them to be chronic or stable.

The Investigator should file all copies of the laboratory reports in the subject's study chart.

Note: Clinical laboratory testing may be performed at any time during the study if clinically indicated.

8.8 Serum Pregnancy Tests

Serum pregnancy tests will be performed during the Screening Period from all female subjects of child bearing potential. Pregnant females will be excluded from the study.

8.9 Vital Signs

Vital signs will be recorded at study visits as described in Appendix A and will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature.

8.10 Electrocardiograms

Standard supine triplicate 12-lead ECG (sequential, within 15 minutes total) will be performed by qualified technicians during the Screening Period, at Day 0 prior to HCT, and at Day +100. Electrocardiograms will be reviewed at the site for treatment of any urgent issues. The clinical significance of any ECG change must be assessed by the Investigator in the context of the subject's medical history, physical examination, and concomitant medications. The Investigator or delegated physician will review, sign, and date all ECGs. For the purposes of QTc interval calculation, QTcF is the preferred calculation.

8.11 Physical Examinations

During the Screening Period, and at Subject Conditioning and Hospital Admission, a complete physical examination will be performed. The complete examination should include height, body weight, skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, and appearance.

A subset of follow-up physical examination assessments (with the exception of height) will be performed on the subject at Day 0 prior to HCT and weekly from Day +1 through Day +91, then on Days +100, +180, +270, and +365.

All physical examination findings must be documented in the subject's study chart and also recorded in the appropriate eCRF.

8.12 Donor History

During the Screening Period, the following should be documented in the eCRF, including (but not limited to) donor age, sex, race or ethnicity, parity, CMV status, and blood type.

8.13 Medical History and Concomitant Medications

Significant medical history will be collected from the subject at the Screening Visit and should include (but not be limited to) demographic information, current and past medical conditions, co-morbid diseases, prior treatment history information for hematological malignancy, and medications up to 30 days prior to the Screening Visit. The medical history must be documented in the subject's study chart (the on-site source document) prior to study treatment administration and also recorded on the appropriate eCRF.

Updated medical history information is to be collected at Subject Conditioning and the Hospital Admission Visit (to include any event that has occurred since the Screening Visit that could be considered clinically significant). Furthermore, any clinically significant that occurs after the ICF

is signed but prior to administration of the study treatment is to be recorded as an update to the Medical History.

All concomitant medication usage will be collected and recorded on the appropriate eCRF starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.

8.14 Cardiac Function

During the Screening Period, either an ECHO or MUGA scan will be obtained to assess for left ventricular ejection fraction or shortening fraction for eligibility criteria assessment by the Investigator, if not performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.

8.15 Pulmonary Function Tests

Pulmonary function tests will be assessed during the Screening Period, if not performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population for Phase 1 will include all subjects who received ProTmune.

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.

9.1.2 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population will include all subjects in the ITT Population who receive IP (defined as either ProTmune or Control mBP units). Subjects who are randomized and 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 are not part of mITT. Despite the exclusion of these subjects, the ITT principle would be considered preserved since 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.

9.1.3 Per-Protocol Population

The Per-Protocol (PP) Population will include all Phase 2 subjects in the mITT Population who do not have any major protocol violations deemed to impact the results as defined in the statistical analysis plan prior to locking the database.

9.1.4 Safety Population

The Safety Population will include all subjects who receive 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 randomization. For example, if a single dose of ProTmune is received by a subject randomized to the control arm, the subject will be analyzed in the ProTmune arm.

9.2 Statistical Methods

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report.

All reporting and analyses will be conducted at the end of the study, which is defined as the date when the last subject last visit occurs or the date at which the last data point is collected for the completion of 1-year on study (Day +365), whichever occurs later. Analysis of the 2-year survival follow-up will be conducted upon completion of the Day +730 follow-up. The initial clinical study report will be completed following final analysis of the 1-year data and will be appended to include the 2-year survival data upon completion.

Summary statistics will be presented by treatment group. Unless otherwise stated, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics. Categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as descriptive statistics.

Statistical analyses will be performed using SAS® (Version 9.3, or higher).

9.2.1 Analysis of Efficacy

Based on the timing from randomization to infusion of IP (defined as ProTmune or Control mPB units), 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). As such, the ITT population will only be used to summarize subject disposition.

Efficacy analyses will be performed based on the mITT Population. Additional sensitivity analyses will be performed based on the PP Population for the primary and key secondary efficacy endpoint for Phase 2. Efficacy data from the Phase 1 part of the study and Phase 2 part of the study will be summarized separately. Summary tables will present results for each phase by treatment group.

The primary efficacy endpoint is the cumulative incidence of CIBMTR Grades II through IV aGvHD through Visit Day +100 based on investigator results; death and relapse without Grades 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.

Phase 1: Cumulative incidence curves will be constructed for the primary efficacy endpoint along with curves for death and relapse without CIBMTR Grades II-IV aGvHD as competing risks. The first day of Grades II-IV aGvHD will be used to calculate the cumulative incidence curve. The estimate of the cumulative incidence rate of Grades II-IV aGvHD by Day +100 and the associated 2-sided 95% confidence intervals will be estimated based on the cumulative incidence function with variance estimated using the Delta method.

Phase 2: The cumulative incidence curves and estimates of the cumulative incidence rate along with the associated 2-sided 95% confidence intervals will be presented in the same manner described in Phase 1. The cumulative incidence functions for CIBMTR Grades II-IV aGvHD by 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 sub-distribution hazard model (Fine and Gray 1999) with treatment and age as a covariate. Other covariates may be considered for model inclusion.

The 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 using observed cases. Subjects meeting these criteria will be considered a responder.

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. Summaries will also include the number of subjects that are considered non-responders.

Phase 2: The same summaries described in Phase 1 will be presented by treatment group. Statistical comparisons between treatment groups will be performed using a logistic regression with treatment and age as a covariate. Other covariates may be considered for model inclusion.

