Official Title:	A Phase IB-II Study Of High-Dose Post-Transplant Cyclophosphamide, Abatacept, and Short-Duration Tacrolimus for the Prevention of Graft-Versus-Host Disease (GvHD) Following Haploidentical Hematopoietic Stem Cell Transplantation (HSCT)
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A PHASE IB-II STUDY OF HIGH-DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE, ABATACEPT, AND SHORT-DURATION TACROLIMUS FOR THE PREVENTION OF GRAFT-VERSUS-HOST DISEASE (GVHD) FOLLOWING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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NYULH Medical Monitor:	David L. Green, MD
Study Product:	Cyclophosphamide, abatacept, and tacrolimus
Study Product Provider:	Cyclophosphamide, abatacept, and tacrolimus are covered as standard of care.
ClinicalTrials.gov Number:	NCT04503616

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Amended v5: Dec 2021
Administrative Amendment v5.1: 2022 Jun 07

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

PROTOCOL APPROVAL SIGNATURES

Protocol Title: **A PHASE IB-II STUDY OF HIGH-DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE, ABATACEPT, AND SHORT-DURATION TACROLIMUS FOR THE PREVENTION OF GRAFT-VERSUS-HOST DISEASE (GVHD) FOLLOWING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)**

Protocol Number: s20-00136

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Signature

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Date

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List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse Event or Adverse Experience
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATG	Anti-thymocyte globulin
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CNI	Calcineurin inhibitors
CrCl	Creatinine Clearance
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CTO	Clinical Trials Office
DC	Dendritic cell
DSMC	Data Safety Monitoring Committee
ECI	Event of Clinical Interest
ECRF	Electronic Case Report Form
EMR	Electronic Medical Record
GRFS	GvHD and relapse-free survival
GvHD	Graft-versus-Host Disease
GvT	Graft-versus-tumor
HSCT	Hematopoietic stem cell transplantation
LFTs	Liver function tests
LPS	Lipopolysaccharide
MMF	Mycophenolate mofetil
MTX	Methotrexate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PI	Proteasome inhibitors
PTC	Post-Transplant cyclophosphamide
rATG	Rabbit anti-thymocyte globulin

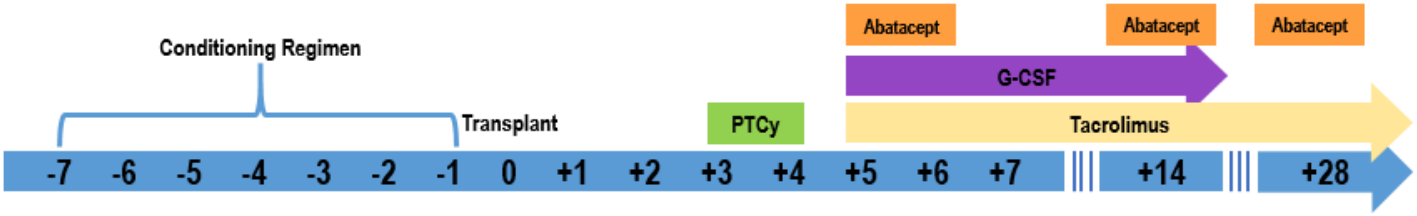
RR	Relapse rate
TRM	Treatment-related mortality
UP	Unanticipated Problems

Protocol Summary

Title	A PHASE IB-II STUDY OF HIGH-DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE, ABATACEPT, AND SHORT-DURATION TACROLIMUS FOR THE PREVENTION OF GRAFT-VERSUS-HOST DISEASE (GVHD) FOLLOWING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)
Short Title	Cyclophosphamide, abatacept, and tacrolimus for GvHD prevention
Brief Summary	This is a single arm, open label, optimal 2-stage Simon design phase Ib-II clinical trial. Adult patients with hematological malignancies undergoing allogeneic HSCT from first- or second-degree haploidentical donor are eligible for the study if they meet the standard criteria defined in our institutional standard operation procedures (SOPs), meet all inclusion criteria, and do not satisfy any exclusion criteria. Patients will receive non-myeloablative, reduced-intensity or myeloablative conditioning regimen followed by peripheral blood hematopoietic stem cells. Patients will receive cyclophosphamide, abatacept, and short-duration tacrolimus for GvHD prophylaxis.
Phase	Phase Ib-II
Objectives	Primary Objective: • Estimate the incidence of grade II-IV acute GvHD in patients receiving cyclophosphamide, abatacept, and tacrolimus as GvHD prophylaxis. Secondary Objectives: • Estimate the incidence of chronic GvHD in patients receiving cyclophosphamide abatacept, and tacrolimus as GvHD prophylaxis • Estimate the incidence of the following: primary graft failure, poor graft function, and secondary graft failure, treatment-related mortality (TRM), relapse rate (RR), and relapse-free survival (GRFS), and overall survival (OS). • Assess immune reconstitution by quantifying CD3+, CD4+, CD8+, and CD19+ in comparison to established reference data
Methodology	Interventional, non-randomized open label, 2- stage optimal Simon design with interim futility analysis.
Endpoint	Primary: Grade II-IV acute GvHD by day +120. Secondary: Chronic GvHD, TRM, RR, GRFS, and OS.
Study Duration	Study will complete 2 years after the final participant's date of transplant. Anticipate 4 years to complete enrollment and thus a 6-year total duration.
Participant Duration	Up to 2 years
Enrollment Period	Up to 4 years
Duration of IP administration	Up to 4 weeks
Number of participants	46 participants enrolled

Description of Study Procedure	Cyclophosphamide 50 mg/kg IV over 1 hour on Day +3 and +4 Abatacept 10 mg/kg IV on days +5, +14, and +28 Tacrolimus 0.02 mg/kg IV by continuous infusion, starting on day +5. May switch to oral when tolerated, adjusted to maintain a drug level between 5-12ng/mL. Treatment is discontinued on day +60 after a 4 week-taper
Key Procedures	Examinations to include toxicity and GvHD assessments and blood draws to assess immune reconstitution.
Statistical Analysis	Sample size: The primary outcome variable for this study is the incidence of grades II-IV acute GvHD. We assume that the rate of grade II-IV acute GvHD, with the standard of care is 50%, as reported in the literature and 30% in the experimental group. Based on a 2-stage optimal Simon design, we can detect a reduction in the grade II–IV acute GvHD incidence to 30% for high-dose post-transplant cyclophosphamide abatacept, and tacrolimus, with alpha = 0.05 and power of 82% at the conclusion of the 2-stage design with 46 patients. The trial would stop for futility at the end of the first stage if 9 or more patients have grade II-IV acute GVHD, of the 22 patients enrolled. Otherwise, the trial will continue to the second stage with the total 46 patients enrolled. If the total number of patients with grade II-IV acute GVHD is 19 or greater at the end of stage II, the regimen will not be considered for further study. The rate of grade II-IV acute GVHD will be estimated at the end of the trial with exact 95% Clopper Pearson confidence intervals. If the observed rate is 30%, this exact confidence interval with 46 patients, the corresponding confidence interval will be 17.4% to 45.3%. Calculations from PASS 2019, NCSS, J. Hintze, Kaysville, Ut. The primary analyses will include all patients who are transplanted and receive treatment. All endpoints will be evaluated using cumulative incidence functions; exact 95% confidence intervals will be provided for the day +120 incidence for acute GvHD. Secondary analyses will estimate the occurrence of chronic GvHD, primary graft failure, poor graft function, secondary graft failure, TRM, RR, GRFS, and OS.

Schematic of Study Design



1. KEY ROLES

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2. BACKGROUND AND RATIONALE

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for a variety of benign and malignant hematological conditions [1]. According to the Center for International Bone Marrow Transplant Research (CIBMTR), more than 13,000 allogeneic HSCTs are performed annually in the US alone (http://www.cibmtr.org).

The stem cell source for allogeneic HSCT has historically been from an HLA-matched related donor (MRD) or matched unrelated donor (MUD). However, such donor can be identified or mobilized in less than 50% of cases [2]. In particular, the availability of a MUD can be lower for members of certain ethnic groups who are underrepresented in the donor registries, including African Americans, Hispanics, and Asians [2]. In contrast, an HLA-haploidentical first- or second-degree relative can be identified and mobilized rapidly for nearly any patient [3]. At Johns Hopkins University, More than 95% of patients were found to have at least 1 HLA-haploidentical first-degree donor with an average number of donors per patient of 2.7 [3].

The Outcomes of HLA-haploidentical transplantation have improved substantially over the past decade [4]. Multiple studies have now demonstrated that the outcomes of HLA-haploidentical transplantation and MUD are comparable (Table 1) [4]. Furthermore, the Blood and Marrow Transplant Clinical Trial Network (BMT CTN) has completed a two parallel phase II studies of either HLA-haploidentical related donor bone marrow transplants or double-unrelated donor cord blood transplantation in patients with hematological malignancies. The outcomes of the two cohorts were comparable. The 100-day incidence of grade II-IV acute GvHD was 32% in HLA-haploidentical transplantation and 40% in cord blood transplantation. The 1-year cumulative incidence of treatment-related mortality (TRM) and relapse rate (RR) were 7% and 45% for HLA-haploidentical transplantation and 24% and 31% for cord blood transplantation. The 1-year probability of overall survival (OS) was 62% and 54%, respectively [5]. Nowadays, HLA-haploidentical transplantation represents an acceptable alternative in patients who lack a MRD [4]. According to the CIBMTR, the use of MUD and cord blood transplantation has declined in recent years in favor of HLA-haploidentical donor transplantation (Figure 1).

