Official Protocol Title:	A Randomized, Double blind, Placebo-controlled, Multi-center, Phase III Study of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation
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A Randomized, Double blind, Placebo-controlled, Multi-center, Phase III Study of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation

Short name: CD24Fc Administration for Prevention of Acute GVHD in Myeloablative HSCT (CATHY)

Protocol Number: CD24Fc-005

Posted on ClinicalTrials.gov as NCT04095858.

Sponsor: **OncoImmune, Inc.**
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1 SYNOPSIS

A Randomized, Double-blind, Placebo-controlled, Multi-Center, Phase III Study of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplant (CATHY)

Principal Investigator:	John Magenau, MD
Study Design:	The study is designed as a randomized, placebo-controlled, double blind, multicenter, Phase III trial comparing two acute graft-versus-host disease (aGVHD) prophylaxis regimens: CD24Fc/tacrolimus/methotrexate (CD24Fc/Tac/MTX) versus placebo/tacrolimus/methotrexate (placebo/Tac/MTX) in the setting of myeloablative conditioning (MAC), matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplantation in patients with acute leukemia (AML/ALL).
Primary Objective:	To establish the efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT.
Secondary Objectives:	To improve the relapse free survival (RFS) and overall survival (OS) in leukemia patients after allogeneic HCT through (1) reduction of the myeloablative conditioning toxicity; (2) reduction of severe acute GVHD; and (3) reduction of relapse.
Primary Endpoint:	180 day grade III-IV acute GVHD free survival (aGFS), event defined as the earlier time of GVHD or death within 180 days of HCT.
Secondary Endpoints:	Disease Free Survival (DFS), event defined as the earlier time of leukemia relapse or death after HCT. Overall Survival (OS), event defined as time of all-cause mortality after HCT. 180 day grade II-IV acute GVHD free survival (aGFS), the earlier time of event defined as Grade II-IV GVHD or death within 180 days of HCT. 180 day grade III-IV acute GVHD relapse-free survival (aGRFS), the earlier time of event defined as GVHD, relapse or death within 180 days of HCT.
Eligibility Criteria:	Eligible patients are at least 18 years of age undergoing allogeneic HCT (bone marrow or PBSC) for the treatment of AML/ALL with less than 5% blasts in the bone marrow. Patients will undergo myeloablative conditioning regimens.

	Patients must have a matched unrelated donor. Unrelated donor must be an 8/8 match at HLA-A, -B, -C, and -DRB1 at high resolution using DNA-based typing; must be willing to donate BM or PBSCs; and be medically eligible to donate stem cells according to NMDP criteria.
Treatment Description:	The study will be randomized and double blind. Patients will be randomized 1:1 to receive one of the following GVHD prophylaxis regimens: Arm A: CD24Fc/Tac/MTX, Arm B: placebo/Tac/MTX, CD24Fc or placebo will be given at the dose level of 480mg, 240mg and 240mg on Day -1, +14 and +28. MTX will be dosed at 15 mg/m^2 Day +1, and 10 mg/m^2 Days +3, +6, and +11. Tacrolimus will begin on day -3. For intravenous dosing the recommended starting dose is 0.03 mg/kg/day based on adjusted body weight as a continuous infusion. For oral dosing the recommended starting dose is 0.045 mg/kg/dose twice daily. In the absence of GVHD or relapse, it is recommended that tacrolimus tapering begin on day +100 post-transplant.
Accrual Objective:	The clinical trial will enroll 180 patients, or 90 per arm.
Accrual Period:	The estimated accrual period is 24 months.
Study Duration:	Patients will be followed for 180 days for primary endpoint, and 1 year for other secondary and exploratory endpoints.
Interim Analysis:	The study will include one interim analysis for efficacy and futility, for the primary endpoint at the time when the required number of events is reached. A sample size re-estimation will also be conducted at this interim analysis.
Data Monitoring Committee:	The DMC consists of experts outside of the Sponsor will be responsible for the planned interim analyses.

FIGURE 1: STUDY DIAGRAM

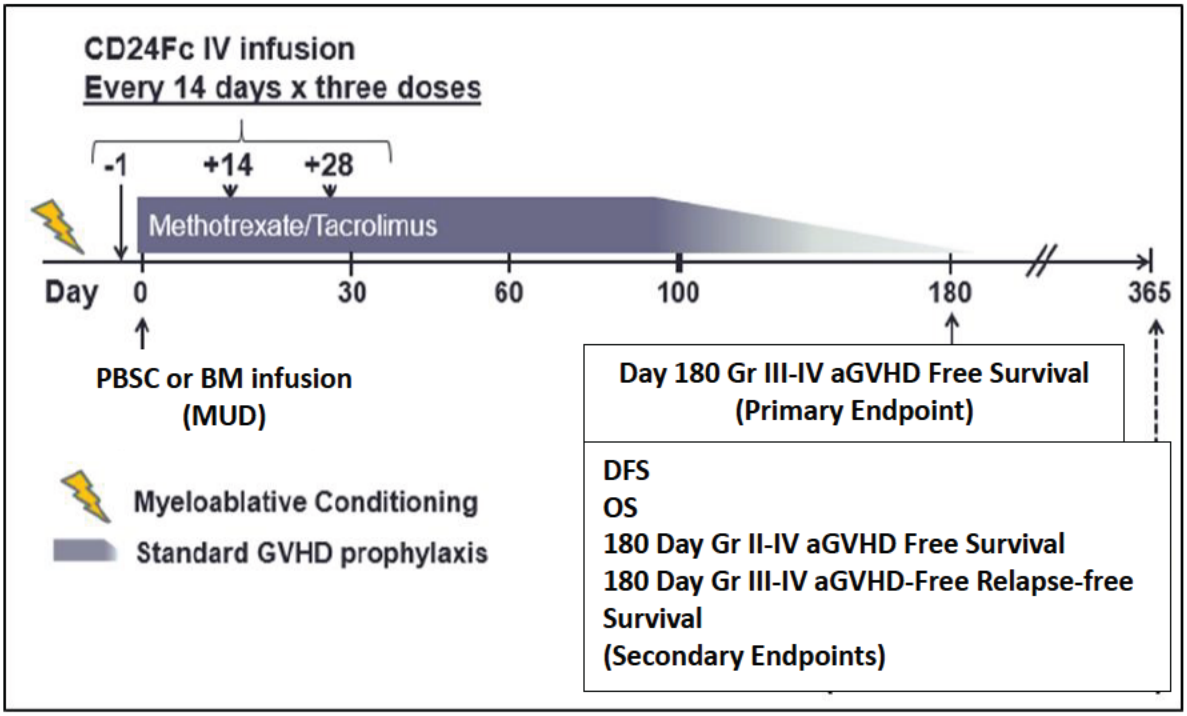

FIGURE 2: RANDOMIZATION

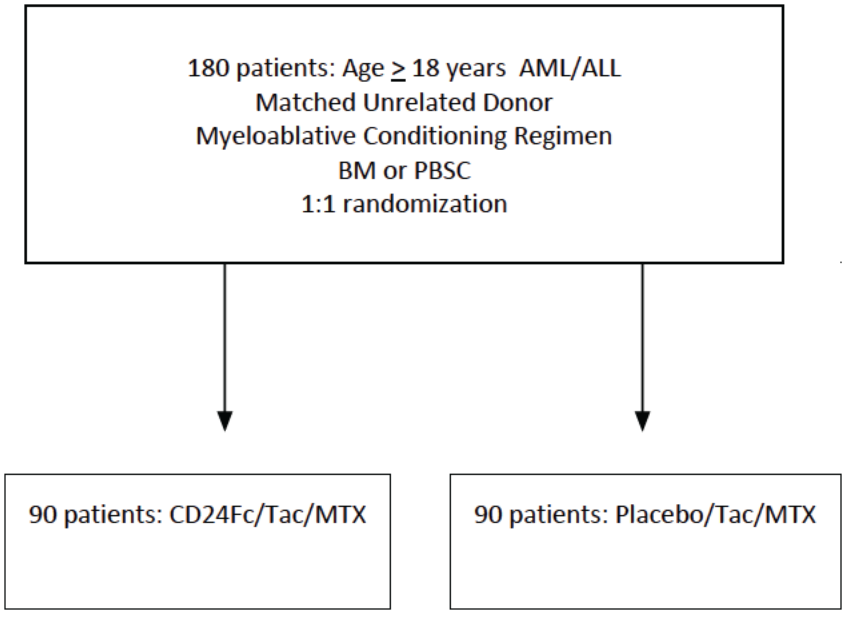

TABLE 1: STUDY CALENDAR FOR PHASE III STUDY

	PRE-HCT	PRE-HCT			POST-HCT				
Observations	Day -28 to -2 (Screening and Randomization)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 4)	+ 28 (± 4)	Weekly from + 0 to +100 (± 3)
Informed Consent	x								
Medical History and Examination	x	x			x	x	x	x	x
Pre-HCT organ function and infectious disease testing[1]	x								
Pregnancy test (if applicable)	x								
Karnofsky Performance Status	x	x							
Laboratory testing[2]	x	x				x	x	x	
ECG monitoring[3]		x		x			x	x	
CD24Fc (Study Agent) [4]			x				x	x	
Hematopoietic Stem Cell Transplant (HCT)					x				
Vital Sign monitoring[5]		x		x			x	x	
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
AE Assessment (NCI CTCAE V5.0)				x	x	x	x	x	x
Assess Engraftment								x	
Bone marrow aspirate & biopsy[7]	x								
Chimerism									
Fasting Lipid Panel including LDL		x					x		
Survival Follow-Up									

TABLE 1 (CONT): STUDY CALENDAR FOR PHASE III STUDY CONTINUED.

	FOLLOW-UP PERIOD					SURVIVAL FOLLOW-UP[8]
Observations	+ 100 (± 7)	Monthly from +100 to +180 (± 7)	+270 (± 14)	+365 (± 14)	GVHD Onset (± 3)	Every 6 months post +365 (± 3 months)
Informed Consent						
Medical History and Examination	x	x	x	x	x	
Pre-HCT organ function and infectious disease testing[1]						
Pregnancy test (if applicable)						
Karnofsky Performance Status						
Laboratory testing[2]	x	x				
ECG monitoring[3]						
CD24Fc (Study Agent)[4]						
Vital Sign monitoring[5]						
Acute GVHD assessment[6]	x	x			x	
Chronic GVHD assessment	x	x	x	x		
Concomitant Medications	x				x	
AE Assessment (NCI CTCAE V5.0)	x	x				
Assess Engraftment						
Bone marrow aspirate & biopsy[7]						
Chimerism	x					
Fasting Lipid Panel including LDL						
Survival Follow-Up						x

NOTE: **Pre and Post-transplant observations. Patient condition and scheduling issues may impact the time of post-HCT observations. The acceptable time frame for completing these observations is ± 3 days through day 60, ± 5 days for observations from day 61 until day 100, and ± 7 to 14 days for observations from day 100 to day 365.**

1) Per institution practice guidelines: Recipient organ function testing will include MUGA or Echocardiography, Electrocardiogram, and Pulmonary Function Testing. Donor safety and eligibility assessments and screening for infectious disease markers will be performed according to national marrow donor program (NMDP) guidelines. These include but are not limited to screening for HIV, Hepatitis B and C, HTLV I/II, HSV antibody, Trypanosoma cruzi, west nile virus, syphilis and CMV. The organ function testing may be collected up to 10 weeks prior to enrollment.
2) Laboratory tests include CBC with differential, serum chemistries with creatinine, AST, ALT, and total bilirubin in pre-HCT period. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin will be performed at a minimum on the day of CD24Fc infusion and three times weekly from day 0 until ANC > 500/ul, while hospitalized for HCT. Tacrolimus levels will be monitored per institution clinical practice guidelines. Laboratory testing may be more frequent per standard HCT practice.
3) ECG monitoring will be performed on treatment days (Day -1, Day 14 and Day 28). The ECG should be measured within four hours of the start of study drug infusion and 2 hours ± 15 min after the start of infusion.
4) Per protocol, CD24Fc will be administered on day -1, day 14± 4 and day 28± 4. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Vital signs will be recorded prior to infusion and after CD24Fc infusion (+/- 30 min).
6) Assessment for acute GVHD will occur weekly through day 100. The weekly visits and the follow up visits can be done through telemedicine to decrease the exposure risk of COVID-19. Following day 100 acute and chronic GVHD assessments will occur monthly. The follow up visits can be done through telemedicine in case of COVID-19. MAGIC acute GVHD grading will be used to report disease severity (APPENDIX C). NIH Consensus chronic GVHD grading will be used to report chronic GVHD (APPENDIX F).
7) The Pre-HCT bone marrow biopsy may be assessed up to 6 weeks prior to enrollment.
8) The follow up of relapse and survival will be up to 3 years after HCT. If a subject withdraws from the study and does not consent to continued follow-up of associated clinical outcome information, a public records search can be performed for survival.