Sensitivity analyses of the primary efficacy and key secondary efficacy endpoints will be repeated using the PP population. For the responder/non-responder endpoint, analyses using non-responder imputation cases will also be performed; other methods may be explored to account for missing data such as multiple imputation methods.

All exploratory efficacy endpoints will be summarized descriptively by phase and treatment groups using the mITT Population, unless otherwise noted. For Phase 2, nominal 2-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.

Exploratory time-to-event endpoints in the presence of competing risks (e.g., aGvHD and cGvHD) will be performed using the cumulative incidence function in the same manner as the primary efficacy endpoint.

Exploratory time-to-event endpoints will be summarized using Kaplan-Meier estimates and a two-sided log-rank test to compare treatment groups. In addition, the hazard ratio along with the 95% confidence intervals will be calculated using a Cox proportional hazards model with treatment and age as covariates. Other covariates may be considered for model inclusion.

9.2.2 Analysis of Safety

The safety profile will be based on adverse events, vital signs, physical examinations, engraftment, graft failure, chimerism, clinical laboratory assessments, and ECGs. All safety analysis will be based on the Safety Population.

Safety analyses in general will be descriptive and will be presented by phase and treatment group in tabular format. 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, Q1, Q3, minimum, and maximum).

A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the administration of investigational product. AEs that are designated as GvHD-related events per the investigator as indicated on the eCRF are considered signs and symptoms of GvHD. GvHD-specific details are also collected on separate eCRFs to assess efficacy. As such, non-serious GvHD-related adverse events will not be included in the AE analyses and will be summarized separately; GvHD-related AEs that meet the criteria of SAEs will be included in the summaries of AEs and SAEs. The number and percentage of subjects with TEAEs will be tabulated by System Organ Class and Preferred Term for each treatment group and by severity and relationship to treatment. Adverse events leading to discontinuation of the study and serious adverse events will be summarized by treatment group. By-subject listings will also be provided for any deaths, SAEs, and adverse events leading to discontinuation of the study.

Non-CMV infections are defined as bacterial, fungal, viral (excluding CMV), and parasitic infections. The number of subjects with non-CMV infections will be summarized using frequency counts and percentages overall and by System Organ Class and Preferred Term.

Febrile neutropenia, as collected on the eCRF and defined by the Infectious Disease Society of America Fever and Neutropenia Guidelines Panel (Freifeld et al. 2011):

- Fever is defined as a single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-hour period
- Neutropenia is defined as an ANC of $<0.5 \times 10^9$/L

The number of subjects with febrile neutropenia will be summarized using frequency counts and percentages.

The following safety endpoints will be summarized using descriptive statistics:

- proportion of subjects with neutrophil engraftment per CIBMTR through Visit Day +28
- proportion of subjects with platelet engraftment per CIBMTR through Visit Day +100 per CIBMTR will be summarized using
- time to neutrophil engraftment
- time to platelet engraftment
- proportion of subjects with primary graft failure
- proportion of subjects with secondary graft failure

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline over time. Abnormal physical examination findings will be presented in a by-subject data listing.

Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline. Details of any abnormalities will be included in subject listings.

9.2.3 Interim Analysis

During Phase 1, the 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. There are no formal interim analyses for efficacy planned.

9.2.4 Hypotheses

The following hypothesis statements are given to provide some context to the comparisons being performed.

Primary efficacy endpoint

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.

Key secondary efficacy endpoint

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.

Hypothesis testing will be described in the statistical analysis plan.

9.2.5 Sample Size Determination

The background cumulative incidence rate of 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 be 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 Grades II-IV aGvHD through Visit Day +100 from 55% to 25% (i.e., a hazard ratio of 0.3464) in the Control versus ProTmune treatment arms 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 10%, approximately 90 subjects will be randomized to include approximately 80 treated subjects in the mITT Population. The sample size was calculated using PASS Sample Size Software (PASS 16 Power Analysis and Sample Size Software, 2018).

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of investigational product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, ProTmune IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Conference on Harmonisation (ICH) require that approval be obtained from an IRB/IEC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/IEC.

No investigational product will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

It is the responsibility of the Sponsor or their designee (i.e., Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.4 Subject Card

On enrollment in the study, the subject will receive a subject card to be carried at all times. The subject card will state that the subject is participating in a clinical research study, type of treatment, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, applicable regulatory requirements, the Declaration of Helsinki (for United States sites), and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, ProTmune IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e., initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Address List

12.2.1 Sponsor

Fate Therapeutics, Inc.
3535 General Atomics Court, Suite 200
San Diego, CA 92121
USA
Telephone: 858-875-1800
Facsimile: 858-875-1843

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
USA
Telephone: +1-800-730-5779
Facsimile: +1-513-579-0444

12.2.3 Drug Safety

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
USA
Telephone: +1-800-730-5779, ext. 2999
Facsimile: +1-866-336-5320

12.2.4 Biological Specimens

Refer to the current PT-001 Laboratory Manual for a complete list of testing facilities.