Reference	RIC or MAC	N		aGVHD II-IV (%)		cGVHD (%)		NRM (%)		Relapse (%)		Overall survival (%)		Event-free survival (%)	
AML ± MDS		Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD	Haplo	MUD
19	MAC	104	1245	**16**	**33‡**	**30**	**53‡**	14	20	44	39	45	50	42	41
	RIC	88	737	**19**	**28***	**34**	**52†**	**9**	**23‡**	**58**	**42†**	46	44	33	35
20	RIC	32	108	–	–	–	–	24	25	33	23	–	–	43	42
21	Mix	52	88	40	36	10	9	27	27	29	43	42	37	44	30
22	Mix	62	21§	40	19	6	5	22	16	31	26	53	58	–	–
Hodgkin lymphoma															
23	RIC	28	38	43	50	35	63	9	8	40	63	58	58	**51**	**29***
Non-Hodgkin lymphoma															
24	RIC	185	491	52	60	**15**	**62‡**	17	22	36	28	60	62	47	49
25	RIC	26	28	–	–	15	29	15	27	19	7	77	71	65	68
Mix															
26	Mix	92	43	14	21	15	22	18	33	35	23	52	43	43	36
27	MAC	30	32	43	63	56	69	3	16	24	28	78	62	73	56
28	RIC	54	59	63	53	32	20	30	29	44	49	–	–	26	22
29	RIC	31	63	**23**	**44***	13	24	10	34	23	31	70	51	**67**	**38***
30	Mix	116	178	41	48	**31**	**47†**	17	16	29	34	57	59	54	50

Significant differences are shown in bold type: *.01 ≤ P ≤ .05; †.001 ≤ P < .01; ‡P < .001.
aGVHD, acute graft-versus-host disease; AML, acute myeloid leukemia; cGVHD, chronic graft-versus-host disease; NRM, nonrelapse mortality; RIC, reduced intensity conditioning (includes nonmyeloablative conditioning); MAC, myeloablative conditioning; MDS, myelodysplastic syndrome.
§Mixture of matched sibling and MUD transplants.

Table 1

The major drawback of HLA-haploidentical transplantation is the intense bidirectional alloreactivity [2]. The early studies of HLA-haploidentical transplantation have demonstrated the fundamental challenge inherent in crossing HLA barriers. Without T-cell depletion, the incidence of GvHD is high with TRM in excess of 50%. On the other hand, if T-cells are depleted from the graft, there is an unacceptable risk of graft failure, opportunistic infections and disease relapse. To overcome these challenges, selective T-cell depletion and add on strategies are being explored [6-8]. Alternatively, post-transplantation cyclophosphamide (PTC) can circumvent the need to graft manipulation and has emerged as an alternative approach to graft manipulation [9].

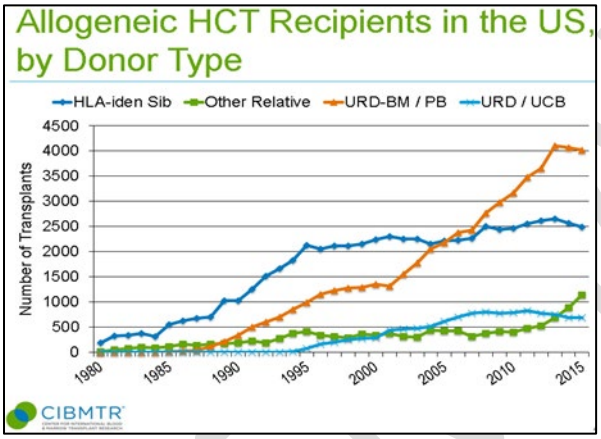


Figure 1

PTC for GvHD prevention:

Since introduced by the Johns Hopkins University group, PTC has been extensively studied in HLA-haploidentical transplantation, following non-myeloablative and myeloablative conditioning regimens. Contrary to calcineurin inhibitors (CNI), methotrexate (MTX), and mycophenolate mofetil (MMF), PTC selectively destroys rapidly proliferating host-reactive T cells, fosters regulatory T cells (T_{reg}) expansion and induces long-lasting tolerance by deleting intra-thymic alloreactive T cells [9]. Because of its selective activity, targeting proliferating rather than resting T cells, PTC has been claimed to nurture rapid immune reconstitution and preserve GvT effect [10]. Several studies, using non-myeloablative and myeloablative conditioning regimens and HLA-haploidentical related-donor transplantation have now validated this approach with PTC, tacrolimus and MMF used as GvHD prevention. Although the original studies focused on the use of bone marrow as the source of grafts, recent studies using peripheral blood grafts have reported comparable outcomes [11-16].

Abatacept for GvHD prevention:

Abatacept is a recombinant soluble fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) fused to the Fc region of IgG1. Abatacept blocks CD28-CD80I86 axis T-cell co-stimulation thus preventing T-cell activation [17]. Abatacept is FDA approved for adult rheumatoid arthritis, juvenile idiopathic arthritis and adult psoriatic arthritis.

A phase I feasibility study using a short-course of abatacept in unrelated-donor allogeneic HSCT suggested the safety and potential efficacy of abatacept in the prevention of severe acute GvHD.

In a recent larger study the role of abatacept in the prevention of aGvHD was examined in two cohorts of patients. The first cohort received a one locus-HLA mismatched unrelated-donor transplant. Patients received a combination of tacrolimus and methotrexate and in addition, abatacept, given at 10mg/kg on day -1, +5, +14, and +28. The cohort was compared to a registry-matched cohort receiving tacrolimus and methotrexate with or without rabbit anti-thymocyte globulin (rATG). The outcomes were improved in the group that received abatacept with a reduced rate of grade III-IV acute GvHD (3% v 32%, p=0.0003 in comparison to the group that did not receive rATG and 3% v 22%, p=0.0054 in comparison to the group that received rATG). GvHD and relapse-free survival was also improved, as was disease-free survival. The rates of relapse were 8%, 21%, and 18% respectively (p=0.099 and 0.23). The second cohort included 140 patients receiving HLA-matched donor transplant, randomized in a double-blinded fashion to receive tacrolimus and methotrexate with either placebo or abatacept. Grade III-IV acute GvHD was reduced in the group that received abatacept in comparison to placebo (7% v 15%, p=0.66). GRFS was also reduced (89% v 77%, p=0.05). There was no difference in TRM or relapse rate between the two groups. The authors concluded that a short-course of abatacept was safe and effective in the prevention of aGvHD without increasing relapse-rate [18]. In a smaller study, abatacept was combined with PTC and tacrolimus in patients receiving MRD or MUD transplants. Abatacept was given at 10mg/kg on day +5, +14, and +28. The treatment was deemed safe and no patients developed acute GvHD [19].

Abatacept has now been granted a breakthrough therapy designation for the prevention of moderate to severe acute GvHD.

Duration of tacrolimus for GvHD prevention:
Tacrolimus targets T-cells indiscriminately. Its use following allogeneic HSCT is therefore associated with delayed immune reconstitution and impairment of graft-versus-tumor effect. Tacrolimus is also burdensome to use due to narrow therapeutic index that requires close drug level monitoring with multiple drug interactions and side effects including renal impairment and electrolyte wasting. Lastly, prolonged administration of tacrolimus delays the introduction of immune maneuvers and small molecules aimed to reduce the risk of relapse following allogeneic HSCT.
There is paucity of prospective data on the optimal duration of CNI following allogeneic HSCT. The Johns Hopkins group recently reported the results of a single arm trial. Tacrolimus was pre-specified to stop on day +60, +90, or +120 without pre-taper following HLA-haploidentical transplant with bone marrow grafts and PTC, tacrolimus and MMF for GvHD prevention. Safety stopping rules were not met. The incidence of grade II-IV and grades III-IV acute GvHD were <40% and <8% in both day +60 and day +90 arms. The GRFS rate was higher in the +60 arm. The authors concluded that stopping tacrolimus at day +60 was feasible and safe [20].

Based on the above, we propose a phase Ib-II study using PTC, abatacept and short-duration tacrolimus for GvHD prevention following HLA-haploidentical allogeneic HSCT in patients with hematological malignancies.

2.1. Potential Risks & Benefits
2.1.1. Known Potential Risks

2.1.1.1. Cyclophosphamide

The most common side effects of cyclophosphamide (Cytoxan®):

- Hematopoietic system: Neutropenia occurs in patients treated with cyclophosphamide. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.
- Gastrointestinal system: Nausea and vomiting occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.
- Skin and its structures: Alopecia occurs in patients treated with cyclophosphamide. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.

Full prescribing information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf

2.1.1.2. Abatacept

The most common side effects of abatacept (Orencia®):

The most common adverse reactions events (≥ 10%) are headache, upper respiratory tract infection, nasopharyngitis, and nausea.