CD24Fc-005 PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document may be signed and dated electronically through submission and approval by the Principal Investigator at institutional IRB Electronic Research Integrity and Compliance Administration (ERICA) system or be signed and dated with a hand-written signature on this signature page.

Instructions to multi-site Principal Investigators:

Return the electronically signed and dated or scanned hand-written signed and dated copy to OncoImmune Research Compliance Office at PPD Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

_____

Name of Institution

_____ _____ _____

Sponsor Representative **Printed Name** **Date**

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2 STUDY OBJECTIVES

The primary goal of the Phase III CATHY study is to confirm the safety and efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT. The CATHY study is a Phase III randomized, double blind, placebo-controlled, multi-center trial comparing CD24Fc vs placebo with standard Tac/MTX acute GVHD prophylaxis in patients with controlled AML/ALL receiving a matched unrelated donor allogeneic HCT after a myeloablative conditioning regimen.

2.1 PRIMARY OBJECTIVES

- To establish the efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT.

2.2 SECONDARY OBJECTIVES

- To improve the relapse free survival (RFS) and overall survival (OS) in patients with AML/ALL after allogeneic HCT through (1) reduction of the myeloablative conditioning toxicity; (2) reduction of severe acute GVHD; and (3) reduction of relapse.

2.3 PHASE III CATHY STUDY ENDPOINTS

2.3.1 Primary Efficacy Endpoint

- 180 day grade III-IV acute GVHD free survival (aGFS), event defined as time of GVHD or death within 180 days of HCT.

2.3.2 Secondary Efficacy Endpoints

- Disease Free Survival (DFS), event defined as the earlier of time of leukemia relapse or death after HCT.
- Overall Survival (OS), event defined as time of all-cause mortality after HCT.
- 180 day grade II-IV acute GVHD free survival (aGFS), the earlier time of event defined as Grade II-IV GVHD or death within 180 days of HCT.
- 180 day grade III-IV acute GVHD relapse-free survival (aGRFS), the earlier time of event defined as GVHD, relapse or death within 180 days of HCT.

2.3.3 Other Exploratory Evaluations

- To describe incidence of chronic GVHD at one year.
- To describe incidence of relapse at one year.
- To describe incidence of non-relapse mortality (NRM) at one year.
- To describe incidence and rate of infection at day 100.
- To describe incidence of Grade 3-4 oral mucositis at Day 28 or when patient is discharged, whichever comes first.
- To estimate the OS and DFS at 3 year.

3 BACKGROUND AND SIGNIFICANCE

3.1 IMPORTANCE OF IMPROVING GVHD PREVENTION

Allogeneic HCT is an expanding therapeutic modality for a growing number of malignant and non-malignant conditions. Each year allogeneic HCT is performed in greater than 21,000 patients worldwide as a potentially curative option for hematologic diseases.[1] However, its success is limited by transplantation related mortality (TRM), particularly when utilizing unrelated or non-HLA matched donors. Acute GVHD is the most frequent life threatening complication after HCT and often contributes to mortality related to infection.[2, 3] Because GVHD is the principle contributor to TRM, it poses a fundamental barrier to improving outcomes after HCT.[4, 5]

For over 20 years, the combination of a calcineurin inhibitor (e.g. cyclosporine and tacrolimus) with methotrexate has remained the standard of care for the prevention of GVHD.[2] Despite routine administration of immune prophylaxis, clinically significant GVHD (Grade II-IV) occurs in approximately 50 to 80% of patients receiving unrelated donor HCT.[6-10]

Several recent single center or large CIBMTR data analyses suggest that moderate, Grade II severity, which comprises the majority of acute GVHD events, may have less demonstrable effects on overall survival [11, 12]. Nonetheless, in patients with very severe Grade III-IV GVHD (Figure 3), mortality rates are 50-90%.[4, 13, 14] One explanation for this is that, once grade III-IV GVHD is established, ineffective responses occur to front-line therapy with high dose corticosteroids in greater than 50% of patients.[15] Survival is significantly diminished for patients who demonstrate steroid refractoriness or who require prolonged treatment.[14, 16, 17] Even when successful, high doses of corticosteroids are a major source of morbidity due to increased infections and deconditioning that places patients at significant risk for TRM.[18, 19] These factors highlight the importance of improving our current approaches for the prevention of grade III-IV acute GVHD.[13-15]

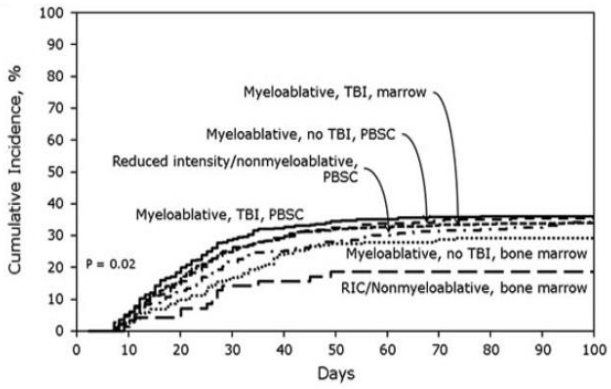

FIGURE 3: INCIDENCE OF GRADE III-IV ACUTE GVHD FOLLOWING UNRELATED DONORS HCT
(as reported by CIBMTR; Jagasia et al: Blood 2012, 119: 296-307).

3.2 PATHOGENESIS OF GVHD

Acute GVHD results from immunologically-mediated injury to host tissues.[20] Experimental data have shown that GVHD stems from allogeneic donor lymphocytes responding to host tissues that express polymorphic human leukocyte antigens,[10] that culminate in clinical manifestations, namely inflammatory responses that primarily involve the skin, intestine, and liver. These events are driven by interactions between antigen presenting cells (APCs), specifically dendritic cells that activate donor T cells.[21-23] The subsequent immunologic cascade results in the release of pro-inflammatory cytokines and expansion of antigen specific allo-reactive T cells that target host tissues. A key inciting event is believed to be direct tissue damage from pre HCT conditioning regimens,[24, 25] which are routinely employed for immune-ablation of host immunity and control of primary malignancy. Unfortunately, conditioning therapy also causes broad tissue injurious effects that result in the release of pro-inflammatory cytokines, and damage-associated molecular patterns (DAMPs) capable of initiating and propagating the inflammatory cascade of GVHD (Figure 4).

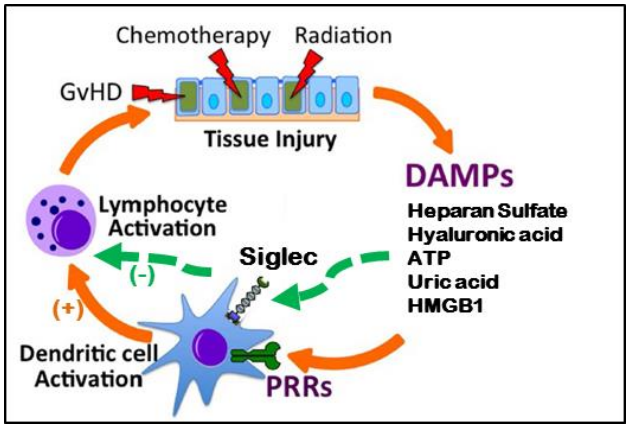

FIGURE 4: TISSUE INJURY AFTER ALLO-HCT. DAMAGE-ASSOCIATED MOLECULAR PATTERNS (DAMPS) INTERACT WITH PATTERN RECOGNITION RECEPTORS (PRRS) TO PROMOTE APC (DENDRITIC CELL) ACTIVATION (+) THAT ACTIVATES DONOR LYMPHOCYTES THAT RESULT IN GVHD. INTERACTIONS OF DAMPS WITH SIGLECS CAN PROMOTE NEGATIVE REGULATION (-) CAPABLE OF OVERCOMING PRR MEDIATED ACTIVATION. ATP, ADENOSINE TRIPHOSPHATE; HMGB1, HIGH-MOBILITY GROUP BOX 1 PROTEIN. (ADAPTED FROM BRENNEN ET AL. FRONT. IMM. 6(101): 1-9)

3.3 CURRENT THERAPEUTIC APPROACHES FOR GVHD

To date, treatment and prevention of GVHD has predominantly focused on either pharmacologic inhibition[2, 26] or depletion of T cells through *in vitro*[27] or *in vivo* approaches to limit expansion of alloreactive T cells that mediate tissue injury.[28] While non-selective T-cell depleting strategies (e.g. anti-thymocyte globulin (ATG)) are efficacious in preventing GVHD, they do not improve survival due to offsetting risks for relapse, infection and graft rejection.[19, 29, 30] A recent prospective, randomized, double-blind, placebo controlled, Phase III clinical trial comparing adding ATG to standard GVHD prophylaxis showed that although ATG reduced the incidence of Grade II-IV acute GVHD and chronic GVHD, ATG may have an overall negative impact on neutrophil and platelet engraftment, increased rates of CMV reactivation, as well as significantly reduced overall survival and relapse free survival [31]. Conversely, more selective inhibition by targeting single pro-inflammatory cytokines to prevent GVHD has not demonstrated clinical benefit on overall survival and relapse free survival [32, 33] [34, 35].

3.4 ROLE OF SIGLEC-G IN APC MEDIATED RESPONSE TO TISSUE INJURY

We and others have demonstrated a critical role of host APCs in the induction of experimental GVHD.[21-23, 36, 37] Through highly conserved toll-like receptors (TLRs) and other pattern recognition receptors (PRRs), APCs acutely sense endogenous "danger" signals from DAMPs such as HMGB1 and heat-shock proteins released during tissue damage.[38] Mounting experimental evidence now recognizes innate immune activation via DAMPs as a key initiating, step in promoting allogeneic T cell responses that drive GVHD.[39-41] These findings suggest that targeting APC responses to DAMPs might be exploited as a novel approach to GVHD prevention and therapy. To limit their activating responses to DAMPs, murine APCs express Sialic-acid–binding immunoglobulin-like lectin-G (Siglec-G; its homolog in humans is Siglec-10) proteins that serve as negative regulators of DAMP driven immune activation.[42] Recent preclinical data demonstrate Siglec-G expression on hematopoietic APCs mediates significant protective effects against GVHD in multiple models of allogeneic HCT. [43] Following HLA matched and mismatched HCT, Siglec-G$^{-/-}$ deficient animals have heightened release of multiple pro-inflammatory cytokines, stimulate greater numbers of alloreactive T cells and ultimately experience inferior survival due to increased GVHD severity compared to allogeneic controls (Figure 5). These findings identify Siglec-G, particularly on hematopoietic APCs, as highly relevant for regulating inflammatory responses, and subsequent adaptive T cell responses that produce GVHD.