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES FOR THE PHASE 1 AND PHASE 2 PARTS OF THE STUDY

Study Period	SCRN[1]	Subject COND	Hospital ADM	Day of HCT	Days Post-Transplant																		Early Withdrawal Visit[3]
Study Day	**-53 to -11**	**-10 to -1**	**INST Policy**	**0**	**+1**	**+7**	**+14**	**+21**	**+28**	**+35**	**+42**	**+49**	**+56**	**+63**	**+70**	**+77**	**+84**	**+91**	**+100**	**+180**	**+270**	**+365**	**+730[2]**	
Visit window (days)	-	-	-	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±14	±28	±28	±28	-
Study Procedures																								
Informed consent	X																							
Inclusion and exclusion	X																							
HLA typing[4]	X																							
ECHO or MUGA scan[5]	X																							
Demographics	X																							
Medical history	X	X	X																					
Qualification of mPB[6]	X																							
Karnofsky Performance Status[7]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Bone marrow aspirate[8]	X							X																
Infectious disease titers and plasma CMV PCR viremia[9,10]	X																							
Physical examination[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECG[13]	X			X															X					
Concomitant medications[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse events[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary function tests	X																							
Blood typing and RBC antibody screen	X																							
Hematology[16]	X		X	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X		X

APPENDIX A: SCHEDULE OF PROCEDURES FOR THE PHASE 1 AND PHASE 2 PARTS OF THE STUDY (CONTINUED)

Study Period	SCRN[1]	Subject COND	Hospital ADM	Day of HCT	Days Post-Transplant																		Early Withdrawal Visit[3]
Study Day	**-53 to -11**	**-10 to -1**	**INST Policy**	**0**	**+1**	**+7**	**+14**	**+21**	**+28**	**+35**	**+42**	**+49**	**+56**	**+63**	**+70**	**+77**	**+84**	**+91**	**+100**	**+180**	**+270**	**+365**	**+730[2]**	
Visit window (days)	-	-	-	-	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±14	±28	±28	±28	-
Study Procedures																								
Serum chemistry[17]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Immune reconstitution assays[18]	X					X	X		X				X					X		X	X	X		
Serum pregnancy test[19]	X																							
Randomization (Phase 2 only)[20]		X																						
CMV assessment for pre-emptive therapy[21]		X				X (ad hoc if subject is seen at an unscheduled visit)																		
Conditioning regimen[22]		X																						
GvHD prophylaxis[23]		X																						
Admission to hospital unit			X																					
Prepare investigational product				X																				
Transplantation				X																				
Viral assessment[24]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
aGvHD assessment[25]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
cGvHD assessment[26]																				X	X	X		X
Chimerism testing[27]									X										X	X		X		
Serum immunoglobulin[28]																			X	X		X		
GvHD biomarkers[29]						X	X	X	X	X	X								X					
Survival																							X	