2.1.1.3. Tacrolimus

The most common side effects of tacrolimus (Prograf®):

The most common adverse reactions (≥ 15%) are abnormal renal function, hypertension, diabetes mellitus, fever, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, constipation, diarrhea, headache, abdominal pain, insomnia, paresthesia, peripheral edema, nausea, hyperkalemia, hypomagnesemia, and hyperlipidemia.

2.1.2. Other Risks of Study Participation

Additional risks associated with participation in this study, include risks associated with phlebotomy and breach of confidentiality. Risks associated with phlebotomy include weaknesses, redness, pain, bruising, bleeding, or infection at the needle site. Privacy protection procedures are in place and good clinical practice guidelines are followed to minimize the risks associated with research procedures and participation.

2.1.3. Known Potential Benefits

It is possible that some study subjects receiving therapies may experience an improvement during the study. Also, some subjects may not get any benefit from being in this research study. The information learned in this study may benefit future individuals with acute and chronic GvHD.

3. OBJECTIVES AND PURPOSE

STUDY DESIGN:

3.1. Study hypothesis: We hypothesize that the administration of cyclophosphamide, abatacept, and a short-course of tacrolimus in the setting of HLA-haploidentical HSCT peripheral blood transplantation is effective in the prevention of GvHD and allows prompt immune reconstitution.

3.2. Study overview: This is a phase Ib-II clinical trial. Adult patients with hematological malignancies undergoing HLA-haploidentical HSCT from first- or second-degree family donors are eligible for the study if they meet the standard criteria defined in our standard operation procedures (SOPs), meet all inclusion criteria, and do not satisfy any exclusion criteria. Patients will receive non-myeloablative, reduced-intensity, or myeloablative conditioning regimen at the discretion of the transplant physician.

3.3. Objectives

3.3.1. Primary objectives:

- Estimate the incidence of grades II-IV acute GvHD in patients receiving cyclophosphamide, abatacept, and tacrolimus as GvHD prophylaxis.

3.3.2. Secondary objectives:

- Estimate the incidence of the following: chronic GvHD, primary graft failure, poor graft function, and secondary graft failure, TRM, RR, GRFS, OS.
- Assess immune reconstitution by quantifying CD3+, CD4+, CD8+, and CD19+ in comparison to established reference data.

3.4. Study Endpoints

3.4.1. Primary study endpoints

Acute GvHD: The first day of acute GvHD of any grade will be used to calculate the cumulative incidence for that grade. This endpoint will be evaluated through day +120 post-transplant.

3.4.2. Secondary study endpoints

Chronic GvHD: The first day of chronic GvHD will be used to calculate the cumulative incidence of chronic GvHD. This endpoint will be evaluated through day +365 post-transplant.

Primary graft failure is evaluated to day +45 and as defined below.

Poor graft function is evaluated to day +30 and as defined below.

Secondary graft failure is evaluated following engraftment through day +730, as defined below.

TRM are participant deaths not attributable to disease relapse or progression and will be evaluated to day +730.

RR is evaluated to day +730 and is considered the date in which the disease for which transplant is performed is evident by methods of disease detection.

GRFS is evaluated to day +730 and considers the number of participants that are without reported grade III-IV acute GvHD, chronic GvHD requiring systemic therapy and have not experienced relapse or death.

OS is evaluated to day +730 and considers all participants alive at the end of the study's evaluation period.

3.5. Definitions

3.5.1. Engraftment of Neutrophils: Absolute neutrophil count (ANC) recovery is defined as an ANC of ≥ 0.5 x 10^9/L for three consecutive laboratory values obtained on different days. The day used as neutrophil engraftment is the date of the first of three laboratory values.

3.5.2. Engraftment of Platelets: Platelet engraftment is defined as a platelet count ≥ 20 x 10^9/L for 3 consecutive measurements obtained on different days. The patient must not have received a platelet infusion for seven consecutive days prior to the first day being considered. The day used as platelet engraftment is the date of the first of three laboratory values.

3.5.3. Primary graft Failure: Graft failure is defined as failure to achieve neutrophil engraftment by day +28 or lack of donor chimerism > 50% by day 45, not due to the underlying malignancy.

3.5.4. Poor graft function is defined by at least 2 of the following 3 criteria: Hemoglobin < 8 g/dL, ANC < 0.5 x 10^9/L, and platelets < 20 x 10^9/L. The cytopenia must be unexplained (such as by disease relapse) and unresponsive to cytokines and must last at least 4 weeks.

3.5.5. Secondary graft failure is defined as poor graft function associated with donor chimerism < 5%.

3.5.6. Acute GvHD: The first day of acute GvHD of any grade will be used to calculate the cumulative incidence for that grade (e.g., onset of grade III 70 days post-transplant - time to grade III is 70 days). This end point will be evaluated through day +120 post-transplant. The diagnosis of acute GvHD is based on clinical and pathological evaluation by the principal investigator in collaboration with the treating physician. The acute GvHD grading system is described in appendix B.

3.5.7. Chronic GvHD: The first day of chronic GvHD will be used to calculate the cumulative incidence of chronic GvHD. The diagnosis of chronic GvHD is based on clinical and pathological evaluation by the principal investigator in collaboration with the treating physician. The chronic GvHD grading system is described in appendix C.

4. STUDY ENROLLMENT AND WITHDRAWAL

ELIGIBILITY: Patients with hematological malignancies undergoing an allogeneic transplant with a conditioning regimen, as described in Appendix B, using an eligible HLA-haploidentical related donor. Donors are excluded in case of donor-specific HLA antibodies or positive cross-matching. Patients must meet all of the following inclusion criteria and none of the exclusion criteria. All testing performed per BMT SOP: CLNAL002: Related (MRD, Haplo) Allogeneic RECIPIENT Evaluation and Management – Adult and Pediatric and CLNAL003: Related (MRD, Haplo) DONOR Evaluation and Management – Adult and Pediatric.

4.1. Inclusion Criteria:

4.1.1. Age ≥ 18 years

4.1.2. Karnofsky score ≥ 70%
4.1.3. No evidence of progressive bacterial, viral, or fungal infection
4.1.4. Creatinine clearance > 50 mL/min/1.72m^2
4.1.5. Total bilirubin, ALT and AST < 2 x the upper limit of normal (except for diagnosed Gilbert's syndrome)
4.1.6. Alkaline phosphatase ≤ 250 IU/L
4.1.7. Left Ventricular Ejection Fraction (LVEF) > 45%
4.1.8. Adjusted Carbon Monoxide Diffusing Capacity (DLCO) > 60%
4.1.9. Negative HIV serology
4.1.10. Negative pregnancy test: confirmation per negative serum β-human chorionic gonadotropin (β-hCG) for women of childbearing age and potential.

4.2. Exclusion Criteria:

4.2.1. Donors are excluded in case of donor-specific HLA antibodies or positive cross-match.
4.2.2. Pregnant or nursing females or women of child bearing age or potential, who are unwilling to completely abstain from heterosexual sex or practice 2 effective methods of contraception from the first dose of conditioning regimen through day +180. A woman of reproductive capability is one who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed, or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row.
4.2.3. Male subjects who refuse to practice effective barrier contraception during the entire study treatment period and through a minimum of 90 days after the last dose of study drug, or completely abstain from heterosexual intercourse. This must be done even if they are surgically sterilized (i.e., post-vasectomy).
4.2.4. Inability to provide informed consent.
4.2.5. Patient had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix E), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
4.2.6. Known allergies to any of the components of the investigational treatment regimen.
4.2.7. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
4.2.8. Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
4.2.9. Prisoners

4.3. Inclusion of Women, Minorities and Vulnerable Subjects:

Both men and women of all races and ethnic groups are eligible for this trial.
Pregnant women are not included in this study, due to the unknown safety effects to the developing fetus. Prisoners are not eligible

4.4. Strategies for Recruitment and Retention

4.4.1. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment.

4.4.2. Patients will be recruited from physicians participating in this study. Consenting, screening, and treatment will take place at the NYU Langone Health PCC under the supervision of the principal investigator, Dr. AS Al Homsi. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions will be answered by the PI or qualified research personnel.

4.4.3. The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed. Consent may be delegated to a trained and qualified licensed professional, as delegated by the principal investigator.
2. Determine patient eligibility; see Section 4.1 and 4.2
3. Submit registration to NYU Langone Health PCC CTO.
4. Receive registration confirmation from the NYU Langone Health PCC CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient. Confirmation of subject registration must be obtained before any treatment is administered or study procedures are performed.

4.4.4. Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows that established procedures of NYULH Human Subject Research Standard Operating Procedures (HSR 301 Informed Consent Process and Documentation). .

4.5. Registration Procedures:

4.5.1. General Guidelines:

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC CTO. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study. Confirmation of subject registration is required before any treatment is administered or

study procedures are performed (unless a procedure is being performed as part of the patient's standard of care.

4.5.2. Data Reporting to the Center for International Blood and Transplant Research (CIBMTR):

All transplant centers are required to register patients with the Center for International Blood and Marrow Transplant Research (CIBMTR) and complete pre-transplant essential data forms, day 100 report forms and follow-up forms. CIBMTR data is covered under NYULH IRB: S11-00861.

4.6. Duration of Study Participation:

Subjects may remain on study for as long as 2 years, with treatment as detailed in the protocol. Withdrawal due to toxicity, withdrawal of consent, or at the discretion of the investigator may occur.