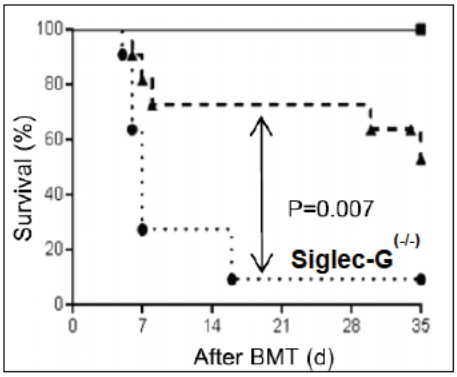

FIGURE 5: LOSS OF SIGLEC-G SIGNALING RESULTS IN EXACERBATION OF GVHD. FOLLOWING MYELOABATIVE TBI, SIGLEC-G (-/-) B6 MICE HAD SIGNIFICANT REDUCED SURVIVAL COMPARED TO ALLOGENEIC AND SYNGENEIC CONTROL ANIMALS.

3.5 CD24-SIGLEC INTERACTIONS IN THE HOST RESPONSE TO TISSUE INJURY

Host tissue injury caused by myeloablative hematopoietic cell transplantation (HCT) conditioning regimens, including high-dose chemotherapy and/or total body irradiation (TBI), not only promote release of DAMPs[44-46] but also have been shown experimentally in mice to reduce Siglec-G expression.[43] Thus, conditioning therapy may itself limit the capacity of Siglec-G to attenuate inflammatory responses triggered by DAMPs.

Recent data has identified a critical interaction between Siglec-G (and Siglec-10) and CD24 (also known as cluster of differentiation 24 or heat stable antigen (HSA)), which is a small glycosyl-phosphatidyl-inositol (GPI)-anchored glycoprotein expressed on the membrane surface of hematopoietic cells, including lymphocytes, dendritic cells and

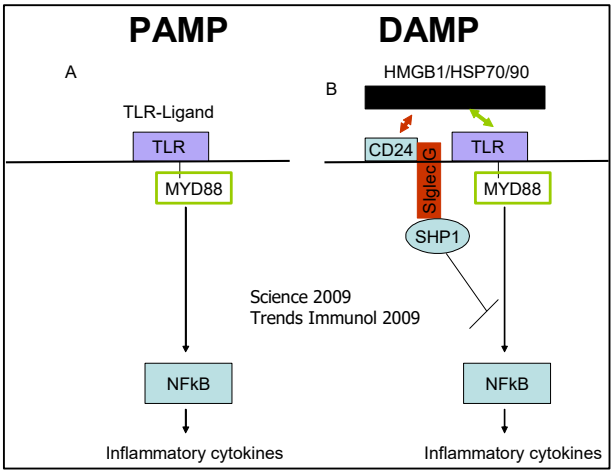

FIGURE 6: CD24-SIGLEC G (10) INTERACTION DISCRIMINATES BETWEEN PATHOGEN ASSOCIATED MOLECULAR PATTERNS (PAMPS) SUCH AS LIPOPOLYSACCHARIDE (LPS) AND DAMPS.
A) HOST RESPONSE TO PAMPS WAS UNAFFECTED BY CD24-SIGLEC G(10) INTERACTION. B) CD24-SIGLEC G (10) INTERACTION REPRESSES HOST IMMUNE RESPONSE TO DAMPS. THIS IS PROPOSED TO OCCUR THROUGH DIRECT INTERACTION OF CD24 WITH DAMPS, AND INHIBITION OF TLR SIGNALING BY SHP-1. SHP-1, SRC HOMOLOGY REGION 2 DOMAIN-CONTAINING PHOSPHATASE-1; NFKB, NUCLEAR FACTOR KAPPA B; TLR, TOLL LIKE RECEPTOR; MYD88, MYELOID DIFFERENTIATION PRIMARY RESPONSE GENE 88.

macrophages.[47] When expressed on T cells, CD24 is essential for down-modulating immune stimulation by DAMPs.[48, 49] It has been shown that CD24 directly associates with DAMPs thereby ameliorating their stimulatory activity (Figure 6). The interaction of CD24 with Siglecs (murine Siglec-G or human Siglec 10) also results in inhibition of nuclear factor kappaB (NF-kappaB), facilitating an attenuated damage response.[49] It is postulated that the CD24-Siglec G/10 pathway affords the host protection against exaggerated responses to pathological cell death, and most importantly discriminates between tissue damage (i.e. DAMP) versus pathogen (i.e. PAMP) immune activation. Since HCT is associated with tissue injury from conditioning and GVHD, and places immune deficient hosts at risk for infectious complications, the CD24 - Siglec G/10 pathway is a compelling therapeutic target for more selectively mitigating GVHD while leaving the pathogen-specific immune responses intact and thus addressing one of the limitations of T cell directed therapy.

3.6 PRECLINICAL STUDIES OF CD24FC FOR PREVENTION OF GVHD

Consistent with the loss of Siglec-G, in murine models of allogeneic HCT we observed that lack of CD24 expression on T cells promotes greater GVHD severity. This provides evidence of a crucial interaction between Siglec-G and CD24 in modulating immune response. CD24Fc (CD24 Ig) is a fusion protein consisting of the extracellular domain of mature human CD24 linked to the human immunoglobulin G1 (IgG1) Fc domain (OncoImmune, Inc.). Similar to native CD24, *in*

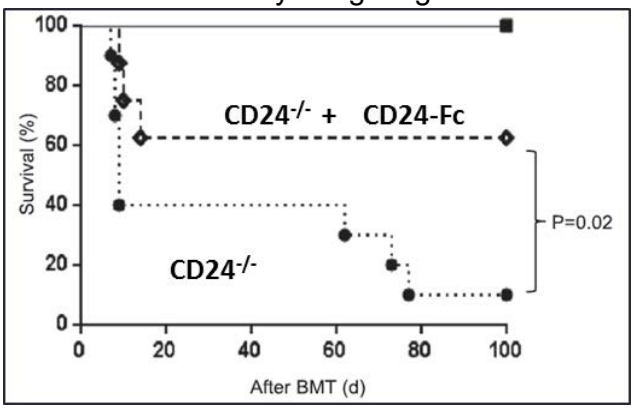

FIGURE 7: CD24FC PREVENTS EXPERIMENTAL ACUTE GVHD.
B6 MICE WERE ADMINISTERED MYELOABLATIVE XRT FOLLOWED BY INFUSION OF $CD24^{-/-}$T CELLS FROM ALLOGENEIC AND SYNGENEIC DONORS. RECIPIENTS WERE INJECTED WITH CD24FC (5MG/KG) OR PLACEBO ON DAY -1 BEFORE HCT.

vitro studies demonstrate that CD24Fc binds to murine Siglec-G (and its human orthologue, Siglec 10).[48] CD24Fc also stimulates tyrosine-phosphorylation of, and SHP-1 association to Siglec G. In preclinical models of HCT, administration of exogenous CD24Fc restores Siglec G signaling and reverses the exaggerated GVHD observed with $CD24^{-/-}$ T cells (Figure 7) [43]. Moreover, CD24Fc also ameliorates GVHD from wild type allogeneic T cells by enhancing CD24 – Siglec-G signaling. Taken together, these multiple lines of experimental evidence support suppression of innate immune responses, specifically by enhancing CD24-Siglec-G interactions that are capable of regulating severe tissue damage mediated inflammatory disorders such as GVHD. The availability of clinical grade

3.7 RATIONALE FOR CLINICAL STUDY OF CD24FC FOR GVHD PREVENTION

Several lines of evidence provide compelling rationale to support clinical investigation of CD24Fc for GVHD prevention. First, preclinical evidence in several well-established HCT models suggest that CD24Fc is effective in preventing GVHD. Second, the mechanism of immune modulation by CD24Fc is ideally suited to the inflammatory state immediately preceding HCT, which results from exacerbated immunologic responses to DAMPs that are released through generalized tissue damage by myeloablative conditioning, a necessary component of the HCT procedure for reducing leukemic relapse [64]. As opposed to standard GVHD therapies that directly inhibit T cell responses, targeting Siglec-10 – CD24 interactions with CD24Fc provides a completely novel strategy for preventing GVHD by directly interrupting the immune response to chemotherapy-associated inflammatory signaling or DAMPs, a major GVHD initiating event. Third, CD24Fc has demonstrated initial safety in healthy human subjects and a Phase IIa dose finding clinical trial in patients undergoing allogeneic HCT, coupled with a good tolerability, making it suitable for additional study in this vulnerable population. Fourth, GVHD occurs at a high incidence and is associated with significant morbidity and mortality thus reflecting an unmet clinical need. Therefore, improving standard of care GVHD prevention strategies could expand the curative potential of HCT. Finally, establishing proof-of-concept and efficacy in a prototypical immune disorder would provide key evidence for further definitive investigations of CD24Fc for the treatment and prevention of GVHD and other inflammatory conditions.

3.8 CLINICAL EXPERIENCE OF CD24FC IN HUMANS

3.8.1 Phase I Summary:

OncoImmune Inc. has developed and manufactured clinical grade CD24Fc for use in humans. CD24Fc has been tested in a Phase I clinical trial in healthy human subjects, and this study showed preliminary safety of single dose CD24Fc by IV administration. A total of 40 subjects were randomized in 5 cohorts of 8 subjects, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour at doses

ranging from 10 to 240 mg, and the subjects were followed over a six-week period. A MTD was not encountered.

In general, adverse events were mild to moderate in severity. The most common AEs were headache (6 [15.0%] subjects), accidental burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects). The rates of the AEs were similar in the placebo control group. The SAE of ventricular tachycardia was considered mild in severity by the investigator and did not lead to discontinuation of the subject from the study. This SAE was considered to be drug related due to its close temporal proximity to dosing, though similar short, isolated episodes of non-sustained ventricular tachycardia may be seen in up to 4% of normal, healthy populations. No deaths or adverse events leading to discontinuation occurred during the study.

3.8.2 Phase IIa Summary:

A Phase IIa prospective randomized double-blind clinical trial of CD24Fc for acute GVHD prophylaxis in myeloablative matched unrelated donor HCT was initiated in July 2016. The first patient was enrolled in Sept 2016. A total of 24 patients were enrolled in three cohorts, 240mg single dose given at day -1, 480mg single dose at day -1, 480-240-240mg multi-dose given on day -1, day 14 and day 28, with 6 patients receiving CD24Fc and 2 patients receiving placebo in each cohort. The last patient was enrolled in Dec 2017. The last patient reached one year post-HCT in December 2018. Data was locked and the final clinical study report (CSR) was submitted to FDA in April 2019. In total there are 18 patients in the CD24Fc group and 6 patients in the placebo group (3:1 randomization). All planned dosages were delivered on schedule.

3.8.2.1 Phase IIa Clinical Study Overview

The primary objectives of the Phase IIa are to assess the safety and tolerability of CD24Fc in combination with methotrexate and tacrolimus prophylaxis in subjects undergoing matched unrelated donor HCT following myeloablative conditioning, and to define the recommended Phase II dose (RP2D) or maximum tolerated dose (MTD). In addition, secondary efficacy objectives in the Phase IIa include:

- assessing grade II – IV aGVHD free survival (GFS) at day 180 after HCT,
- assessing the incidence of chronic GVHD (cGVHD) at one year following HCT
- assessing the incidence of relapse one year following HCT
- assessing the incidence of transplant-related mortality (TRM) one year following HCT
- assessing infection rates at day 100 following HCT
- evaluating overall survival (OS), absence of grade III-IV GVHD, and relapse-free survival one year following HCT
- evaluating conditioning toxicity including oral mucositis and organ failure

Other exploratory objectives include assessment of the pharmacokinetic (PK) profile of CD24Fc, examining the immune cell profile and functional responses of APCs and T cells

after HCT in the CD24Fc and placebo groups, and assessing pharmacodynamics (PD) biomarkers such as the plasma concentrations of pro-inflammatory cytokines, DAMPs, lipids, and GVHD biomarkers in the CD24Fc and placebo groups.