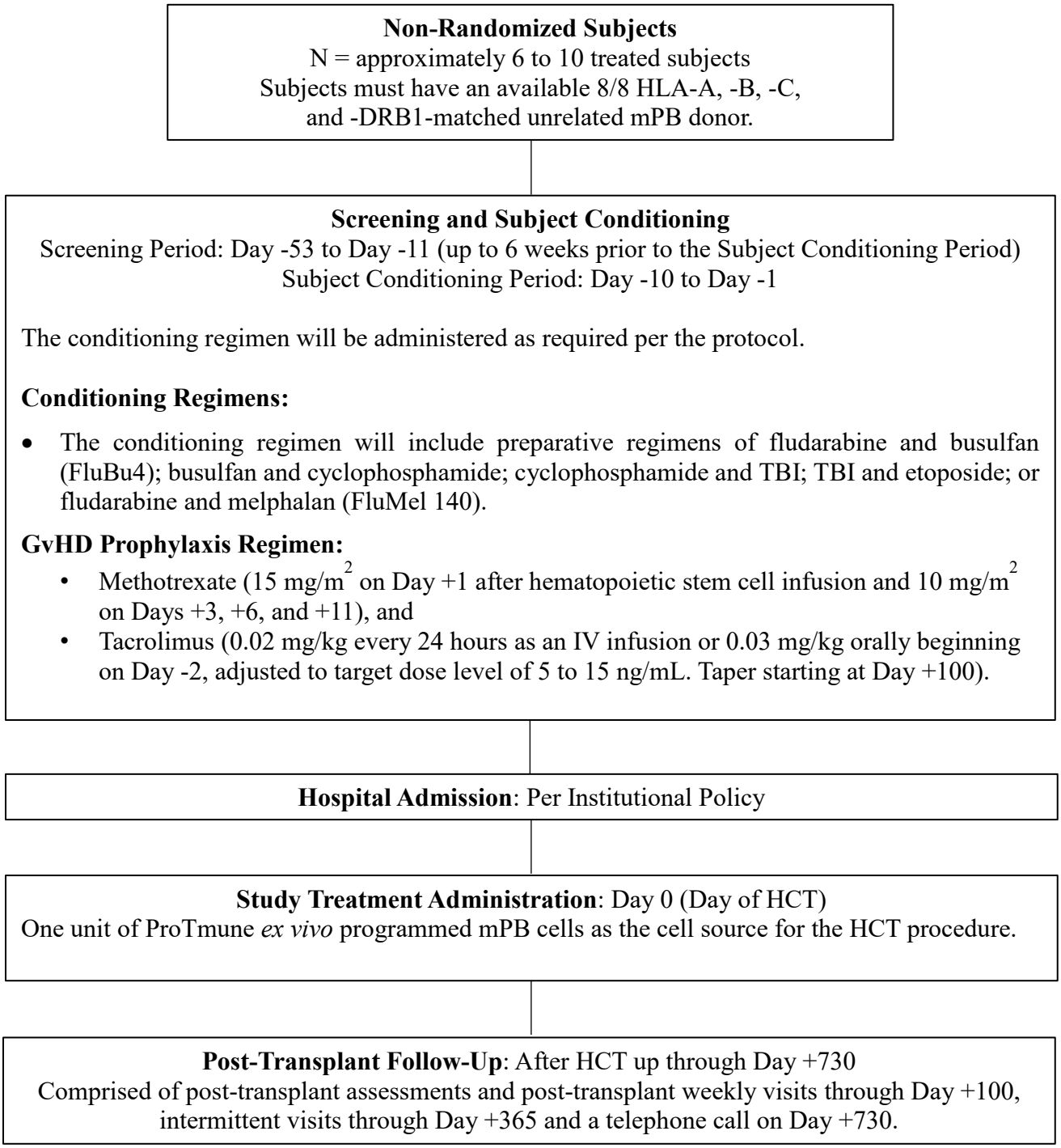
1. The study will consist of a Screening Period of up to 6 weeks prior to administration of conditioning regimen (subject conditioning will occur between Day -10 to Day -1). General donor history will be collected in the eCRF, including (but not limited to) donor age, sex, race or ethnicity, CMV status, and blood type. Upon completion of all screening procedures and determination of eligibility, subjects will be scheduled for administration of conditioning regimen and admission for transplant, per institutional procedures. Screening procedures must be completed within 6 weeks prior to initiation of conditioning regimen. There may be situations in which a subject is not able to begin the conditioning within 6 weeks of the study screening. In these instances, the subject may need to be re-screened. This will involve repeating select or all screening procedures, as advised by the Medical Monitor.
2. The Day +730 visit will occur by conducting a telephone contact report for capture of survival status and adverse event reporting.
3. If a subject withdraws or is withdrawn from the study prior to Day 0, the subject's mPB will not be processed to a ProTmune unit, they will not be considered evaluable for any study-related endpoint analyses, and the subject will be replaced. If a subject withdraws from the study after transplantation, information regarding secondary graft failure, disease relapse, serious adverse events involving GvHD and infections, and survival outcomes will be collected on Days +180, +365, and +730 by phone.
4. Investigator is required to verify that the subject completed HLA typing. HLA typing can be completed prior to the Screening Period.
5. During the Screening Period, either an ECHO or MUGA scan will be obtained to assess for LVEF or shortening fraction for eligibility criteria assessment by the Investigator. The results of an ECHO/MUGA performed prior to consent may be used for subject qualification as long as performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.
6. Qualification of mPB unit must be conducted by a Fate representative.
7. Karnofsky Performance Status will be assessed during the Screening Period, at Day 0 after HCT, and all subsequent study visits up through Day +365 (which should include, but are not limited to, weekly from Day +1 through Day +91, then on Days +100, +180, +270, and +365). If applicable, Karnofsky Performance Status will be assessed at the Early Withdrawal Visit. Refer to Appendix D for details and the grading scale.
8. Bone marrow aspirate will be sent to pathology and to cytogenetics during the Screening Period, on Day +21 in those subjects whose ANC is <500/µL, and as clinically indicated. Flow cytometry is required on BM aspirate. The results of the bone marrow aspirate performed prior to consent may be used for subject qualification as long as performed within 6 weeks prior to the Subject Conditioning Period, from Day -53 to Day -11.
9. All subjects will be tested for baseline CMV antibody titer (IgG/IgM) and plasma CMV viremia. This baseline testing will be performed by a central laboratory and results will be provided to the clinical site prior to the initiation of randomization.
10. Infectious diseases screen during the Screening Period by peripheral blood sample will include titers for EBV, CMV, hepatitis panel (hepatitis A antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody), BK virus, HSV, HHV-6, HIV, HTLV types I/II antibody, syphilis, and VZV. Titer testing will be done by central laboratory testing during the Screening Period.
11. During the Screening Period, Subject Conditioning Period, and Hospital Admission, a complete physical examination will be performed. The complete examination should include height, body weight, skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities and appearance. A subset of follow-up physical examination assessments (with the exception of height) will be performed on the subject at Day 0 prior to HCT and weekly from Day +1 through Day +91, then on Days +100, +180, +270, and +365. If applicable, a follow-up physical examination assessment will be performed at the Early Withdrawal Visit. All physical examination findings must be documented in the subject's study chart and also recorded in the appropriate eCRF.
12. Vital Signs will be obtained at the Screening Period, Subject Conditioning Period, Hospital Admission, and at the following intervals on Day 0: prior to infusion of the cells, and at 15, 30, 45, and 60 minutes after the start of infusion of the cells (Note: these are targeted collection times; protocol deviations will only be documented when a collection is missed). Vital Signs will be obtained weekly from Day +1 through Day +91, then on Days +100, +180, +270, and +365. If applicable, vital signs will be obtained at the Early Withdrawal Visit. Vital signs will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and temperature.
13. A 12-lead triplicate ECG (sequential, within 15 minutes total) will be obtained during the Screening Period, at Day 0 (prior to HCT), and at Day +100.
14. All concomitant medications will be recorded starting at Day -30 through Day +100. From Day +100 through Day +730, only concomitant medications given as TKI maintenance, or that were ongoing at the time of, and for the treatment of, an AE of GvHD, infection or secondary engraftment failure or any SAE, will be recorded.
15. All SAEs will be recorded from Day -10 through Day +365, and only SAEs related to the infused cells (ProTmune *ex vivo* programmed mPB cells or Control mPB cells) from Day +366 through Day +730. From Day -10 through Day +100: adverse events will be collected as per CTCAE 4.0 (as well as BMT CTN for infections) as follows: Adverse events associated with infusion reactions, GvHD, infections, or engraftment failure (Grades 1 through 5). All other adverse events (Grades 2 through 5). Laboratory abnormalities will only be recorded as adverse events if deemed clinically significant by the Investigator. From Day +100 through Day +365: Only adverse events associated with GvHD, infections or secondary engraftment failure (Grades 1 through 5).
16. Peripheral blood testing for hematology (CBC and when possible per institutional practice to include a differential (automated or manual) including total white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, bands, lymphocytes, eosinophils, and monocytes; manual differential will include blasts if present and ANC calculation) will be performed once during the Screening Period, once at Hospital Admission, once at Day 0 (prior to HCT), and daily from Day +1 through Day +28 (or until the subject achieves neutrophil engraftment, whichever event occurs first), and on

Day +35, +42, +49, +56, +63, +70, +77, +84, +100, +180, and +365. If applicable, peripheral blood testing for hematology will be performed at the Early Withdrawal Visit. Following engraftment, blood for hematology is to be collected per institutional policy. Blood samples will be collected and forwarded to the local laboratory for analysis.