4.7. Total Number of Participants and Sites:

There will be one site participating in the study, with a total of 46 participants enrolled, accrued over up to 4 years.

4.8. Participants Withdrawal or Termination:

4.8.1. Reasons for Withdrawal or Termination:

A subject has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator has the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for subject withdrawal from the study may include, but are not limited to:

- Subject withdrawal of consent at any time.
- Disease progression (if applicable)
- Intolerable toxicity (If applicable)
- Any medical condition that the investigator determines may jeopardize the patient's safety if the patient continues in the study or continues treatment with study drug.
- The investigator determines it is in the best interest of the patient.
- Failure of the subject to adhere to protocol procedure requirements
- Pregnancy (if applicable)

4.8.2. Handling of Participant Withdrawals or Termination:

Withdrawal from the study can be made in writing to the Principal Investigator, Dr. AS Al-Homsi.

4.9. Premature Termination or Suspension of Study:

This study may be temporarily suspended or prematurely terminated if there is sufficient, reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. A Samer Al-Homsi and any regulatory authorities. If the study is prematurely terminated or suspended,

the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

4.10. Stopping Rules

4.10.1. Excess TRM

With 46 patients planned, we will test the hypothesis that the **TRM rate is ≤8.2%** versus the alternative hypothesis that the **TRM rate is ≥20%** with one sided α=0.05 and power of 80%, using an O'Brien Fleming group sequential alpha stopping boundary with three (3) interim and one (1) final look as summarized in Table 1 below.

Table 1: Stopping Boundaries for Excess Transplant Related Mortality (TRM) (1 sided α=0.05, power=80%, Ho: TRM≤0.082, Ha: TRM≥0.20) [Calculations from EAST 6.5 Cytel, Inc.].

Interim Look	Number of Patients	Cumulative Alpha Spent	Stopping Boundaries: Reject TRM≤0.082	
			≥Number Events	≥Proportion Observed
1	12	0	5	0.39
2	23	0.006	6	0.23
3	35	0.025	7	0.18
Final	46	0.05	7	0.15

4.10.2. Stopping for excess day-30 grade 4 non-hematologic or any grade 5 regimen-related toxicity

With 46 patients planned, we will test the hypothesis that the **day-30 grade 4 non-hematologic or any grade 5 regimen-related rate is ≤8.2%** versus the alternative hypothesis that the **day-30 grade 4 non-hematologic or any grade 5 regimen-related rate is ≥20%** with one sided α=0.05 and power of 80%, using an O'Brien Fleming group sequential alpha stopping boundary with three (3) interim and one (1) final look as summarized in Table 2 below.

Table 2: Stopping Boundaries for Proportion of Patients with Excess Day-30 Grade 4 non-hematologic or any grade 5 regimen-related Toxicity at Least Possibly Related to Study Drugs at day 30 (1 sided α=0.05, power=80%, Ho: 30 day proportion ≤0.082, Ha: 30 day proportion ≥0.2) [Calculations from EAST 6.5 Cytel, Inc.]

Interim Look	Number of Patients	Cumulative Alpha Spent	Stopping Boundaries: Reject grade 4 non-hematologic or any grade 5 regimen-related toxicity ≤0.082	
			≥Number Events	≥Proportion Observed
1	12	0	5	0.39
2	23	0.006	6	0.23
3	35	0.025	7	0.18
Final	46	0.05	7	0.15

4.10.3 Stopping for excess primary graft failure

With 46 patients planned, we will test the hypothesis that the **primary graft failure rate is ≤5%** versus the alternative hypothesis that the **graft failure rate is ≥15%** with one sided α=0.05 and power of 83%, using an O'Brien Fleming group sequential alpha stopping boundary with three (3) interim and one (1) final look as summarized in Table 3 below.

Table 3: Stopping Boundaries for Proportion of Patients with Graft Failure Rate (1 sided α=0.05, power=83%, Ho: 30 day proportion ≤0.05, Ha: 30 day proportion ≥0.15) [Calculations from EAST 6.5 Cytel, Inc.]

Interim Look	Number of Patients	Cumulative Alpha Spent	Stopping Boundaries: Reject graft failure ≤0.05	
			≥Number Events	≥Proportion Observed
1	12	0	4	0.29
2	23	0.006	4	0.17
3	35	0.025	5	0.13
Final	46	0.05	5	0.11

5. STUDY AGENTS

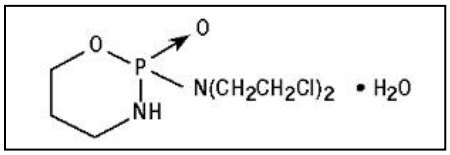
All study agents are FDA-approved for other indications and are commercially available for purchase. Cyclophosphamide and abatacept will be supplied by NYULH pharmacy. Tacrolimus is commercially available and prescribed to subjects to pick up from their pharmacy.

5.1. Cytoxan® (cyclophosphamide) – Bristol-Myers Squibb

5.1.1. Therapeutic Class: nitrogen mustard alkylating agent

5.1.2. Description: Cytoxan® (cyclophosphamide for injection, USP) is a sterile white powder containing cyclophosphamide monohydrate. Cytoxan Tablets (cyclophosphamide tablets, USP) are for oral use and contain 25 mg or 50 mg cyclophosphamide (anhydrous). Inactive ingredients in Cytoxan Tablets are: acacia, FD&C Blue No. 1, D&C Yellow No. 10

Aluminum Lake, lactose, magnesium stearate, starch, stearic acid and talc. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P•H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis (2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



5.1.3. Indications: Treatment of malignant lymphomas, Hodgkin's disease, lymphocytic lymphoma, mixed-cell type or histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia, chronic granulocytic leukemia, acute myelogenous and monocytic leukemia, acute lymphoblastic leukemia in children, mycosis fungoides, neuroblastoma, ovary adenocarcinoma, retinoblastoma, breast carcinoma. Treatment of biopsy proven "minimal change" nephrotic syndrome in children, but not as primary therapy.

5.1.4. Mechanism of Action: Nitrogen mustard alkylating agent; exerts action by cross linking of tumor cell DNA.

5.1.5. Pharmacokinetics:

5.1.5.1. Absorption: Well absorbed; bioavailability (≥75%).

5.1.5.2. Distribution: Plasma protein binding (≥60% as metabolites).

5.1.5.3. Metabolism: Liver; active metabolites.

5.1.5.4. Elimination: Urine (5-25% unchanged); $T_{1/2}$=3-12 hrs.

5.1.6. How Supplied: Inj (Lyophilized): 500mg, 1g, 2g; Tab: 25mg, 50mg

5.1.7. Administration and Storage:

5.1.7.1. Administration: Oral, IV, IM, intraperitoneal, intrapleural route. Inspect drug product visually for particulate matter and discoloration prior to parenteral administration.

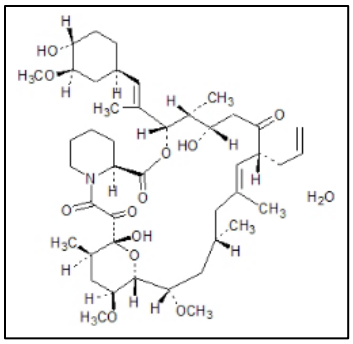
5.1.7.2. Storage: Vial: Below 25°C (77°F). Tab: Below 25°C (77°F); excursions permitted to 30°C (86°F); protect from temperatures above 30°C (86°F).

5.2. Prograf® (tacrolimus) – Astellas

5.2.1. Therapeutic Class: calcineurin-inhibitor

5.2.2. Description: Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a calcineurin-inhibitor immunosuppressant produced by Streptomyces tsukubaensis.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO12•H2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

Prograf is available for oral administration as capsules (tacrolimus capsules USP) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus USP. Inactive ingredients include croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, and magnesium stearate NF. The 0.5 mg capsule shell contains ferric oxide NF, gelatin NF and titanium dioxide USP, the 1 mg capsule shell contains gelatin NF and titanium dioxide USP, and the 5 mg capsule shell contains ferric oxide NF, gelatin NF, and titanium dioxide USP. Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus USP in 1 mL for administration by intravenous infusion only. Each mL contains the following inactive ingredients: dehydrated alcohol USP, 80.0% v/v and polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use. Prograf Granules is available for oral administration as a suspension containing the equivalent of 0.2 mg or 1 mg of anhydrous tacrolimus USP. Inactive ingredients include croscarmellose sodium NF, hypromellose USP, and lactose monohydrate NF.

5.2.3. Indications: Prograf is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants.

5.2.4. Mechanism of Action: Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed, after which the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB). Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

5.2.5. Pharmacokinetics:

5.2.5.1. Absorption: Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17 ± 10% in adult kidney transplant patients (N = 26), 22 ± 6% in adult liver transplant patients (N = 17), 23 ± 9% in adult heart transplant patients (N = 11) and 18 ± 5% in healthy volunteers (N = 16). A single dose trial conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose trial in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg. In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94. In 25 heart transplant patients over a concentration range of 2 to 24 ng/mL, the correlation coefficient was 0.89 after an oral dose of 0.075 or 0.15 mg/kg/day at steady-state. In a healthy volunteer adult study, the systemic exposure to tacrolimus (AUC) for Prograf Granules was approximately 16% higher than that for Prograf capsules when administered as single doses. If pediatric patients are converted between formulations, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Food Effects: The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers. The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively. In healthy volunteers (N = 16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition. In 11 liver transplant patients, Prograf administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27 ± 18%) and C_{max} (50 ± 19%), as compared to a fasted state. Prograf capsules should be taken consistently every day either with or without food because the presence and composition of food decreases the bioavailability of Prograf.