Subjects between the ages of 18-70 years old undergoing matched unrelated donor allogeneic HCT for a malignant hematologic condition (AML, ALL, CML, CMML, MDS) with a Karnofsky performance score ≥ 70% were eligible for the trial. An 8/8 HLA allelic match between the unrelated donor and the recipient at HLA-A, HLA-B, HLA-C, and HLA-DRB1 was required. All subjects received myeloablative conditioning and standard of care GVHD prophylaxis with methotrexate and tacrolimus per the Phase IIa protocol. Patients received a myeloablative conditioning regimen consisting of either fludarabine and busulfan (Flu/Bu) or cyclophosphamide and total body irradiation (Cy/TBI), as decided by the treating physician, followed by an infusion of stem cells on day 0. The source of donor stem cells was either peripheral blood stem cells (PBSC) or bone marrow (BM). GVHD prophylaxis was administered to all subjects and consisted of tacrolimus (initiated Day -3 before transplant) and methotrexate (initiated Day +1 after transplant) in combination with CD24Fc in the treatment arms, and tacrolimus/methotrexate plus saline solution in the placebo arm. In the absence of GVHD, tacrolimus tapering started on day +100.

Overall, CD24Fc was well tolerated in the Phase IIa study. There were no infusion-related toxicities. There was one possible drug related treatment emergent adverse event (TEAE) of ≥ grade III-IV hyperglycemia in the 480 mg CD24Fc group, which was managed with insulin. One dose-limiting toxicity (DLT) was observed in the placebo group, and no DLTs were observed in the CD24Fc group. There were no adverse events leading to death in subjects administered CD24Fc within the 180 days. There was one adverse event of pneumonia that led to the death of a subject at Day 48 in the placebo group. The development of anti-drug antibodies (ADA) were not detected in any of the 24 subjects at any point out to day 100 after HCT.

The most common TEAEs ≥ grade III (> 10%) included a decrease in platelet counts (83.3% placebo and 94.4% CD24Fc), decrease in WBC counts (66.7% placebo and 88.9% CD24Fc), decrease in neutrophil counts (50% placebo and 83.3% CD24Fc), decrease in lymphocyte counts (50% placebo and 77.8% CD24Fc), anemia (50% placebo and 66.7% CD24Fc), stomatitis (83.3% placebo and 50% CD24Fc), and nausea (0% placebo and 11.1% CD24Fc). These are expected SAEs were anticipated as they were hematologic in nature and were otherwise considered related to the myeloablative conditioning regimen of HCT.

In the Phase IIa study summarized in Table 2, compared to treatment with placebo, treatment with CD24Fc resulted in trends toward:

1. Higher Grade III to IV acute GFS rate at Day 180 (94.4% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.1),
2. Higher DFS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),

3. Higher OS rate at 1 year (83.3% in CD24Fc treatment group, 50.0% in placebo) (hazard ratio = 0.2),
4. Higher Grade III to IV acute GRFS rate at Day 180 (83.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.2),
5. Lower incidence of Grade III-IV acute GVHD by Day 180 (5.6% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.1),
6. Lower cumulative incidence of leukemia relapse at 1 year (11.1% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.3),
7. Lower incidence of non-relapse mortality at 1 year (5.6% in CD24Fc treatment group, 16.7% in placebo) (hazard ratio = 0.3),
8. Similar cumulative incidence of Grade II to IV acute GVHD by Day 180 (38.9% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 2.6),
9. Similar 1 year GRFS (Grade III-IV acute GVHD / chronic GVHD requiring systemic immunosuppressive treatment /relapse free survival) (32.4% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 0.7),
10. Higher cumulative incidence of all grade chronic GVHD at 1 year (63.3% in CD24Fc treatment group, 33.3% in placebo) (hazard ratio = 2.1).

TABLE 2: UNIVARIATE RESULTS FROM THE CD24FC PHASE IIA STUDY

Outcome		Placebo/Tac/MTX N=6	CD24Fc/Tac/MTX N=18
Grade III-IV Acute GVHD Free Survival (aGFS)	HR (90% CI)	1.00	0.1 (0.0-0.7)
	Incidence at 6 mo (95%CI)	50% (11-80%)	94% (67-99%)
Relapse	HR (90% CI)	1.00	0.3 (0.1-1.4)
	Incidence at 12 mo (95%CI)	33% (2.9-71%)	11% (1.7-30%)
Overall Survival	HR (90% CI)	1.00	0.2 (0.1-1.0)
	Probability at 12 mo (95%CI)	50% (11-80%)	83% (57-94%)
Disease free survival	HR (90% CI)	1.00	0.2 (0.1-0.9)
	Probability at 12 mo (95%CI)	50% (11-80%)	83% (57-94%)
Chronic GVHD	HR (90% CI)	1.00	2.1 (0.6-7.4)
	Probability at 12 mo (95%CI)	33% (2.5-72%)	63% (34-82%)

HR=Hazard Ratio, CI=Confidence Interval. The event for overall survival was death and the event for disease free survival was death or relapse. A hazard ratio (HR) less than 1 implies that CD24Fc group has less events at any time compared to the Tac+MTX Control reference group (indicated by a HR of 1.00).

3.8.2.1.1 Historical Control From the Phase IIa Study Sites: UM/OSU Control.

Considering the limited sample size of available placebo controls in the Phase IIa portion, a post-hoc analysis of patients was conducted at the highest enrolling centers involved in this trial (UM, OSU) the relapse incidence in 92 similarly treated patients receiving myeloablative unrelated donor HCT using tacrolimus and methotrexate GVHD prophylaxis. The rates of 180 day Grade III-IV acute GVHD free survival, 1 year relapse free survival and 1 year overall survival are compared with CD24Fc group (see Figure 8, Figure 10, and Figure 11).

3.8.2.1.2 Registered Matched Control from the CIBMTR

In order to better evaluate the efficacy of novel approaches for GVHD prophylaxis, a registered matched control analysis was performed using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) for patients with myeloablative matched unrelated donor hematopoietic cell transplantation and with TAC/MTX as GVHD prophylaxis.

The Center for International Blood and Marrow Transplant Research (CIBMTR) is an observational registry for allogeneic and autologous transplantations since 1972. Transplant centers report consecutive transplants and patients are followed longitudinally until death or lost to follow up. In person audits and continuous process improvement for all centers ensure data accuracy and completeness of follow up of transplanted patients.

Eligibility criteria were identical to the Phase IIa portion of the trial and included recipients of HLA-matched unrelated donor hematopoietic cell transplantation (HCT), from 2015 to 2017, for treatment of acute myeloid leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, and chronic myelomonocytic leukemia. Potential controls were restricted to those with a performance score ≥ 70, myeloablative conditioning regimens (busulfan + fludarabine or cyclophosphamide + total body irradiation) and tacrolimus with methotrexate for graft-versus-host disease (GVHD) prophylaxis.

Up to 4 Controls per Case was selected from the CIBMTR's database at the CRF level, matched on age (±5 years), HCT-comorbidity score, and disease status (1st complete remission or 2nd complete remission or primary induction failure for acute leukemia, 1st and 2nd chronic phase or blast phase for chronic myelogenous leukemia, refractory anemia, refractory cytopenia, refractory anemia with excess blasts I or II for myelodysplastic syndrome, and CPSS score for chronic myelomonocytic leukemia).

Most Cases (N=16) were matched to 4 CIBMTR Controls. Two Cases were matched to 2 CIBMTR Controls. The final study population compared 18 Cases to their 68 matched CIBMTR Controls.

The primary objective was grade III-IV acute GVHD-free survival (aGFS) and secondary objectives included grades II-IV and III-IV acute GVHD, chronic GVHD, relapse, disease free survival and overall survival.

Table 3 describes the study population in Cases vs. CIBMTR Controls. Table 4 presents the 180 day probabilities and the hazard ratio (95% confidential interval) generated from marginal Cox regression models to accommodate Case-Control matching. Multivariate adjusted models were not done due to the small sample size and low even rate. Probability estimates for acute and chronic GVHD and relapse were considered competing events.

TABLE 3: CHARACTERISTICS OF PATIENTS: CASES VS. CONTROLS

	Cases	Controls
Number of patients	18	68
Number of centers	2	34
Age at transplant		
Median (range)	64 (24-69)	64 (23-70)
18-29	3 (17)	8 (12)
30-39	1 (6)	5 (7)
40-49	2 (11)	3 (4)
50-59	0	10 (15)
60-69	12 (67)	42 (62)

	Cases	Controls
Age at transplant (cutoff at 65 years)		
>65	11 (61)	39 (57)
⩽65	7 (39)	29 (43)
Sex		
Male	11 (61)	42 (62)
Female	7 (39)	26 (38)
Race		
Caucasian	17 (94)	62 (91)
African-American	0	1 (1)
Asian	0	3 (4)
Native American	0	1 (1)
Not reported	1 (6)	1 (1)
Ethnicity		
Hispanic or Latino	1 (6)	2 (3)
Non-Hispanic or non-Latino	17 (94)	63 (93)
Not reported	0	3 (4)
Disease		
AML	7 (39)	19 (28)
ALL	3 (17)	12 (18)
CML	2 (11)	2 (3)
MDS	5 (28)	32 (47)
CMMol	1 (6)	3 (4)
Disease status		
Early stage [a]	10 (56)	40 (59)
Late stage [b]	8 (44)	28 (41)
Disease Risk Stratification (DRI)		
Low to Intermediate	10 (56)	34 (50)
High	8 (44)	34 (50)
Karnofsky score		
70	0	5 (7)
80	17 (94)	24 (35)
90	0	22 (32)
100	1 (6)	17 (25)
HCT comorbidity index		
0	6 (33)	22 (32)
1-2	5 (28)	20 (29)
⩾ 3	7 (39)	26 (38)
Donor/recipient CMV serostatus		
+/+	5 (28)	19 (28)

	Cases	Controls
+/-	1 (6)	7 (10)
-/+	4 (22)	22 (32)
-/-	8(44)	20 (29)
Conditioning intensity		
Myeloablative	18	68
Conditioning regimen		
TBI + cyclophosphamide	3 (17)	12 (18)
TBI + cyclophosphamide + thiotepa	0	1 (1)
TBI + other(s)	1 (6)	0
Fludarabine + busulfan	14 (78)	55 (81)
Transplant year		
2015	0	23 (34)
2016	5 (28)	31 (46)
2017	13 (72)	14 (21)
Median follow-up of survivors (range), months (Oct. 2018)	13 (9-21)	24 (6-37)

[a] MDS early stage: Refractory Anemia; CML early stage: Hematologic CR or First chronic phase;

CMMol late stage: CPSS score = 0; AML early stage: CR1; ALL early stage: CR1 or CR2

[b] MDS late stage: RAEB-I, RAEB-II; CML late stage: Accelerated or Blastic phase; CMMol late stage: CPSS score > 0; AML late stage: PIF; ALL late stage: PIF

TABLE 4: UNIVARIATE ANALYSIS OF 180 DAYS GRADE III-IV ACUTE GVHD-FREE SURVIVAL, 180 DAYS ACUTE (GRADES II-IV AND III-IV) GVHD, 1 YEAR CHRONIC GVHD, 1 YEAR RELAPSE, 1 YEAR NON-RELAPSE MORTALITY, 1 YEAR DISEASE-FREE SURVIVAL, AND 1 YEAR OVERALL SURVIVAL. CONTROLS (CIBMTR REFERENCE GROUP) VS. CASES.