17. A peripheral blood sample for serum chemistry will be collected once during the Screening Period, once at Hospital Admission, once at Day 0 prior to HCT, and weekly from Day +1 through Day +100, then at Day +180. If applicable, a peripheral blood sample for serum chemistry will be obtained at the Early Withdrawal Visit. Serum chemistry assessment will include creatinine, blood urea nitrogen, albumin, ALT, AST, bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase, calcium, sodium, potassium, phosphorus, chloride, CO_2, and magnesium.
18. Peripheral blood samples for immune reconstitution assays will be collected at baseline (during the Screening Period), and at Days +7, +14, +28, +56, +91, +180, +270, and +365. The peripheral blood sample will be sent to a central laboratory for analysis.
19. A serum pregnancy test will be performed for females of child-bearing potential.
20. For the Phase 2 part of the study only, after meeting eligibility and no later than Day -7, subjects will be randomized using the IWRS to either the Control arm or ProTmune arm.
21. If pre-emptive CMV therapy is being initiated per local Institutional policy at a timepoint that does not have a regularly scheduled viral assessment (e.g., at conditioning or at an unscheduled visit), 2 peripheral blood samples (1 blood sample to be utilized locally, per institutional policy as required, at the site for subject management and 1 blood sample for central laboratory testing) will be collected for CMV assessments of DNA by quantitative PCR prior to starting the preemptive therapy.
22. The conditioning regimen will be administered to subject per Section 3.4.
23. GvHD prophylaxis will be initiated per Section 3.4.
24. Two peripheral blood samples at each testing time point (1 blood sample to be utilized locally at the site for subject management and 1 blood sample for central laboratory testing) will be collected for viral assessments of DNA by quantitative PCR for EBV, CMV, HHV-6, and BK virus weekly from Days +7 through Day +100, and at Days +180, +270, and +365. For CMV assessment: Assessment of infection will be performed based on the NCI CTCAE and the BMT CTN Definitions. Study sites will monitor CMV viremia using local assays and frequencies as determined by local practices for in-patient and out-patient care. Therefore, if a blood sample is being drawn for a CMV PCR at a local virology laboratory, a sample must also be drawn at the same time and sent to the central virology laboratory for a CMV PCR result. If applicable, a peripheral blood sample for CMV assessment will be obtained at the Early Withdrawal Visit.
25. Clinical and laboratory assessments of aGvHD will be performed weekly from Day +1 through Day +100, and on Day +180. If applicable, aGvHD assessments will be performed at the Early Withdrawal Visit. Acute GvHD assessments (incidence and maximum severity) of Grades I through IV aGvHD of the skin, liver, and gut as per the CIBMTR aGvHD Grading Scale (Appendix E) will be performed.
26. Chronic GvHD assessments of mild, moderate, or severe cGvHD as per NIH Consensus Criteria for cGvHD (Appendix F) will be performed on Days +180, +270, and +365. If applicable, cGvHD assessments will be performed at the Early Withdrawal Visit.
27. Neutrophil and T-cell chimerism will be assessed on the third consecutive day of ANC >500 cells/µL (neutrophil only) and on Days +28, +100, +180, and +365 (both neutrophil and T-cell). Chimerism will be measured by PCR amplification of recipient-and-donor-derived cells; which may include single nucleotide polymorphism and/or DNA microsatellites (short tandem repeats) analyses consistent with Institutional Standards. Chimerism will be measured by restriction fragment length polymorphism or microsatellite. Chimerism studies will be performed by short tandem repeats and/or flow cytometry according to local laboratory practices. When feasible, fractional chimerism (total, myeloid, lymphoid) will be performed from peripheral blood samples. If there is no evidence for donor engraftment by Day +21, then the subject will undergo BM and peripheral blood chimerism studies. If donor engraftment is not present by Day +28 BM examination, and the subject's disease is not present, the subject should be considered a primary graft failure (in the absence of relapsed disease).
28. Serum IgG, IgM, and IgA will be collected by a peripheral blood sample at Days +100, +180, and +365.
29. Peripheral blood samples for GvHD exploratory biomarkers will be obtained once weekly from Days +7 through Day +42, then on Day +100. Samples will be banked.

ADM = Admission; aGvHD = Acute graft-versus-host disease; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BM = Bone marrow; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CBC = Complete blood count; cGvHD = Chronic graft-versus-host disease; CMV = Cytomegalovirus; CO_2 = Carbon dioxide; COND = Conditioning; CTCAE = Common Terminology Criteria for Adverse Events; DNA = Deoxyribonucleic acid; EBV = Epstein-Barr Virus; ECG = Electrocardiogram; ECHO = Echocardiogram; eCRF = Electronic case report form; GvHD = Graft-versus-host disease; HCT = Hematopoietic cell transplantation; HSV = Herpes simplex virus; HHV-6 = Human herpes virus 6; HIV = Human immunodeficiency virus; HLA = Human leukocyte antigen; HTLV = Human T-cell lymphotropic virus; Ig = Immunoglobulin; INST = Institutional; LVEF = Left ventricular ejection fraction; mPB = Mobilized peripheral blood; MUGA = Multiple gated acquisition; NCI = National Cancer Institute; NIH = National Institutes of Health; SAE = serious adverse event; SCRN = Screening; PCR = Polymerase chain reaction; VZV = Varicella zoster virus.