5.2.5.2. Distribution: The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. trial, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

5.2.5.3. Metabolism: Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

5.2.5.4. Elimination: The mean clearance following IV administration of tacrolimus is 0.040, 0.083, 0.053, and 0.051 L/hr/kg in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, and adult heart transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

5.2.6. How Supplied: Intravenous Infusion (Injection): 5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus USP per mL) supplied as a sterile solution in a 1 mL ampule, in boxes of 10 ampules Capsule: 0.5 mg, 1 mg and 5 mg.

5.2.7. Administration and Storage:

5.2.7.1. Administration: Tacrolimus can cause fetal harm. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a polyvinyl chloride (PVC) container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, Prograf injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir). **Storage:** Injection: Store between 5°C and 25°C (41°F and 77°F). Capsule: Store at 20°C to 25 C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

5.3. Orencia® (abatacept) – Bristol-Myers Squibb

5.3.1. Therapeutic Class: selective T cell co-stimulation modulator

5.3.2. Description: is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

5.3.3. Indications: Treatment of adult rheumatoid arthritis (RA), moderately to severely active RA in adults and may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Juvenile idiopathic arthritis, moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older (may be used as monotherapy or concomitantly with methotrexate). Adult psoriatic arthritis (PsA active PsA in adults. Should not be given concomitantly with TNF antagonists.

5.3.4. Mechanism of Action: Abatacept, a selective co-stimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and PsA and are found in the synovium of patients with RA and PsA. In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNFα), interferon-γ, and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon-γ. The relationship of these biological response markers to the mechanisms by which ORENCIA exerts its clinical effects is unknown.

5.3.5. Pharmacokinetics

Healthy Adults and Adult RA: Intravenous Administration: The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions (table below):

Table 5: Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg Intravenous Infusion(s)

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses[a]) n=14
Peak Concentration (C_{max}) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life ($t_{1/2}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

[a] Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple intravenous infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady state by day 60 with a mean (range) trough concentration of 24 mcg/mL (1 to 66 mcg/mL). No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients. Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

Adult RA - Subcutaneous Administration: Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for C_{min} and C_{max} at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration is 78.6%. Mean estimates for systemic clearance (0.28 mL/h/kg) volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration. Study SC-2 was conducted to determine the effect of

monotherapy use of ORENCIA on immunogenicity following subcutaneous administration without an intravenous load. When the intravenous loading dose was not administered, a mean trough concentration of 12.6 mcg/mL was achieved after 2 weeks of dosing. Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance. Juvenile Idiopathic Arthritis - Intravenous Administration: In Study JIA-1 among patients 6 to 17 years of age, the mean (range) steady state serum peak and trough concentrations of abatacept were 217 mcg/mL (57 to 700 mcg/mL) and 11.9 mcg/mL (0.15 to 44.6 mcg/mL). Population pharmacokinetic analyses of the serum concentration data showed that clearance of abatacept increased with baseline body weight. The estimated mean (range) clearance of abatacept in the juvenile idiopathic arthritis patients was 0.4 mL/h/kg (0.20 to 1.12 mL/h/kg). After accounting for the effect of body weight, the clearance of abatacept was not related to age and gender. Concomitant methotrexate, corticosteroids, and NSAIDs were also shown not to influence abatacept clearance. Juvenile Idiopathic Arthritis - Subcutaneous Administration: In Study JIA-2 among patients 2 to 17 years of age, steady state of abatacept was achieved by Day 85 following the weekly body-weight–tiered subcutaneous abatacept dosing. Comparable trough concentrations across weight tiers and age groups were achieved by the body-weight– tiered subcutaneous dosing regimen. The mean (range) trough concentration of abatacept at Day 113 was 44.4 mcg/mL (13.4 to 88.1 mcg/mL), 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in pediatric JIA patients weighing 10 to <25 kg, 25 to <50 kg, and ≥50 kg, respectively. Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in JIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance. Adult Psoriatic Arthritis - Intravenous and Subcutaneous Administration: In Study, PsA-I, a dose ranging study, IV abatacept was administered at 3 mg/kg, 10 mg/kg (weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg), or two doses of 30 mg/kg followed by weight range-based dose of 10 mg/kg. Following monthly IV administration, abatacept showed linear PK over the dose range of 3 mg/kg to 10 mg/kg. At 10 mg/kg, the steady state of abatacept was reached by Day 57 and the geometric mean (CV%) trough concentration (C_{min}) was 24.3 mcg/mL (40.8%) at Day 169. In Study, PsA-II following weekly SC administration of abatacept at 125 mg, the steady state of abatacept was reached at
Day 57 and the geometric mean (CV%) C_{min} was 25.6 mcg/mL (47.7%) at Day 169. Consistent with the RA results, population pharmacokinetic analyses for abatacept in psoriatic arthritis patients revealed that there was a trend toward higher clearance (L/h) of abatacept with increasing body weight. In addition, relative to the RA patients with the same body weight, abatacept clearance in psoriatic arthritis patients was

approximately 8% lower, resulting in higher abatacept exposures in patients with PsA. This slight difference in exposures, however, is not considered to be clinically meaningful.

5.3.6. How Supplied: Intravenous Infusion (Injection): 250 mg lyophilized powder in a single use vial for reconstitution and dilution prior to intravenous infusion. Subcutaneous Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in single-dose prefilled syringes for subcutaneous use or 125 mg/mL solution in a single-dose prefilled ClickJect autoinjector for subcutaneous use.

5.3.7. Administration and Storage:

5.3.7.1. Administration: ORENCIA for Injection is a lyophilized powder for intravenous infusion. ORENCIA for Injection is supplied as a sterile, white, preservative-free, lyophilized powder for reconstitution and dilution prior to intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, USP, the solution of ORENCIA is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of ORENCIA for Injection provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration. ORENCIA Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution with a pH range of 6.8 to 7.4 for subcutaneous administration. ORENCIA Injection is supplied as a single-dose prefilled syringe or as a single-dose ClickJect autoinjector.

5.3.7.2. Storage: ORENCIA lyophilized powder supplied in a vial should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use. ORENCIA solution supplied in a prefilled syringe or ClickJect autoinjector should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date on the prefilled syringe or autoinjector. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe or autoinjector to freeze.

5.4. Study Agent Accountability Procedures:

Cyclophosphamide, abatacept, will be purchased per standard of practice from a commercial source and compounded according to the package insert by the main hospital pharmacy. If any portion of the study drug is not administered, the amount infused will be recorded, the principal investigator notified and unused medications will be returned to the main hospital pharmacy for disposal. Tacrolimus is commercially available and is prescribed to subjects to pick up from their pharmacy. During each visit, the dose used of tacrolimus and any adjustments in dosing are reviewed with the subject and documented in the subject's EMR.

5.5. Product Complaints:

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the PI and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions.

6. REQUIRED STUDY ACTIVITIES (APPENDIX A)

6.1. Recipient Pre-Transplant Work-Up and Eligibility for Transplant: The patient will undergo pre-transplant work-up per standard of care and in timeframes defined by standard operating procedures (SOPs). This will include but is not limited to: history and physical examination, ABO and Rh type, CBC, CMP, PT-INR, PTT, creatinine clearance, high resolution HLA typing (including KIR for patients with myeloid malignancies), infectious disease markers (IDMs), β-HCG serum pregnancy test (females of reproductive capability only – refer to exclusion criteria), chest x-ray (CXR), ECG, pulmonary function tests (PFT) with DLCO, ECHO to measure left ventricular ejection fraction (LVEF), informed consent for transplant, and final medical clearance by their treating physician.

6.2. Donor Work-Up: The donor will also undergo a pre-transplant donor evaluation and eligibility per institutional BMT SOPs (SOP CLNAL003: Related (MRD, Haplo) DONOR Evaluation and Management – Adult and Pediatric). Study procedures will not impact the donor. The attending physician will review all donor eligibility prior to the initiation of the conditioning chemotherapy.

6.3. Pre-Transplant

6.3.1. Work up as outlined in 6.1.

6.3.2. Daily, from Day -7 through day 0: CBC, CMP, liver function tests (LFTs), and a physical exam, including toxicity assessment.

6.4. Post-Transplant

6.4.1. CBC and CMP daily until neutrophil engraftment, then at least weekly until day +100 (+/- 3 days), and at least monthly until day +180 (+/- 7 days).

6.4.2. LFT twice weekly until engraftment, then at least weekly until day +100 (+/- 3 days), and at least monthly until day +180 (+/- 7 days).

6.4.3. Physical examination including toxicity and GvHD assessments daily until discharge, then weekly until day +100 (+/- 3 days), and at least monthly until day +180 (+/- 7 days).

6.4.4. From day +180 until day +730: CBC, CMP, LFTs, and a physical exam including toxicity and GvHD assessments will be done at least every three months (+/- 7 days).