	Cases (N=18)		Controls (N=68)		HR: Ctr=1	P-value
Outcomes	Events/Eval	Prob (95% CI)	Events/Eval	Prob (95% CI)	(95% CI)	
Grade III-IV acute GVHD-free survival at 180 days	1/18	94% (80-100)%	22/68	68% (56-78)%	0.34 (0.13-0.91)	0.03
Grade II-IV acute GVHD-free survival at 180 days	7/18	61% (38-84)%	43/68	37% (25-48)%	0.54 (0.28-1.02)	0.06
Grade III-IV acute GVHD-free relapse free survival at 180 days	3/18	83% (57-94)%	30/68	56% (44-68)%	0.44 (0.20-0.96)	0.04
Grade II-IV acute GVHD at 180 days	7/18	39% (18-62)%	36/68	53% (41-65)%	0.57 (0.25-1.28)	0.17
Grade III-IV acute GVHD at 180 days	1/18	6% (0-20)%	13/68	19% (11-30)%	0.27 (0.03-1.96)	0.21

	Cases (N=18)		Controls (N=68)		HR: Ctr=1	P-value
Outcomes	Events/Eval	Prob (95% CI)	Events/Eval	Prob (95% CI)	(95% CI)	
Chronic GVHD at 1 year (with systemic immunosuppression)	8/18	44% (22-69)%	23/68	34% (23-46)%	1.26 (0.41-2.08)	0.85
Relapse at 1 year	2/18	11% (1-29)%	22/68	32% (22-45)%	0.25 (0.06-1.06)	0.06
Non-relapse mortality at 1 year	1/18	5.6% (0.3-23)%	12/68	18% (9.5-29)%	0.27 (0.04-2.1)	0.21
Disease-free survival at 1 year	3/18	83% (57-94)%	34/68	48% (38-62)%	0.34 (0.08-0.81)	0.03
Overall survival at 1 year	3/18	83% (57-94)%	27/68	58% (48-72)%	0.42 (0.09-0.96)	0.04

The 180 days probability of grade III-IV acute GVHD-free survival was 94% for the CD24Fc Cases and 68% for the CIBMTR Controls (HR=0.346, 95% CI: 0.13-0.91, P=0.03) as shown in Figure 8.

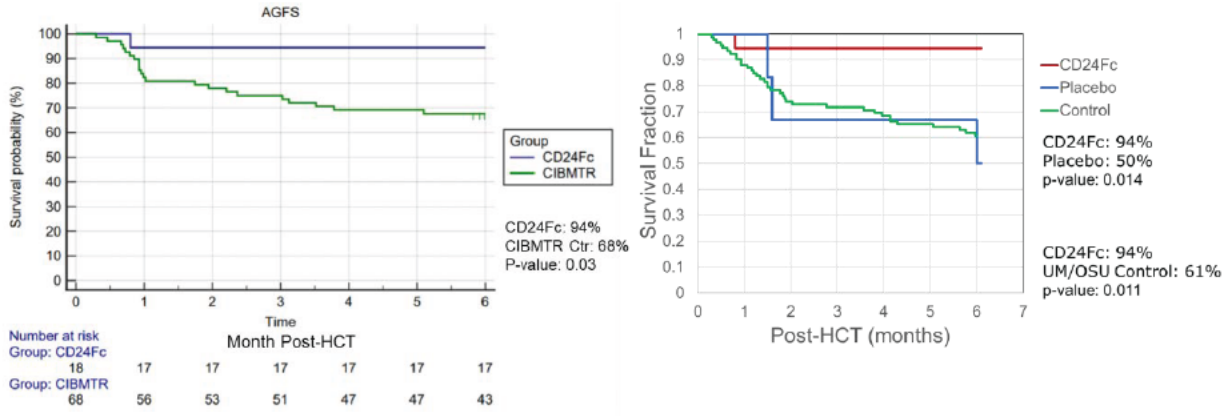

FIGURE 8: CD24FC TREATMENT SIGNIFICANTLY IMPROVES 180 AGFS.
Left panel: CD24Fc treatment compared with CIBMTR matched control group (HR=0.346). Right panel: CD24Fc treatment compared with placebo group and the UM/OSU control group of 92 patients.

The 180 days probability of grade II-IV acute GVHD-free survival was 61% for the CD24Fc Cases and 37% for the CIBMTR Controls (HR=0.54, 95% CI: 0.28-1.02, P=0.057) as shown in Figure 9.

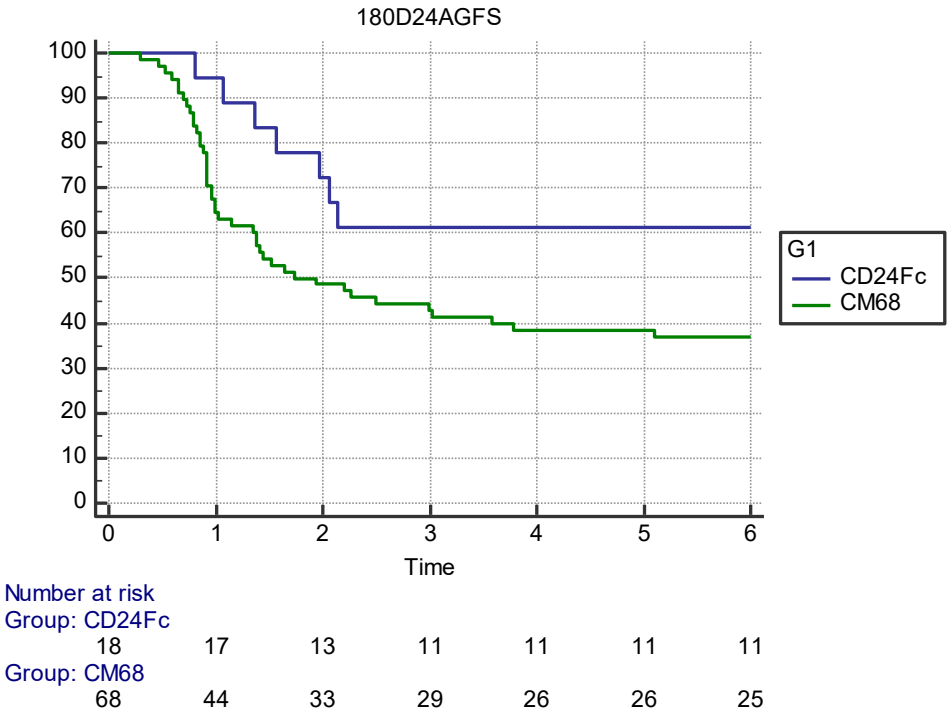

Figure 9: 180 DAY GRADE II-IV GVHD-FREE SURVIVAL. CD24FC-TREATED VS MATCHED CIBMTR HISTORICAL CONTROLS (CM68).

The 1 year probability of disease free survival (DFS) was 83% for the CD24Fc Cases and 48% for the CIBMTR Controls (HR=0.39, 95% CI: 0.18-0.81, P=0.01) as shown in Figure 10. The DFS for placebo is 50% and for UM/OSU control group of 92 patients is 61%.

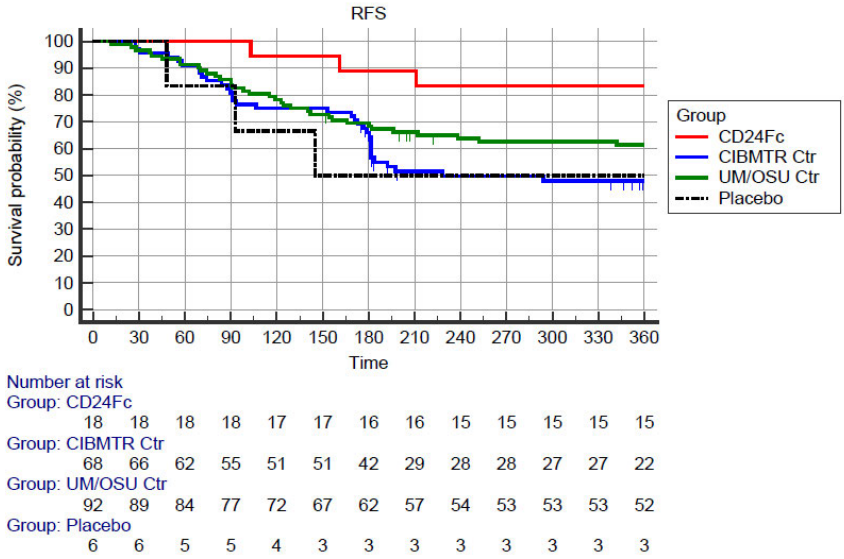

FIGURE 10: CD24FC TREATMENT IMPROVES 1 YEAR RELAPSE FREE SURVIVAL (RFS). CD24Fc treatment compared with CIBMTR matched control group: p=0.011 (HR=0.386); CD24Fc treatment compared with placebo group: p=0.05; CD24Fc treatment compared with UM/OSU control group of 92 patients: p=0.04.

The 1 year probability of overall survival (OS) was 83% for the CD24Fc Cases and 58% for the CIBMTR Controls (HR=0.42, 95% CI: 0.19-0.96, P=0.04) as shown in Figure 11. The OS for placebo is 50% and for UM/OSU control group of 92 patients is 68%.

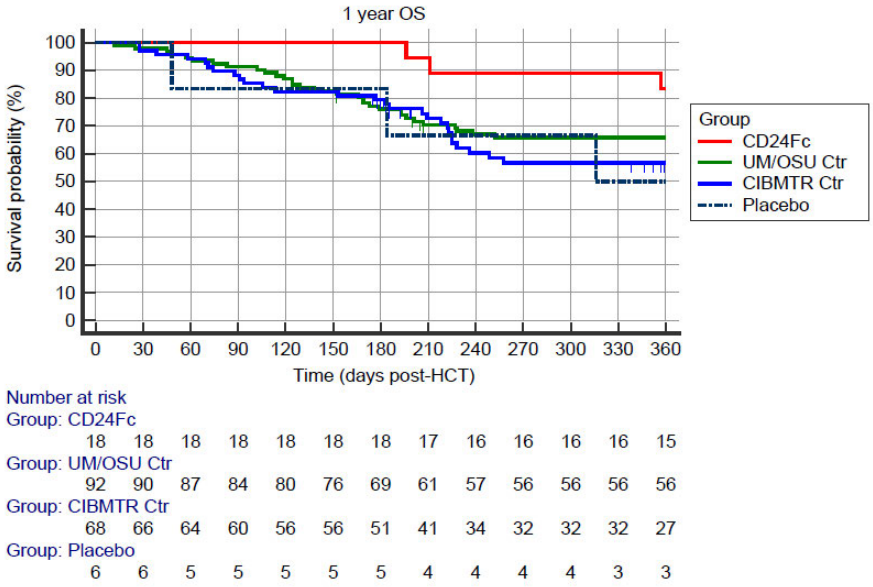

FIGURE 11: CD24FC TREATMENT SHOWS TREND IN IMPROVEMENT OF 1 YEAR OVERALL SURVIVAL (OS). CD24Fc treatment compared with CIBMTR matched control group: p=0.04 (HR=0.425); CD24Fc treatment compared with placebo group: p=0.07; CD24Fc treatment compared with UM/OSU control group of 92 patients: p=0.06.

The 180 days probability of grade III-IV acute GVHD and relapse-free survival was 83% for the CD24Fc Cases and 56% for the CIBMTR Controls (HR=0.443, 95% CI: 0.196-0.974, P=0.04) as shown in Figure 12.