APPENDIX B: STUDY DESIGN SCHEMATIC FOR THE PHASE 1 PART OF THE STUDY

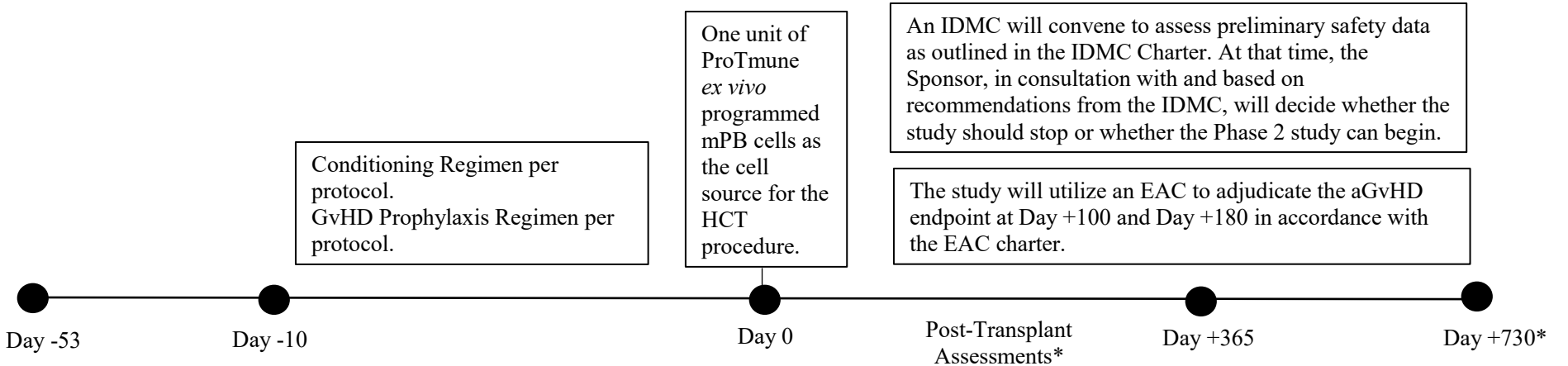


CIBMTR = Center for International Blood and Marrow Transplant Research; GvHD = Graft-versus-host disease; HLA = Human Leukocyte Antigen; HCT = Hematopoietic cell transplant; IV = intravenous; mPB = Mobilized peripheral blood; TBI = Total body irradiation.

APPENDIX C: FLOW SCHEMATIC FOR THE PHASE 1 PART OF THE STUDY

*Comprised of post-transplant assessments and post-transplant weekly visits through Day +100, intermittent visits through Day +365 and a telephone call on Day +730.

aGvHD = Acute graft-versus-host disease; CMV = Cytomegalovirus; EAC = Endpoint Adjudication Committee; ECG = Electrocardiogram; GvHD = Graft-versus-host disease; HLA = Human Leukocyte Antigen; HCT = Hematopoietic cell transplant; IDMC = Independent Data Monitoring Committee; mPB = Mobilized peripheral blood.



Key Assessments:
- Investigator is required to verify that the subject completed HLA typing.
- Infectious disease titers and CMV viremia.
- Peripheral blood baseline sample for immune reconstitution assays.

Key Assessments:
- ECG and safety panels on Day 0 prior to HCT.
- Adverse event monitoring (starting at Conditioning).
- Karnofsky Performance Status.

Key Assessments:
- Adverse event monitoring.
- Karnofsky Performance Status.
- Acute GvHD assessments.
- Chronic GvHD assessments.
- Peripheral blood monitoring for safety panels, viral monitoring, immune reconstitution, chimerism, serum immunoglobulins, and GvHD exploratory biomarkers.
- Bone marrow aspirate.
- ECG.

APPENDIX D: KARNOFSKY PERFORMANCE STATUS SCALE

General Category	Index	Specific Criteria
Able to carry on normal activity; no special care needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do work.
	60	Requires occasional assistance from others but is able to care for most needs.
	50	Requires considerable assistance from others and frequent medical care.
Unable to care for self; requires institutional or hospital care or equivalent; diseases may be rapidly progressing.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization indicated; death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund.
	0	Dead

Source: Mor V, Laliberte L, Morris JN, Wieman M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer. 1984;53(9):2002-2007.

APPENDIX E: 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	--

[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.

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

APPENDIX F: 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 intake.
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 keratoconjunctivits 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 eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca.
GI 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.

*AP may be elevated in growing children, and not reflective of liver dysfunction.
†Pulmonary scoring should be performed using both the symptom and pulmonary function testing (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 Lung Function Score (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 [29]. 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; GvHD = graft-versus-host disease; KPS = Karnofsky Performance Status;LPS = Lansky Performance Status; LFTs = liver function tests; ULN = upper limit of normal.
Source: Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945-956.

APPENDIX F: NIH CONSENSUS CRITERIA FOR CHRONIC GVHD (CONTINUED)

Performance Score:	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Liver	Normal LFT.	Elevated Bilirubin, AP*, AST or ALT.	Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 × ULN.	Bilirubin or enzymes >5 × ULN.
Lungs† **FEVI** **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). • FEVI ≤39% **OR** LFS 10-12
Joints and Fascia	No symptoms.	Mild tightness of arms or legs, normal or mild decreased range of motion (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.)
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 >500µl
- Coronary artery involvement

*AP may be elevated in growing children, and not reflective of liver dysfunction.
†Pulmonary scoring should be performed using both the symptom and pulmonary function testing (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 Lung Function Score (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 [29]. 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; GvHD = graft-versus-host disease; KPS = Karnofsky Performance Status; LPS = Lansky Performance Status; LFTs = liver function tests; ULN = upper limit of normal.
Source: Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945-956.

APPENDIX F: NIH CONSENSUS CRITERIA FOR CHRONIC GVHD (CONTINUED)

Global Severity Scoring of Chronic GvHD

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. Although scoring is often used at the time of initial diagnosis, evaluating the clinical score periodically during the course of chronic GVHD may revise prognostic expectations and better describe the current severity of chronic GVHD.

Note that the global scoring system can be applied only after the diagnosis of chronic GVHD 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 chronic GVHD with the diagnosis supported by histologic, radiologic, or laboratory evidence of GVHD from any site.

Mild chronic GVHD 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 chronic GVHD 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 chronic GVHD.

Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

Source: Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945-956.