6.4.5. Post-chimerism: at engraftment, then at least monthly until day +180, and every 3 months until day +730 (+/- 7 days).

6.4.6. Immune reconstitution studies will be drawn on day +30, +100, +180, and +365 (+/- 7 days), 10-20mL of blood for CD3, CD4, CD8 and CD19.

7. TREATMENT PLAN

7.1. Conditioning Regimen (Study Schema): Eligible patients will receive one of the following conditioning regimens, all of which are standard of care, on an inpatient basis. The choice of the conditioning regimen is determined by the treating physician, based on host factors and disease nature and status. As described by BMT standard operating policy (procedure) (SOP) CLNTX007: Selection of Conditioning Regimens for Blood and Marrow Transplantation – Adult.

7.1.1. Non-myeloablative conditioning:

7.1.1.1. Fludarabine 30mg/m^2 IV once daily on day -6, -5, -4, -3, and -2.

7.1.1.2. Cyclophosphamide 14.5mg/kg IV once daily on day -6 and -5

7.1.1.3. Total-body irradiation (TBI), 2 grays on day -1.

7.1.1.4. Filgrastim (Neupogen®) will begin on day +7. Filgrastim will be stopped when patients achieve an ANC > 1.5 x 10^9/L on two consecutive days.

7.1.2. Reduced-intensity conditioning:

7.1.2.1. Fludarabine 25 mg/m^2 IV once daily on day -6, -5, -4, -3 and -2.

7.1.2.2. Cyclophosphamide 14.5mg/kg IV once daily on day -3 and -2

7.1.2.3. Busulfan 130 mg/m^2 IV, once daily, on day -6 and -5

7.1.2.4. TBI, 2 grays on day -1.

7.1.2.5. Filgrastim (Neupogen®) will begin on day +7. Filgrastim will be stopped when patients achieve an ANC > 1.5 x 10^9/L on two consecutive days.

7.1.3. TBI-based myeloablative conditioning:

7.1.3.1. Fludarabine 25 mg/m^2 IV once daily on day -7, -6 and -5

7.1.3.2. TBI 150 cGrays bid on day –4, -3, 2 and -1.

7.1.3.3. Filgrastim (Neupogen®) will begin on day +5. Filgrastim will be stopped when patients achieve an ANC > 1.5 x 10^9/L on two consecutive days.

7.1.4. Non TBI-based myeloablative conditioning:

7.1.4.1. Fludarabine 25 mg/m^2 IV once daily on day -6, -5, -4, -3 and -2.

7.1.4.2. Cyclophosphamide 14.5mg/kg IV once daily on day -3 and -2

7.1.4.3. Busulfan 110 mg/m^2 IV, once daily, on day -7, -6 , -5, and -4

7.1.4.4. Filgrastim (Neupogen®) will begin on day +5. Filgrastim will be stopped when patients achieve an ANC > 1.5 x 10^9/L on two consecutive days.

7.2. Graft Infusion: At least 2 x 10^6/kg peripheral blood $CD34^+$ cells (HPC-A) will be infused on day 0 per institutional protocol. The goal is to infuse 4.9 - 9 x 10^6/kg $CD34^+$ cells. Stem cells are collected by apheresis after donor mobilization with 10 µg/kg of filgrastim (G-CSF or Neupogen®) per the National Marrow Donor Program and institutional program practice.

7.3. GvHD Prophylaxis: All patients will investigational GvHD prophylaxis based on a combination of PTCy, abatacept and tacrolimus. No other prophylactic treatment will be given.

7.3.1. Cyclophosphamide 50 mg/kg IV over 1 hour on day +3 and +4 with concomitant hydration. The hydration will be NS with or without 20 mEq/L KCl at 250 mL/hr starting 4 hours before and continuing until 24 hours after the second dose is complete. Furosemide is also given on an as needed basis to maintain fluid balance.

7.3.2. Abatacept 10mg/kg IV over 30 minutes on day +5, +14, and +28.

7.3.3. Tacrolimus 0.02 mg/kg IV by continuous infusion starting on day +5. The drug can be changed to oral route when the patient has adequate oral intake. The target trough level is 5-12 ng/mL. Treatment is continued until day +60 (+/-3) and then tapered over a period of 4 weeks in the absence of GvHD.

7.4. Drug Preparation: The drugs will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. All doses will be based on adjusted body surface area if actual body weight is >125% the ideal body weight.

7.5. Supportive care*:* Steroids will **not** be allowed after graft infusion. All supportive care including anti-emetics, anti-seizure, sinusoidal obstruction syndrome (SOS) prophylaxis, transfusion support, and infection prophylaxis will be administered per established routine institutional SOPs. All deviations must be documented by the principal investigator prior to occurrence.

7.6. Management of acute and chronic GvHD: Patients who develop acute or chronic GvHD will be managed by the treating physician according to his or her standard practice and as defined by BMT SOP CLNAL005: Definition, Prevention, Diagnosis, Grading, and Management of Graft-versus-Host-Disease (GvHD) – Adults.

7.7. Patients will remain on study for follow-up and data collection.

7.8. Ancillary Therapy: Patients will continue to receive any other therapy that the treating physician feels necessary according to the routine program practices. Management of shared toxicities and adverse events associated with cyclophosphamide, abatacept and tacrolimus such as nausea, vomiting, diarrhea, etc. will be routinely managed according to the routine practices.

7.9. Dose adjustments: No dose adjustments are allowed for cyclophosphamide. Abatacept must be discontinued in case of severe life threatening allergic reaction and in case of uncontrolled infection. Abatacept therapy can be resumed once the infection is controlled. Tacrolimus dose will be adjusted to maintain drug level as specified above in 7.3.3. The subject will be withdrawn from the study if, at the discretion of the treating physician:

1. The subject cannot receive the planned treatment with cyclophosphamide.
2. The subject cannot receive at least 1 dose of abatacept.
3. The subject cannot receive at least 4 weeks of tacrolimus.

8. ASSESSMENT OF SAFETY

8.1. Specification of Safety Parameters

Adverse Events (AE) and Serious Adverse Events (SAE) are unexpected toxicities that occur in the transplant setting (i.e. hematologic, gastrointestinal toxicities are expected). The Common Terminology Criteria for Adverse Events, Version 5.0, will be used for assessing the severity of adverse events.

8.1.1. The following will be reported and monitored:

- Grade 3 or higher, non-hematologic toxicity directly related to study drugs (such as peripheral neuropathy).
- Grade 2 or higher hepatic bilirubin.

8.1.2. Time Period and Frequency for Event Assessment and Follow-up

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE). AEs and SAEs will be followed from the start of conditioning regimen to day +60 or until treatment-related adverse events, occurring before day +60 resolve or stabilize.

8.2. Adverse Events (AE):

8.2.1. Definition of Adverse Events (AE)

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, which is unexpected. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.2.2. Reporting an Adverse Event: All adverse events, whether observed by the investigator or reported by the patient, must be recorded with details. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), duration of episode, intensity of episode, action taken with respect to the test drug, time of stabilization and resolution of the event and patient outcome. The investigator must evaluate each adverse event for its relationship to the test drug and for its seriousness. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate report forms. All unexpected AEs occurring while on study must be documented appropriately regardless of relationship.

8.3. Serious Adverse Events (SAE):

8.3.1. Definition of Serious Adverse Events (SAE)

Events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as *non-serious adverse events*.

8.3.2. Reporting a Serious Adverse Event: The Principal Investigator (PI), Dr. A. Samer Al-Homsi, (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the ethical and legal obligations of the principal investigator include both those of a sponsor and those of an investigator.

All SAEs, regardless of expectedness or relationship with any study drug, must be reported to the sponsor-investigator, as soon as possible, but no later than 24 hours of the investigator's observation or awareness of the event.
The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated Problems (UP) will be recorded in the data collection system throughout the study.
Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the overall principal investigator. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 10 working days and to the DSMC/Principal Investigator/Medical Monitor for all fatal or life threatening adverse events within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 10 working days of the IR's receipt of the report of the problem from the investigator.

SAE reporting will begin in conjunction with the date of treatment administration. Any SAEs that the investigator believes may have been caused by a protocol procedure must be reported immediately to the principal investigator, assigned medical monitor, and a notification email sent to NYUPCCsafetyreports@nyulangone.org and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to the principal investigator, assigned medical monitor, and NYUPCCsafetyreports@nyulangone.org whether full information regarding the event is known or not.

Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. For laboratory results, include the laboratory normal ranges.

The Serious Adverse Event Form must also be emailed to the principal investigator, assigned medical monitor and DSMC, and NYUPCCsafetyreports@nyulangone.org within 24-hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

Current contact information shall be maintained at the site within the regulatory binder.

All SAEs will be evaluated by the DSMC. The investigator is responsible for reporting all SAEs to the appropriate IRB and DSMC.

8.4. Overdose:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.5. Other Safety Considerations:

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

8.6. Definition of Unanticipated Problems (UP):

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.7. Classification of an Adverse Event:

8.7.1. Severity of Event

As described, AEs will be graded by criteria established by CTCAE, version 5.0. For AEs not able to be defined by this grading system, the following guidelines will be used to describe severity.