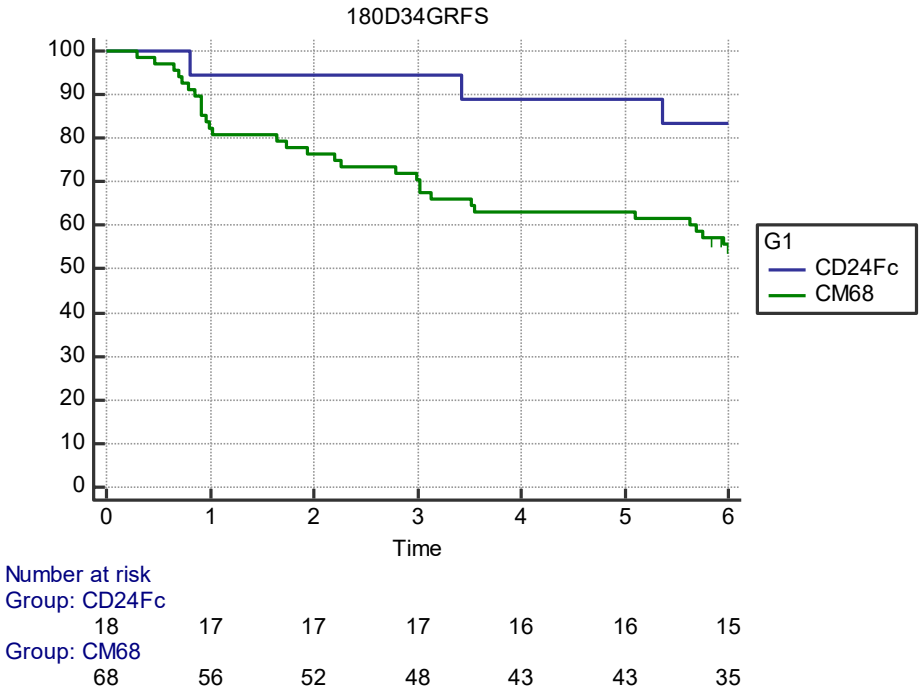

Figure 12: 180 DAY GRADE III-IV GVHD-FREE AND RELAPSE-FREE SURVIVAL. CD24FC VS MATCHED CIBMTR CONTROL (CM68).

3.8.2.1.3 Reduction of Conditioning Related Mucositis

Myeloablative conditioning for HCT is often associated with severe regimen related toxicity including organ failure. Grade 3-4 mucositis occurs in approximately 90% of patients receiving radiation containing regimens [50], which can promote mucosal barrier injury and infection, utilization of opioid analgesia and parenteral nutrition, and prolongation of hospitalization. In the CD24Fc group of 18 patients, none died within the first 100 days post HCT, while 1 out of 6 in the placebo group died on Day 48 due to pulmonary toxicity with respiratory failure. Severe oral mucositis has been reported by HCT patients as the most distressing symptom they experienced [51]. We calculated the grade-day score of severe grade 3-4 mucositis (total number of days patients had grade 3-4 mucositis) in the placebo cohort and three CD24Fc treatment cohorts. CD24Fc multi-dosing had a significant reduction of severe mucositis grade-day score (placebo vs. 960 multi-dose: P=0.03) (Figure 13).

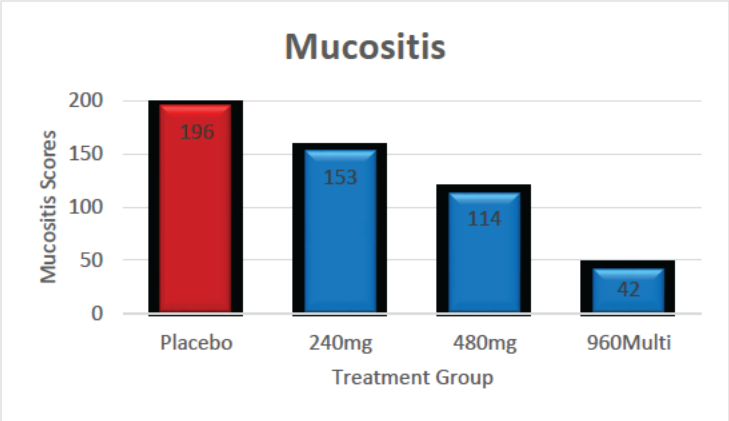

FIGURE 13: MUCOSITIS SCORES CALCULATED AS MULTIPLE OF SEVERE MUCOSITIS GRADE ≥3 AND DURATION (GRADE-DAYS).

3.8.2.1.4 Infection

There are 10 patients in the CD24Fc group that were at risk of CMV reactivation (Donor/Recipient CMV status before HCT: D+/R+, 5; D-/R+, 3; unknown D/R+, 1; D+/R-, 1). Eight patients have status of D-/R- which are not considered to be at risk. Two D-/R+ patients had CMV reactivation at Day 42 and Day 48, representing 20% cumulative incidence of CMV reactivation at Day 100 in the high risk CD24Fc group. Both patients had prior steroid treatment before the CMV reactivation. In comparison, 2 patients in the placebo group are at risk of CMV reactivation (D+/R+, 1; D-/R+, 1; D-/R-, 4). One patient had CMV reactivation at Day 47 (50%) even through the patient was without prior steroid treatment. There were no instances of CMV end organ disease. No patients in either arm received CMV directed antiviral prophylaxis.

Other infections are also comparable between CD24Fc and placebo groups, including bacterial infection (50% vs. 33%) and fungal infection (11% vs. 0%).

Overall there is no noticeable increase of infections in the CD24Fc treated group.

3.8.3 Conclusion and Plans for Clinical Development

The preliminary clinical evidence from the Phase IIa study suggests that CD24Fc is safe and potentially beneficial when administered in combination with methotrexate and tacrolimus in patients who undergo HCT from an unmatched donor following myeloablative conditioning. As described above, the cumulative incidence of grade III – IV aGVHD is 6% in CD24Fc exposed subjects as compared to 17% in the placebo group (methotrexate and tacrolimus plus saline) and 19-24% in the two contemporary control cohorts (methotrexate and tacrolimus alone). Although other data have suggested that rates of ≤ 10% grade III-IV aGVHD are achievable with addition of novel agents (such as Bortezomib or post-transplantation cyclophosphamide) to a tac/MTX background [52] [53] these studies were in the context of reduced intensity conditioning. The reduced intensity conditioning (RIC) has been consistently increased the relapse rate compared to myeloablative conditioning (MAC) [54]. The Phase IIa data suggest that administration of CD24Fc in combination with methotrexate and tacrolimus as prophylaxis reduces the risk of grade III – IV aGVHD in HCT patients receiving MAC, the most serious grades of

aGVHD that are associated with increased risk of non-relapse mortality [55]. A trend of reduction in the incidence of relapse is also observed in subjects who received CD24Fc (11.1%) as compared to subjects who did not, both as compared to the placebo group (33.3%) and two sets of internal and external (CIBMTR) contemporary controls (both 23%), demonstrating that CD24Fc does not affect the GVT effects of the graft and may contain salutary properties that prevent leukemia relapse. The benefit of including CD24Fc in standard GVHD prophylaxis regimens is further supported by the better NRM in CD24Fc exposed subjects (6%) as compared to placebo (17%), better 1-year overall survival (83% versus 50%, CD24Fc versus placebo), a statistically significant improvement in grade III – IV aGFS (94% versus 50%, CD24Fc versus placebo, respectively), a dose-dependent reduction in severe mucositis, and a favorable overall safety profile.

3.8.4 Rationale for a Randomized, double blind, placebo-controlled Phase III Trial

This multicenter Phase III clinical trial will evaluate adding CD24Fc to standard of care TAC/MTX acute GVHD prophylaxis for the efficacy in improving the proportion of patients who survive to 180 days without developing severe (Grade III-IV) acute GVHD. The randomized, double blind and placebo-controlled study will provide the most rigorous analysis to assess the efficacy of the novel biological agent CD24Fc in reduction of severe acute GVHD with clear advantage in improvement of relapse free survival and overall survival.

4 ELIGIBILITY

4.1 INCLUSION CRITERIA

4.1.1 A prospective patient for allogeneic HCT for a malignant hematologic disorder (see section 4.1.3 for eligible diagnoses).

4.1.2 The donor and recipient must have an HLA-8/8 allelic match at the HLA-A, -B, -C, and – DRB1 loci. High-resolution typing is required for all alleles for unmatched donors. Only matched unrelated donors are acceptable for this trial.

4.1.3 The following diagnoses are to be included in the Phase III study:

Acute Myeloid Leukemia (AML) or Acute Lymphoblastic Leukemia (ALL) in remission. Remission is defined as the absence of blasts in the peripheral circulation at the time of enrollment, < 5% blasts in the bone marrow and absence of extramedullary disease including CNS involvement.

4.1.4 Males or non-pregnant, non-lactating females, ≥ 18 years of age. Note there is no defined upper age limited, so long as deemed appropriate candidate for myeloablative conditioning.

4.1.5 Karnofsky Performance Status ≥70%, see Appendix A.

4.1.6 Patients must have normal or near normal organ function as defined by their treating institutions BMT program clinical practice guidelines. In addition, for purposes of this protocol minimum organ function criteria within 30 days of beginning conditioning are listed in Table 5 below:

TABLE 5: ELIGIBILITY ACCORDING TO PRE HCT ORGAN FUNCTION

Total bilirubin	≤2.0 x ULN (unless from Gilbert's disease or disease-related)
AST(SGOT)/ALT(SGPT)	<3.0 X institutional upper limit of normal
Estimated or actual GFR	>50 mL/min/1.73 m2 for patients with creatinine levels above institutional normal (GFR should be corrected for BSA)
Pulmonary Function Tests*	DLCO, FEV1, FVC > 50% DLCO should be corrected for hemoglobin
Ejection Fraction*	>50%
Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI)#	≤ 5

*May be assessed up to 10 weeks prior to the date of enrollment.

#The HCT-Specific Comorbidity Index (HCT-CI) found in Appendix E which states "Prior solid tumor" "requiring treatment with chemotherapy" (HCI-CI score=3) is modified to:

"Prior solid tumor" "requiring treatment with chemotherapy, if the solid tumor chemotherapy is documented to be complete and the tumor has not progressed in the two years before the HCT, the BMT physician may take this into consideration and adjust the HCI-CI score to < 3."

4.1.7 Ability to understand and the willingness to sign a written informed consent document.

4.1.8 Women of child bearing potential and men must agree to use contraception prior to study entry and through day 100 post HCT (hormonal or barrier method of birth control; abstinence). Should a woman become pregnant or suspect she is pregnant while she or her partner is on treatment in this study, she should inform her study physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study until day 100 post HCT (See section 6.0).

4.2 EXCLUSION CRITERIA

4.2.1 Subjects may not have presence of active CNS disease or extramedullary disease.

4.2.2 Prior cytotoxic chemotherapy within 21 days from the initiation of HCT conditioning (i.e. intensive induction / consolidation for AML). Note, certain low intensity treatments not intended to induce remission but rather stabilize disease are acceptable up to 24 hours prior to initiation of HCT conditioning (i.e. Sorafenib).

4.2.3 Matched sibling donor, cord blood and haploidentical donors are not eligible.

4.2.4 HLA-mismatch at the HLA-A, -B, -C, and – DRB1 loci. Note, HLA-DQ mismatches are permissible.

4.2.5 Pregnant and nursing mothers are excluded from this study. This is because the risk to the fetus is unknown.

4.2.6 Any physical or psychological condition that, in the opinion of the investigator, would pose unacceptable risk to the patient or raise concern that the patient would not comply with protocol procedures.

4.2.7 Uncontrolled infections. Patients still under therapy for presumed or proven infection are eligible provided there is clear evidence (radiologic, clinical and/or culture) that the infection is well controlled. Patients testing positive for SARS-CoV-2, whether symptomatic or asymptomatic, are excluded. Patients recovering from COVID-19 and viral testing negative for SARS-CoV-2 are eligible.

4.2.8 Patients seropositive or PCR positive for the human immunodeficiency virus (HIV). Patients with evidence of active Hepatitis B or Hepatitis C PCR positivity.

4.2.9 Prior HCT (allograft or autograft).

4.2.10 Use of T cell depletion either *ex vivo* or *in vivo* (such as ATG or alemtuzumab or *ex vivo* $CD34^+$ selected HCT) is prohibited.