APPENDIX G: BMT CTN SEVERITY GRADING AND RECURRENCE INTERVAL DEFINITION

Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g., urinary tract infection).	Bacteremia (except CoNS) without severe sepsis.*	Bacteremia with deep organ involvement (e.g., with new or worsening pulmonary infiltrates; endocarditis).
	Coag Neg Staph (*S. epi*), Corynebacterium, or Proprioniobacterium bacteremia.	Bacterial focus with persistent signs, symptoms, or persistent positive cultures requiring greater than 14 days of therapy.	Severe sepsis with bacteremia.
	Cellulitis responding to initial therapy within 14 days.	Cellulitis requiring a change in therapy due to progression. Localized or diffuse infections requiring incision with or without drain placement. Any pneumonia documented or presumed to be bacterial.	Fasciitis requiring debridement. Pneumonia requiring intubation.
	C. Difficile toxin positive stool with diarrhea <1 L without abdominal pain (child <20 mL/kg).	C. Difficile toxin positive stool with diarrhea ≥1 L (child ≥20 ml/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g., oral thrush, vaginal candidiasis).	Candida esophagitis (biopsy proven).	Fungemia including Candidemia.
	-	Proven or probable fungal sinusitis confirmed radiologically without orbital, brain, or bone involvement.	Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).
	-	-	Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus. *Pneumonocystis jiroveci* pneumonia (regardless of PaO_2 level).

* For definition of sepsis, see source document.
CMV = Cytomegalovirus; CNS = Central nervous system; EBV = Epstein-Barr virus; HHV-6 = Human herpesvirus 6; PTLD = Posttransplant Lymphoproliferative Disease; VZV = Varicella zoster virus.
Source: Blood and Marrow Transplant Clinical Trials Network Technical Manual of Procedures, Appendix 4-A. Version 3.0, dated March 19, 2013.

APPENDIX G: BMT CTN SEVERITY GRADING AND RECURRENCE INTERVAL DEFINITION (CONTINUED)

Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
Viral Infections	Mucous HSV infection	-	-
	Dermatomal Zoster	VZV infection with 3 or more dermatomes.	Severe VZV infection (coagulopathy or organ involvement).
	Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks therapy.	Clinically active CMV infection (e.g., symptoms, cytopenias) or CMV viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy.	CMV end-organ involvement (pneumonitis, enteritis, retinitis).
	EBV reactivation not treated with rituximab.	EBV reactivation requiring institution of therapy with rituximab.	EBV PTLD
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding, and viermia not requiring treatment.	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment.	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract).
	Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy.	Clinically active HHV-6 infection (e.g., symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy.	-
	BK viremia or viruria with cystis not requiring intervention.	BK viermia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention.	-
	Viremia (virus not otherwise specified) not requiring therapy.	Any viremia (virus not otherwise specified) requiring therapy.	-
	-	Enterocolitis with enteric viruses.	-
	-	Symptomatic upper tract respiratory viruses.	Lower tract respiratory viruses.
	-	-	Any viral encephalitis or meningitis.
Parasitic infections	-	-	CNS or other organ toxoplasmosis Strongyloides hyperinfection.

* For definition of sepsis, see source document.
CMV = Cytomegalovirus; CNS = Central nervous system; EBV = Epstein-Barr virus; HHV-6 = Human herpesvirus 6; PTLD = Posttransplant Lymphoproliferative Disease; VZV = Varicella zoster virus.
Source: Blood and Marrow Transplant Clinical Trials Network Technical Manual of Procedures, Appendix 4-A. Version 3.0, dated March 19, 2013.

APPENDIX G: BMT CTN SEVERITY GRADING AND RECURRENCE INTERVAL DEFINITION (CONTINUED)

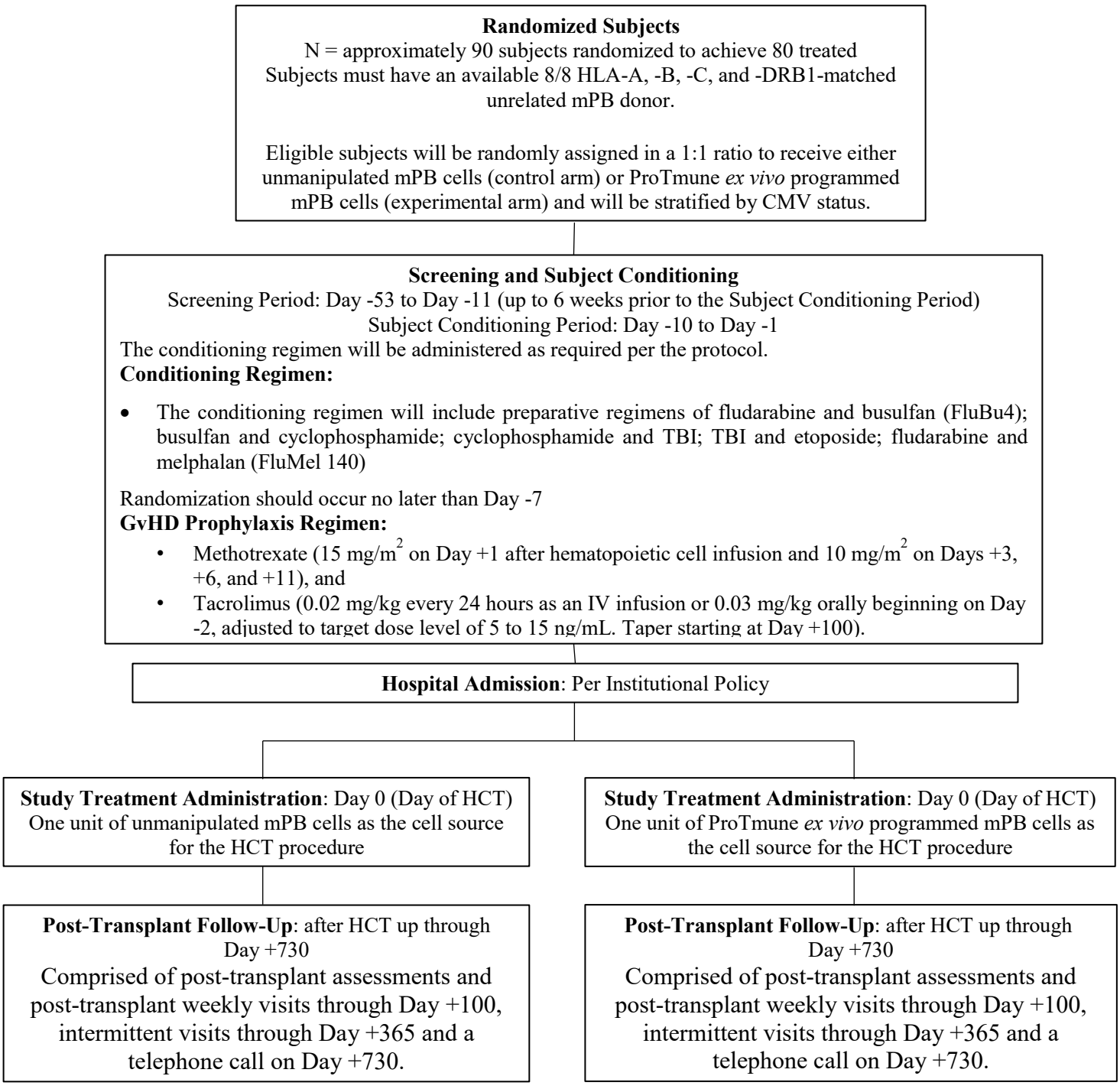
Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days	-	-
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventillation
	-	Typhlitis	-
	-	-	Severe sepsis* without an identified organism