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.7.2. Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must

be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related:** The AE is completely independent of study drug administration, or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.8. Non-serious Adverse Event Collection Reporting:

The collection of non-serious AE information should begin from the start of conditioning regimen. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and to a minimum of day +60 post-transplant.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.9. Expectedness:

The Principal investigator and/or sub-investigator(s) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.10. Reporting of Pregnancy:

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events: If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug(s). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and PI will request this information from the investigator. If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to PI

immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

The pregnancy must be reported immediately to the principal investigator, and the DSMC by emailing: NYUPCCsafetyreports@nyulangone.org. Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication.

8.11. Reporting Procedures - Notifying the IRB:

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULH IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report promptly, but no later than 10 working days:

Researchers are required to submit reports of the following problems promptly but no later than 10 working days from the time the investigator becomes aware of the event:

- Unanticipated problems including adverse events that are unexpected and related and harmful.
  - **Unexpected**: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - **Related to the research procedures**: An event is related to the research procedures if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.
  - **Harmful**: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:

The following events also require prompt reporting to the IRB, though no later than 10 working days:

- Complaint of a research subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol deviations or violations (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- New Information indicating a change to the risks or potential benefits of the

research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

8.12. Reporting Process:

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up and resolution and need for revision to consent form and/or other study documentation). Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.13. Other Reportable events:

Exceptions to the study protocol

Exceptions to the protocol must obtain investigator's IRB approval before they are initiated. Any protocol deviations initiated without the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the investigator's IRB as soon as a possible, but ***no later than 10 working days*** of the protocol deviation.

8.14. Study Halting Rules

8.14.1. Removal of Subjects from Study

8.14.1.1. The investigator will make every reasonable effort to keep each subject in the study until all planned treatments and assessments have been performed. Unplanned discontinuation may occur for any of the following reasons:

- Subject develops allergy to either study drug.
- Treating physician feels that continuation in study is not appropriate. Such a determination may be made if the subject experiences adverse events related to the study protocol of ≥ grade 3 other than hematologic or infection-related toxicity that the physician or PI determines the study is no longer in the subject's best interest. See also 7.9.
- Subject withdraws informed consent.
- Subject is not meeting the follow up requirements

8.14.1.2. If subjects fail to complete the study treatment, alternative GVHD prophylaxis will be instituted immediately at the discretion of the treating physician.

8.14.1.3. The PI can decide to replace subjects withdrawn from the study at his discretion. All subjects who receive cyclophosphamide, at least 1 dose of abatacept and 1 month of tacrolimus, will be evaluated (see 7.9). The study will enroll subjects for a total of 46 evaluable subjects, expected to be accrued over up to four years.

8.14.1.4. Premature Closure of Study: This study may be prematurely terminated, if in the opinion of the sponsor-investigator, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the

terminating party. Circumstances that may warrant termination include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects,
- Failure to enter subjects at an acceptable rate,
- Failure Insufficient adherence to protocol requirements,
- Insufficient complete or evaluable data,
- Plans to modify, suspend, or discontinue the development of the drug.

8.15. Safety Oversight:

All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported to the principal investigator, the medical monitor and the DSMC via email: NYUPCCsafetyreports@nyulangone.org and reviewed within 48 hours by the medical monitor. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate.
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information.
- The committee may request a cumulative review of all SAEs on the study to date. Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next scheduled study review.

9. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of adverse events via email initially, and then reviewed at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.1. Data Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2017 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians,

nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYULH Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this Phase II trial will be monitored by DSMC *quarterly* (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: patient listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications, adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a recommendation is made, if further action is required, the Investigator's must respond within the timeframe specified by the DSMC.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size:

The primary outcome variable for this study is the incidence of grades II-IV acute GvHD. We assume that the rate of grade II-IV acute GvHD, with the standard of care is 50% [21-23], as reported in the literature and 30% in the experimental group. Based on a 2-stage optimal Simon design, we can detect a reduction in the grade II–IV acute GvHD incidence to 30% for high-dose post-transplant cyclophosphamide, abatacept and tacrolimus with alpha = 0.05 and power of 82% at the conclusion of the 2-stage design with 46 patients. The trial would stop for futility at the end of the first stage if 9 or more patients have grade II-IV acute GVHD, of the 22 patients enrolled. Otherwise, the trial will continue to the second stage with the total 46 patients enrolled. If the total number of patients with grade II-IV acute GVHD is 19 or greater at the end of stage II, the regimen will not be considered for further study. The rate of grade II-IV acute GVHD will be estimated at the end of the trial with exact 95% Clopper Pearson confidence intervals. If the observed rate is 30%, this exact confidence interval with 46 patients, the corresponding confidence interval will be 17.4% to 45.3%. Calculations from PASS 2019, NCSS, J. Hintze, Kaysville, Ut.

Additional monitoring rules are provided above for excess transplant related mortality and for excess drug related toxicity or graft failure. Each of these two rules incorporate 3 interim safety evaluations and one final safety evaluation at the completion of the trial.

The study will be stopped for safety at any one of these interim safety evaluations should the criteria for either endpoint be reached without adjustment for the two parallel analyses.

All participants that receive post-transplant cyclophosphamide and at least 1 dose of abatacept and 1 month of tacrolimus will be included in interim safety evaluations.

10.2. Statistical Analysis:

Baseline Descriptive Statistics: Patient characteristics will be summarized using descriptive statistics. For qualitative characteristics (such as gender, co-morbid conditions, donor source, CMV status amongst others) proportions and frequency distributions will be provided. For quantitative characteristics including hematologic parameters, summary and graphical displays will be provided

10.3. Analysis of the Primary Efficacy Endpoint(s):

10.3.1. Grades II-IV Acute GvHD: The first day of grades II-IV acute GvHD will be recorded for that grade. This end point will be evaluated through day +120 post-transplant. The diagnosis of acute GvHD is based on clinical and pathological evaluation by the principal investigator in collaboration with the treating physician. The acute GvHD grading system is described in appendix B. All participants that received a transplant and received cyclophosphamide, and at least 1 dose of abatacept and a month of tacrolimus will be included in the analysis. Cumulative incidence curves will be provided along with 95% confidence intervals for the 120 day cumulative incidence.

10.4. Analysis of the Secondary Endpoint(s):

All analyses of secondary endpoints will be based on cumulative incidence curves of Kaplan Meier curves to estimate the rates of occurrence as defined for each endpoint.

10.4.1. Chronic GvHD: The first day of chronic GvHD will be used to calculate the cumulative incidence of chronic GvHD. This end point will be evaluated through day +365 post-transplant. The diagnosis of chronic GvHD is based on clinical and pathological evaluation by the principal investigator in collaboration with the treating physician. The chronic GvHD system is described in appendix C. The analysis will be based on the maximum grade of chronic GvHD. All participants that completed transplant and any prophylactic treatment will be included in the analysis. An additional analysis will be carried out for all patients that received a transplant and completed prophylactic treatment with evaluation from date of completion of prophylactic treatment. Cumulative incidence curves will be provided along with 95% confidence intervals for the day 365 cumulative incidence. Additional descriptive analyses will be provided for any GvHD TRM

10.4.2. Primary graft failure is evaluated to day +45 and incidence of graft failure will be calculated from date of transplant to failure for all patients who receive a transplant and any prophylactic treatment and from date of completion of prophylactic treatment for all participants that completed treatment.

10.4.3. Poor graft function is evaluated to day +30 incidence of poor graft function will be calculated, from date of transplant to failure for all patients who receive a transplant and any prophylactic treatment and from date of completion of prophylactic treatment for all participants that completed treatment.

10.4.4. Secondary graft failure is evaluated after engraftment is achieved will be calculated from date of engraftment for all patients with engraftment.

10.4.5. TRM will be analyzed based on participants that who received a transplant with any prophylactic treatment and for all patients who received a transplant and completed prophylactic treatment.

10.4.6. RR is evaluated to day +730 and will be analyzed for all patients who received a transplant and for all transplanted patients that completed treatment.

10.4.7. GRFS is evaluated to day +730 and considers as successes participants that are without reported GvHD III-IV acute GvHD, chronic GvHD requiring systemic therapy and have not experienced relapse or death after transplant.

10.4.8. OS is evaluated to day +730 and considers all participants who received a transplant and for all transplanted patients who completed prophylactic treatment as described above.

10.5. Missing Data:

Distribution of patients and disease characteristics will be summarized for patients with missing data regarding key endpoints or who are non-compliant. Comparisons will be made to patients who complete the study to evaluate bias.

10.6. Safety Analyses:

All adverse events (expected and unexpected) will be tracked and graded per CTCAE, version 5.0 over time. In addition, the attributed relationship to study drug will be summarized. All adverse events will be reviewed by the primary investigator, in conjunction with the sub-investigators to determine safety.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA AND DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance (QA) specialists will provide extensive monitoring including real-time review of all eCRFs to ensure completeness and compliance with the protocol. A first subject audit is to be conducted within four weeks of enrollment.