4.2.11 Current or prior diagnosis of antecedent Myelofibrosis is excluded.

5 PHASE III STUDY

5.1 OVERVIEW

The prospective, randomized, double blind, placebo controlled, multi-center Phase III study is designed to assess the safety, tolerability and efficacy of the addition of CD24Fc to standard tacrolimus and methotrexate GVHD prophylaxis in myeloablative matched unrelated donor HCT. The goal of the study is to confirm that adding CD24Fc to standard tacrolimus and methotrexate will improve the 180 day Grade III-IV aGFS. To further limit the heterogeneity to assess the potential toxicity and to facilitate statistical estimates of GVHD and relapse incidence, the Phase III study will restrict the study to AML and ALL patients with matched unrelated donors receiving myeloablative conditioning regimen.

5.2 SCREENING PROCEDURES

The CRO Medpace will serve as the multi-site study coordinator. An IRB-approved informed consent must be obtained from patients (or legal guardians) prior to the initiation of treatment on this protocol. Patient demographics, including the patient's age, gender, race, ethnicity, underlying disease, disease risk index (DRI) (Appendix D) [56], disease remission status, conditioning regimen, cell source, donor/recipient CMV status, HCT-CI, KPS, transplant center and donor age/gender, and eligibility criteria will be recorded at entry into the study. All screening evaluations will be completed as part of the local institutions standard work up for HCT.

5.3 TREATMENT SCHEMA

Based on the Phase IIa clinical safety results and the pharmacokinetic data, the recommended Phase III dose has been determined to be multi-dose 480-240-240 mg administered on day -1, day 14 and day 28, respectively. This regimen will provide biologically active levels of CD24Fc through the acute GVHD peak risk period (median 30 days). The Phase III study schema is shown in Figure 1. Dosing is based on a fixed amount and not based on weight or BSA.

5.4 RATIONALE FOR TREATMENT SCHEMA

We propose early administration of CD24Fc for acute GVHD prevention based on the following rationale: 1) during or immediately following HCT myeloablative conditioning tissue injury ensues resulting in release of inflammatory mediators, including exaggerated levels of DAMPs, that have been implicated in the initiation of acute GVHD; 2) through direct blockade of DAMPs and enhancing Siglec-10 / CD24 interactions, CD24Fc is

capable of markedly reducing the inflammatory responses to DAMPs that initiate acute GVHD; and 3) multiple established models of acute GVHD demonstrate that early administration of exogenous human CD24Fc, prior to infusion of donor cells, attenuates acute GVHD and improves survival after HCT.

5.5 ADMINISTRATION OF GVHD PROPHYLAXIS

5.5.1 CD24Fc

CD24Fc will be administered intravenously on day -1 (480 mg) prior to HCT (day 0), and on day 14 (240 mg) and day 28 (240 mg) post HCT. Subjects will also receive standard of care GVHD prophylaxis with methotrexate and tacrolimus. Attempts should be made to administer the CD24Fc on schedule and to ensure that at least 14 days of interval between dosing. The dose may not be delayed for the first intended administration but may be delayed for up to 4 days for the second (i.e. on day 14 + 4) and the third administration (day 28 + 4 post HCT) for unanticipated events such as toxicity from preceding conditioning chemotherapy, severe infection or scheduling

5.5.2 Tacrolimus

a. Tacrolimus will begin on day -3. IV or PO dosing is permitted. For intravenous dosing the recommended starting dose is 0.03 mg/kg/day based on adjusted body weight as a continuous infusion. For oral dosing the recommended starting dose is 0.045 mg/kg/dose twice daily.

b. Patients who cannot tolerate tacrolimus, then cyclosporine at a dose of 100x the intravenous tacrolimus dose (e.g., 3 mg/kg/day starting dose) is recommended. For oral dosing the recommended conversion is 3x the intravenous dose. When Neoral brand is used, because of greater bioavailability, the conversion is 2x the IV dose.

c. Tacrolimus will be switched to oral administration when applicable based on the patient's ability to take oral medication generally at a daily dose of three times the IV dose.

d. In the absence of GVHD, levels will be monitored for therapeutic dosing only during the first 100 days post-transplant. The therapeutic target trough level for tacrolimus is 5-15 ng/mL. Tacrolimus levels outside of the desired range are not considered protocol deviations.

e. In the absence of GVHD or relapse, it is recommended that tacrolimus tapering begin on day +100 post-transplant.

f. In the presence of GVHD, it is recommended that tacrolimus be continued at the therapeutic dosing.

5.5.3 Methotrexate

Methotrexate will be used in combination with tacrolimus for standard GVHD prophylaxis. Methotrexate will be given intravenously at a dose of 15 mg/m^2/dose once daily on Day 1 after HCT, and at a dose of 10 mg/m^2/dose on days 3, 6, and 11 after HCT. Attempts should be made to deliver all four doses, however, methotrexate may be omitted or

reduced doses at the discretion of the treating physician according to institutional guidelines. Leucovorin rescue may also be administered according to local institutional practice guidelines. Reduced Methotrexate per institutional practice guidelines is allowed, but should inform the study PI.

5.6 MYELOABLATIVE CONDITIONING REGIMENS

Pre HCT conditioning will be selected by the local investigator. Examples of acceptable regimens with dose ranges are outlined below:

5.6.1 Busulfan and Fludarabine (Bu/Flu)

Days -5 to -2: Busulfan (3.2 mg/kg/day IV or 130 mg/m^2/day; total dose of 12.8 mg/kg or 520 mg/m^2, respectively).

Days -5 to -2: Flu (30 to 45 mg/m^2/day, total dose of 120 - 180 mg/m^2)

The specific sequence and timing of busulfan and fludarabine administration in MAC regimens will be done according to institutional standards.

5.6.2 Busulfan and cyclophosphamide (Bu/Cy)

Days -7 to -4: Busulfan (3.2 mg/kg/day IV or 130 mg/m2/day, total dose of 12.8 mg/kg or 520 mg/m2, respectively).

Days -3 to -2: cyclophosphamide (60 mg/kg/day, total dose of 120 mg/kg).

5.6.3 Cyclophosphamide and total body irradiation (Cy/TBI)

Days -7 to -4: TBI (1200-1420 cGy)

Days -3 to -2: Cy (60 mg/kg/day, total dose of 120 mg/kg)

The sequence of cyclophosphamide, and TBI administration practices for myeloablative regimens will be done according to institutional standards.

5.6.4 Etoposide and total body irradiation (VP16/TBI)

Days -7 to -4 (or Day -6 to -4): TBI (1200 – 1320 cGy)

Day -3: Etoposide (VP16) (60mg/kg, IV infusion in 4 hours).

The sequence of etoposide, and TBI administration practices for myeloablative regimens will be done according to institutional standards.

5.6.5 Other Myeloablative Conditioning

This trial is designed to study GVHD prevention in the general context of myeloablative conditioning, thus other myeloablative conditioning regimens are acceptable and do not constitute protocol deviation so long as they fulfill CIBMTR myeloablative criteria (APPENDIX B). Incorporation of T cell depletion either *ex vivo* or *in vivo* (such as ATG, alemtuzumab or *ex vivo* CD34$^+$ selected HCT) is prohibited.

5.7 DONOR ELIGIBILITY, SELECTION, AND RELATED PROCEDURES

Donor selection will be conducted according to local institution's BMT clinical practice guidelines. Participating HCT centers are registered and must remain in compliance with the U.S. Department of Health and Human Services FDA 21 CFR 1271. Donors shall be assessed per National Marrow Donor Program (NMDP) Donor Center and Apheresis Collection Center Procedures of Interaction that will determine compliance with FDA donor eligibility regulations. Matched unrelated donor products undergo comprehensive medical screening to determine that the donor is free of risk factors for infection due to relevant communicable diseases, as well as testing for relevant communicable disease agents prior to administration. Donors are not research subjects.

- No sibling, cord, haploidentical or syngeneic donors are eligible.
- The source of donor stem cells will be peripheral blood stem cells (PBSC) or bone marrow (BM).
- BM or PBSC should be infused into the patient within the time frame according to the institutional guidelines of each BMT site. Due to the COVID-19 situation, the NMDP strongly recommends cryopreservation of all donor products as far in advance of the initiation of patient conditioning as is feasible, dictated by the clinical situation of the patient.
- For PBSC: The recommended stem cells dose is ≥ 5.0 x 10^6, up to 10 x 10^6 CD34 cells/kg recipient weight.
- For BM infusions: The recommended cell dose is ≥ 2.0 x 10^8 mononuclear cells/kg recipient weight.

Note: The day of the stem cell/marrow infusion will be defined as day 0. If more than one day of infusion is required, then these days are defined as day 0a, day 0b accordingly. The first day after the last stem cell infusion will be defined as day 1.

5.8 POST-TRANSPLANT SUPPORTIVE CARE

Post-transplant supportive care outside of the scope of what is delineated in this protocol, for instance infection prophylaxis, will be conducted as per the local institution's BMT clinical practice guidelines.

5.8.1 Growth Factors

G-CSF may be given per institutional guidelines.

5.8.2 Seizure Prophylaxis

Keppra (Levetiracetam) will be administered for the prevention of busulfan-associated seizures to all subjects receiving busulfan. Typically, this will involve initiation of Levetiracetam 12 hours prior to Busulfan through 48 hours after last dosage. Specifics of Dosing of Levetiracetam will be administered as per the institutions BMT guidelines. Alternatively, Phenytoin or another similar seizure prophylaxis agents may be administered starting prior to starting busulfan for the prevention of busulfan-associated seizures, according to institutional practices.

5.8.3 Blood Products

Transfusion thresholds for blood product support will be consistent with the standard institutional guidelines. All blood products will be irradiated.

5.8.4 Prophylaxis Against Infections

Patients will receive infection prophylaxis according to institutional guidelines. Infection prophylaxis should include, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to reduce the risk of bacterial, Herpes simplex, CMV, EBV, *Pneumocystis jiroveci* and fungal infections:

5.8.4.1 Antifungal therapy:

Prophylaxis with fluconazole or other antifungal agents will be given as per local institutional guidelines. Fluconazole, voriconazole and other azoles are expected to increase serum cyclosporine or tacrolimus levels, therefore, dosages of cyclosporine or tacrolimus should be adjusted accordingly.

5.8.4.2 Cytomegalovirus (CMV):

CMV monitoring will be done according to institutional guidelines. It is *recommended* that at minimum weekly assessment for CMV be done through Day 100 post-transplant, and then at each clinical assessment until day 180 post-transplant. Any reactivation of CMV necessitating treatment and/or CMV end organ disease (enteritis, pneumonitis) will be captured in this study. Preemptive treatment (early treatment of CMV viremia detected by PCR) is the preferred strategy for the majority of patients. Patients receiving CMV prophylaxis with FDA approved agents (Letermovir) will be recorded. Other investigational agents for CMV prevention should be avoided while on study treatment. It is recommended that the threshold to initiate preemptive therapy will be according to a value determined by the assay being performed at the institution or a rising trend on successive measurements from patient's baseline. As an example, when using an FDA approved assay that has been calibrated, using WHO CMV standards, a threshold of 3000 international units (IU)/mL may be used.

5.8.4.3 Epstein-Barr Virus (EBV):

EBV monitoring will be done according to institutional guidelines. Any reactivation of EBV necessitating treatment and/or EBV-related post-transplant lymphoproliferative disease will be captured in this study.

5.8.4.4 *Pneumocystis jiroveci*:

Prophylaxis with Bactrim or other agents directed against *Pneumocystis jiroveci* must be administered where clinically feasible per local institutional guidelines.

5.8.4.5 Herpes Virus (HSV or VZV):

Patients must receive acyclovir or valacyclovir through Day 365 post-transplant as standard prophylaxis against HSV and VZV per institutional guidelines or until the CD4 T-cell count has normalized.

5.8.5 Sinusoidal Obstruction Syndrome (SOS) / Veno-occlusive Disease (VOD) of the Liver

Prophylaxis against SOS/VOD with ursodiol will be administered according to local institutional standard practice.