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV, EBV, HHV-6: 2 months (<60 days)
2. VZV, HZV: 2 weeks (<14 days)
3. Bacterial, non-C. difficile: 1 week (<7 days)
4. Bacterial, C. difficile: 1 month (<30 days)
5. Yeast: 2 weeks (<14 days)
6. Molds: 3 months (<90 days)
7. Helicobacter: 1 year (<365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (<14 days)
9. Polyomavirus (BK virus): 2 months (<60 days)

* For definition of sepsis, see source document.
CMV = Cytomegalovirus; CNS = Central nervous system; EBV = Epstein-Barr virus; HHV-6 = Human herpesvirus 6; PTLD = Posttransplant Lymphoproliferative Disease; VZV = Varicella zoster virus.
Source: Blood and Marrow Transplant Clinical Trials Network Technical Manual of Procedures, Appendix 4-A. Version 3.0, dated March 19, 2013.

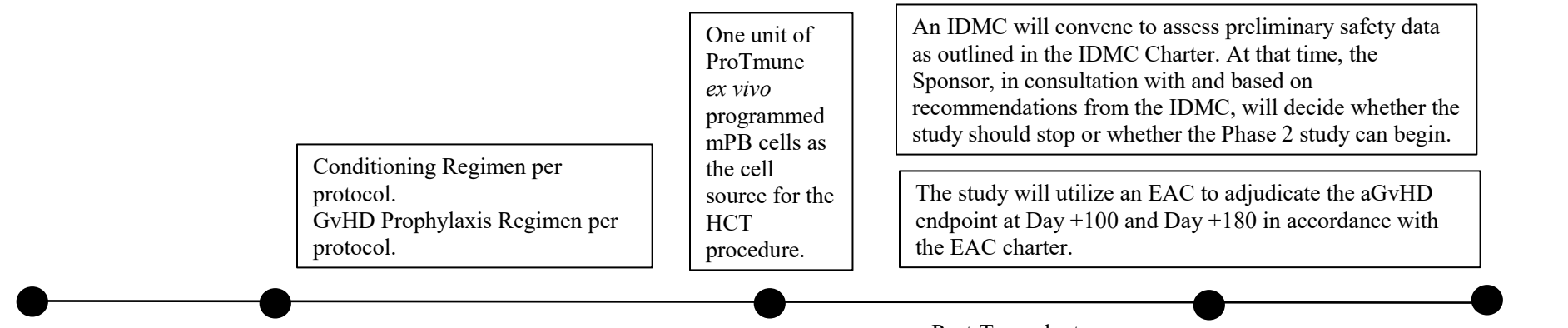
APPENDIX H: STUDY DESIGN SCHEMATIC FOR THE PHASE 2 PART OF THE STUDY



CIBMTR = Center for International Blood and Marrow Transplant Research; GvHD = Graft-versus-host disease; HLA = Human Leukocyte Antigen; HCT = Hematopoietic cell transplant; IV = Intravenous; mPB = Mobilized peripheral blood; TBI = Total body irradiation

APPENDIX I: FLOW SCHEMATIC FOR THE PHASE 2 PART OF THE STUDY

*Comprised of post-transplant assessments and post-transplant weekly visits through Day +100, intermittent visits through Day +365 and a telephone call on Day +730.aGvHD = Acute graft-versus-host disease; CMV = Cytomegalovirus; EAC = Endpoint Adjudication Committee; ECG = Electrocardiogram; GvHD = Graft-versus-host disease; HLA = Human Leukocyte Antigen; HCT = Hematopoietic cell transplant; IDMC = Independent Data Monitoring Committee; mPB = Mobilized peripheral blood.



APPENDIX J: CLINICAL LABORATORY ANALYTES

Hematology (CBC with differential):

Red blood cells

Hemoglobin

Hematocrit

Platelets

White blood cells

Neutrophils

Bands

Lymphocytes

Monocytes

Manual differential includes:

Blasts

ANC calculation

Serum chemistry:

Creatinine

ALT

AST

Alkaline phosphatase

Blood urea nitrogen

Lactate dehydrogenase

Sodium

Potassium

Chloride

CO_2

Bilirubin (total and direct)

Magnesium

Calcium

Phosphorus

Serum pregnancy test