Source documentation should be consistent with data entered into any electronic medical record or TrialMaster. Relevant source documentation to be reviewed by the QA specialists throughout the study includes but are not limited to:

1. Baseline measures to assess pre-transplant status
2. Treatment records
3. Adverse events

12. QUALITY ASSURANCE AND QUALITY CONTROL

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.) as necessary. A risk-based, data-driven monitoring approach will be used to verify data for this trial, which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will regularly review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO of any audit requests by health authorities, and will provide the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

In addition, the quality assurance unit will conduct monitoring of this trial every 4-6 weeks; this includes real-time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Good Clinical Practice:

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s).[85] The investigator will be thoroughly familiar with the appropriate use of the study drugs as described in the protocol and Investigator's Brochures. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

13.1.1. Ethical Considerations: The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

13.1.2. Protocol Compliance: The investigator will conduct the study in compliance with the protocol, and given approval by the IRB, and the appropriate regulatory authorities. Any departures from the protocol must be fully documented in the source documents.

13.2. Patient Information and Informed Consent:

After the study has been fully explained, written informed consent will be obtained from the patient. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). Informed

consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULH PCC CTO.

13.2.1. Informed Consent: Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions the patient may have. The investigator will ask the patient questions to ensure that the patient understands the study. If the investigator determines the subject understands the study, the patient will mark an X where the patient name would go and the witness will sign the consent form.

13.2.2. Documentation of Consent: The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

13.2.3. Posting of Clinical Trial Consent: The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject, as required by the protocol. Per Institutional guidelines, SOP#: HSR-601, instructs the principal investigator on registration and results reporting on clinicaltrials.gov.

13.2.4. Participant and Data Confidentiality: In order to maintain participant privacy, all information obtained in connection with this study which identifies the participant will remain confidential in accordance with state and federal law.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities:

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster, a 21 CFR Part 11-compliant data capture system provided by DataCore. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Investigational product records are maintained by the NYU Langone Health Pharmacy. Cyclophosphamide and abatacept are provided by the NYU Langone Health pharmacy, however, Tacrolimus is commercially available and is prescribed to subjects to pick up from their pharmacy. All prescription records are maintained in subject's EMR.

14.2. Study Records Retention:

The sponsor-investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

14.3. Protocol Deviations:

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the

participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI and study staff is responsible for knowing and adhering to their IRB requirements. All protocol deviations must be addressed in study source documents and reported to IRB Program Official at the time of annual continuing review. If a protocol deviation is determined to be reportable new information, the IRB will be notified immediately.

14.4. Publication and Data Sharing Policy:

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

Study results may be published, and participants may access the results of this study via clinicaltrails.gov or any published media. However, no results will be sent directly to subjects. The study will be available on clinicaltrials.gov.

15. STUDY FINANCES

15.1. Funding Source:

All study elements are standard of care and will be billed to third parties. The data management cost will be covered by the Disease Management Group (DMG).

15.2. Costs to the Participant:

All aspects of care, including conditioning regimen and GvHD prevention is considered standard of care and will be billed to the insurance company or participant.

15.3. Participant Reimbursements or Payments:

No subject will receive payments or stipends for participation in this research study.

16. CONFLICT OF INTEREST POLICY

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan prior to participation in this study. All NYULH investigators will follow the applicable University conflict of interest policies.

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18. APPENDICES

18.1. Appendix A: Required Study Activities
18.2. Appendix B: Acute Graft-Versus-Host Disease Assessment (aGVHD)
18.3. Appendix C: Chronic Graft-Versus-Host Disease Assessment (cGVHD)
18.4. Appendix D: New York Heart Association (NYHA) Classification of Cardiac Disease

18.1 APPENDIX A: REQUIRED STUDY ACTIVITIES

Activity	Pre-Study[1]	Day -7 to Day -1[2]	Day 0	Day +3	Day +4	Day +5	Day +14	Day +28	Daily until Neutrophil Engraftment	Daily until discharge	Twice a week until Engraftment	Weekly until Day +100 (+/- 3 days)	Monthly until Day +180 (+/- 7 days)	Every 3 months until Day+730 (2 years) (+/- 7days)
Study team procedures														
Consent	X													
Medical History	X													
Physical Exam	X	X	X						X	X		X	X	X
KPS	X											X	X	X
Height	X													
Weight	X	X												
Vital Signs	X	X							X	X		X	X	X
Cychlophophamide[3]				X	X									
Tacrolius[4]						X								
Abatacept[5]						X	X	X						
Toxicity Assessment		X	X						X	X		X	X	X
GVHD Assessment									X	X		X	X	X
Chimerism[6]									X				X	X
Immune Reconstitution Samples[7]														
Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
CBC,CMP	X	X	X						X			X	X	X
LFTs		X	X								X	X	X	X

[1]Pre-transplant: per standard of care
[2]Pre-tranplant: collect CBC, CMP, liver function tests, and physical exam, including toxicity assessments
[3] Cyclophosphamide administered Day +3 and Day +4
[4] Tacrolimus initiated on Day +5
[5] Abatacept given on Day +5, +14, +28
[6] Post-chimerism: at neutrophil engraftment, then at least monthly (+/- 7 days) until day +180, and every 3 months (+/- 7 days) until day +730.
[7]Blood samples for immune reconstitution will be collected on day +30, +100, +180, and +365 (+/- 7 days) after transplant.

18.2 APPENDIX B: ACUTE GRAFT VERSUS HOST DISEASE ASSESSMENT (aGvHD)

Clinical staging of aGVHD			
Stage	**Skin**	**Liver (bilirubin)**	**Gastro-intestinal tract**
0	No rash	< 2.0 mg/dL	No persistent nausea, vomiting or anorexia. Diarrhea ≤ 500 ml/day
1	Maculopapular rash < 25% of body surface	2.0-3.0 mg/dL	Persistent nausea, vomiting or anorexia. Diarrhea 501-1000 ml/day with biopsy proof.
2	Maculopapular rash 25-50% body surface	3.1 – 6.0 mg/dL	Diarrhea 1001-1500 ml/day
3	Generalized erythroderma	6.1 – 15 mg/d	Diarrhea > 1500 ml/day
4	Generalized erythro-derma with blister or bullous formation and desquamation	>15 mg/dL	Severe abdominal pain without or with

Overall Grade aGvHD			
	Skin	**Liver**	**Gut**
0 none	0	0	0
1 mild	1-2	0	0
2 moderate	1-3	1	1
3 severe	2-3	2-3	2-3
4 life threatening	2-4	2-4	2-4

18.3 APPENDIX C: CHRONIC GRAFT VERSUS HOST DISEASE ASSESSMENT (cGVHD)

The involved organs are scored as follows:

KPS: Karnofsky's performance status. BSA: body surface area. GI: gastrointestinal. LFT: liver function tests. AP: alkaline phosphatase. SOB: shortness of breath. LFS: lung function score (FEV1 and DLCO are converted into numeric scores and added to each other to get the LFS: > 80% = 1, 70-79% = 2, 60-69% = 3, 50-59% = 4, 40-49% 5, < 40% 6). ADL: activities of daily life.

	Score			
Organ	**0**	**1**	**2**	**3**
KPS	100%	80-90%	60-70%	< 60%
Skin	No symptoms	< 18% BSA	19-50% BSA or sclerotic features but able to pinch	> 50% BSA or sclerotic changes and unable to pinch or with impaired mobility
Mouth	No symptoms	Not limiting oral intake significantly	Limiting oral intake partially	Limiting oral intake severely
Eyes	No symptoms	Dryness, requiring eye-drops ≤ 3/day or asymptomatic keratoconjunctivitis sicca (KCS)	Dryness, requiring eye-drops > 3/day without visual impairment	Unable to work because of ocular symptoms or vision loss
GI tract	No symptoms	< 5% weight loss	5-15% weight loss	> 15% weight loss requiring calorie supplements or esophageal dilation
Liver	Normal LFT	Elevated bilirubin, AP, AST, or ALT < 2 X normal	Elevated bilirubin, AP, AST, or ALT 2-5 X normal	Elevated bilirubin, AP, AST, or ALT 5 X normal
Lungs	No symptoms, FEV1 > 80% or LFS 2	SOB after 1 flight of steps FEV1 60-70% or LFS 3-6	SOB walking flat, FEV1 40-59% or LFS 6-9	SOB at rest or requiring O_2, FEV1 ≤ 39% or LFS 10-12
Joints and fascia	No symptoms	Mild decrease in range of motion not affection ADL	Moderate decrease in range of motion with moderate impairment of ADL	Significant de-crease in range of motion with significant impairment of ADL
Genital tract	No symptoms	Symptoms and with mild signs on exam and no effect on coitus	Symptoms and with moderate signs on exam with discomfort on coitus	Symptoms and with advanced signs on exam such as strictures or ulcerations with severe pain on coitus

The following is checked and scored (0-3) as applicable:

Esophageal stricture or web
Pleural effusions
Pericardial effusion
Ascites
Platelets < 100 109/L
Eosinophils > 0.5 109/L
Peripheral neuropathy
Polymyositis
Myasthenia gravis
Coronary artery disease
Cardiac conduction defects
Cardiomyopathy

Based on the organ scoring the severity of cGVHD is defined as follows:
Mild cGVHD: involvement of 1-2 organs with maximum scores of 1 in all affected organs or sites.
Moderate cGVHD: 1. involvement of 1-2 organ involvement with a maximum score of 2 in any affected organ or site (except for lungs). 2. involvement of 3 or more organs with maximum score of 1 in all affected organs or sites.
Severe cGVHD: a lung score of 2 or a score 3 in any organ or site.

18.4 APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.