5.8.6 Donor Lymphocyte Infusions – Viral-specific cytotoxic T-Lymphocytes (CTLs)

Donor lymphocyte infusions (DLI) should only be performed for therapeutic reasons, including but not limited to relapsed or persistent disease or refractory infections. DLI should not be administered for mixed chimerism only before Day 180.

5.8.7 Intravenous Immune Globulin (IVIG).

IVIG administration for treatment and prevention of infection will be per local institutional practice.

6 STUDY DEFINITIONS

6.1 SCREENING

A patient is considered to be in the “Screening” period from the time they sign consent until the date the eligibility criteria has been determined as either “eligible” or “ineligible” (screen failure). Patients may be consented to this trial based on disease control at the time of consent, but later removed from the trial prior to initiation of transplant conditioning regimen if disease status confirmation between consenting and transplant changes. In the event this occurs, these patients will be replaced.

6.2 RANDOMIZATION

A patient is considered to be “Randomized” onto the study once they have been assigned to one of the treatment arms through randomization process. All patients will be randomized within 48 hours prior to the treatment of first dosing of either CD24Fc or placebo at day -1 (one day before transplantation).

6.3 TREATMENT PERIOD

The “Treatment Period” is defined as the first day of treatment with CD24Fc until 60 days after HCT. The assessment and reporting period for adverse events (AE) potentially related to the study drug (CD24Fc) extend through day 100 post HCT. Based upon PK data for CD24Fc this time period will allow for passage of greater than two half-lives.

6.4 FOLLOW UP PERIOD

The “Follow Up” period is defined as the first day the patient is no longer within the treatment period (i.e. day 101) until the subject comes off study. The follow-up period

can be up to 3 years post HCT. During this time subjects will be followed for acute or chronic GVHD, relapse, and survival. Data collection after one year post HCT will be minimal and can be an office visit, phone contact or review of the subject's medical chart.

6.5 ON STUDY

The "On Study" period is defined as the day the patient signs the protocol consent document, meets the protocol eligibility criteria and is randomized to a study arm, until the subject comes off study. Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons.

6.6 OFF TREATMENT

The "Off Treatment" period is generally defined as the time period where the patient completes the study drug treatment period (Day 100) or if one or more of the following criteria are met:

- Death
- Lost to follow up
- Withdrawal of consent by the patient or clinical PI for any further treatment and follow up observations
- Grade III-IV Acute GVHD requiring high dose corticosteroid therapy
- Relapse of the underlying malignancy or development of new malignancy
- Unacceptable or dose limiting toxicity or complication

Note: Subjects will be continuously monitored for all grade adverse events per local institutional guidelines within 24 hours and severe grade 3 to 5 adverse events through 100 days post-HCT (e.g. for routine post HCT care and measurement of primary clinical endpoint of acute GVHD) and then at minimum quarterly through one year. Severe adverse events occurring beyond day 100 post-HCT will be evaluated, monitored and recorded but not be reported unless related (probably or definitely) to the study drug (CD24Fc). The survival and disease relapse status will be followed for up to 3 years.

6.7 DEFINITION OF ENGRAFTMENT AND ENGRAFTMENT FAILURE

Engraftment: Engraftment for neutrophils is defined as the first of three consecutive days in which the absolute neutrophil count (ANC) is > 500/μL. Engraftment for platelets is defined as the first of three consecutive days in which the platelet count is > 20,000/μL, without transfusion support.

Primary engraftment failure: will be defined as ongoing ANC <500/μL by day 28 post HCT.

Failure to attain platelet count ≥ 20,000/μL will not be considered engraftment failure. Patients who engraft prior to day 28 and later have ANC <500/μL or platelet transfusion

requirements, as frequently occurs in HCT patients due to infection and other complications will not be considered to have engraftment failure.

7 MANAGING TOXICITIES

7.1 MANAGING INFUSION REACTIONS

Infusion reactions were not observed in the Phase I and Phase IIa clinical trials which involved 84 patients. Infusion reactions were not observed in an ongoing Phase III clinical trial in COVID-19 treatment which more than 180 patients have been dosed. However, the administration of any recombinant protein has the potential to elicit infusion reactions. CD24Fc includes the Fc portion of human IgG1. After target binding, CD24Fc may induce FcγR cross-linking, which has been associated with infusion reactions for some therapeutics.

Infusion reactions may include events such as changes in vital signs, fever, difficulty breathing, hypotension, generalized or facial edema, nausea, chills, mental status changes, urticaria or vomiting during or up to 2 hours following infusion.

Outlined below are generalized procedures designed to closely monitor, minimize and manage any potential infusion reactions:

1) CD24Fc dosing can be administered in an inpatient or an outpatient hospital unit. Premedications do not need to be administered prior to the infusion of CD24Fc to prevent infusion reactions but patients should be closely monitored during CD24Fc administration. Sites should also follow-up with the patient within 24 hours post CD24Fc administration.

2) The duration of the infusion will be over a minimum of 60 minutes. The IV rate may be reduced to prolong the duration of infusion at the discretion of the investigator and clinical team based upon symptoms suggestive of a Grade 2 infusion-related reaction. If an infusion reaction is deemed severe (e.g. severe hypotension, hypoxemia) the infusion should be stopped. Patients who develop a grade 3 or higher infusion reaction will be taken off study drug but continued on study follow up.

3) Supportive care will be provided as clinically indicated and commiserate with the intensity of the infusion reaction. The grade 2 or above infusion reaction can be treated following NCI CTEP guidelines, such as supplemental oxygen, diphenhydramine, acetaminophen, ibuprofen, IV corticosteroids (i.e. hydrocortisone) and iv fluids.

4) If a subject experiences a grade 2 infusion reaction but responds promptly to symptomatic treatment, premedication with diphenhydramine up to 4 hours prior to study drug infusion is recommended for the subsequent treatment.

5) In accordance with the preparedness for treatment of hypersensitivity reactions, severe infusion reactions, and/or cytokine release syndrome emergency resuscitation equipment, advanced cardiac life support equipment, and medications (e.g. epinephrine kit) must be readily available during CD24Fc administration.

7.2 MANAGING ACUTE GVHD

a. Acute GVHD will be graded and recorded according to MAGIC score system [57] (APPENDIX C). Patients are evaluable for the primary endpoint of acute GVHD following receipt of HCT on day 0 until day 180 after HCT. Assessment for the secondary endpoints of late onset acute GVHD or chronic GVHD endpoints will continue until one year after HCT. Acute GVHD secondary to disease relapse treatments such as reduction of immunosuppressive agents or administration of immunotherapy drugs and targeted therapy drugs should be graded and recorded until day 180 after HCT. However the study primary endpoint analysis will not include the acute GVHD secondary to the treatment to leukemia relapse.

b. The diagnosis and severity of GVHD will be determined clinically (see APPENDIX C, adults). If stool volumes are incomplete or not recorded stool frequency may be considered in grading assessment [57]. Biopsies of affected organs are strongly encouraged whenever possible. Overall acute GVHD will be assessed and graded weekly through day +100 after transplant, then at minimum monthly from Day 100 to Day 180 with quarterly thereafter. If the acute GVHD is diagnosed, the assessment and grading should be weekly until GVHD is resolved. The first day of GVHD of a certain clinical grade will be counted as the day of onset. The first day of maximum GVHD severity will also be recorded.

c. Individual organ stages will be scored by the attending physician. Stages will be reviewed by the PI, including reasons for declaring an individual organ potentially un-evaluable. For example, elevated indirect bilirubin consistent with acute hemolysis may impede liver specific GVHD grading.

d. If a patient develops acute GVHD, treatment with standard of care is recommended according to institutional BMT program clinical practice guidelines (e.g. 2 mg/kg/day of prednisone or equivalent). Other GVHD therapy, including immunosuppressives can be added at the discretion of the treating physician.

8 DOSE MODIFICATIONS BASED ON LABORATORY VALUES

8.1 HEPATIC FUNCTION

Patients receiving HCT with myeloablative conditioning may have transient elevations in LFTs and total bilirubin. However, if ALT or AST is greater than 20 times above the upper limit of normal (≥ grade 4 CTCAE v4.0 ALT/ST elevation) OR total bilirubin ≥ 5 mg/dl, CD24Fc will be temporarily suspended. If ALT, AST, and total bilirubin fall to < 5 x upper limit of normal (< grade 2 CTCAEv4.0) OR total bilirubin falls to < 2.5mg/dl within the protocol defined treatment period (up to Day +1) then CD24Fc may be administered.

9 REQUIRED OBSERVATIONS (STUDY CALENDAR):

In general, pre- and post- HCT care will follow local BMT program clinical practice guidelines for myeloablative conditioning. For example, routine history, physical, organ function testing (PFT, Echocardiogram), and laboratory evaluations (including serologic and/or PCR based viral studies) will follow institutional practice guidelines. The following assessments/samples will be obtained pre-therapy and post-therapy (Table 6). These procedures will be conducted as required observations for study unless indicated otherwise.

9.1 SPECIAL CONSIDERATIONS FOR COVID-19

The study sites should follow the ASTCT and NMDP guidelines for HCT during the COVID-19 pandemic. The study schedule has been adjusted to minimize the SARS-CoV-2 exposure risk. The post-HCT visits can be in person or by telemedicine. When a patient has acute GVHD, it is recommended that they have in person visits for more accurate assessment and grading.

TABLE 6: STUDY CALENDAR FOR PHASE III STUDY

	PRE-HCT	PRE-HCT			POST-HCT				
Observations	Day -28 to -2 (Screening and Randomization)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 4)	+ 28 (± 4)	Weekly from + 0 to +100 (± 3)
Informed Consent	x								
Medical History and Examination	x	x			x	x	x	x	x
Pre-HCT organ function and infectious disease testing[1]	x								
Pregnancy test (if applicable)	x								
Karnofsky Performance Status	x	x							
Laboratory testing[2]	x	x				x	x	x	
ECG monitoring[3]		x		x			x	x	
CD24Fc (Study Agent)[4]			x				x	x	
Hematopoietic Stem Cell Transplant (HCT)					x				
Vital Sign monitoring[5]		x		x			x	x	
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
AE Assessment (NCI CTCAE V5.0)				x	x	x	x	x	x
Assess Engraftment								x	
Bone marrow aspirate & biopsy[7]	x								
Chimerism									
Fasting Lipid Panel including LDL		x					x		
Survival Follow-Up									

TABLE 6 (CONT): STUDY CALENDAR FOR PHASE III STUDY CONTINUED.

	FOLLOW-UP PERIOD					SURVIVAL FOLLOW-UP[8]
Observations	+ 100 (± 7)	Monthly from +100 to +180 (± 7)	+270 (± 14)	+ 365 (± 14)	GVHD Onset (± 3)	Every 6 months post +365 (± 3 months)
Informed Consent						
Medical History and Examination	x	x	x	x	x	
Pre-HCT organ function and infectious disease testing[1]						
Pregnancy test (if applicable)						
Karnofsky Performance Status						
Laboratory testing[2]	x	x				
ECG monitoring[3]						
CD24Fc (Study Agent)[4]						
Vital Sign monitoring[5]						
Acute GVHD assessment[6]	x	x			x	
Chronic GVHD assessment	x	x	x	x		
Concomitant Medications	x				x	
AE Assessment (NCI CTCAE V5.0)	x	x				
Assess Engraftment						
Bone marrow aspirate & biopsy[7]						
Chimerism	x					
Fasting Lipid Panel including LDL						
Survival Follow-Up						x

NOTE: **Pre and Post-transplant observations. Patient condition and scheduling issues may impact the time of post-HCT observations. The acceptable time frame for completing these observations is ± 3 days through day 60, ± 5 days for observations from day 61 until day 100, and ± 7 to 14 days for observations from day 100 to day 365.**

1) Per institution practice guidelines: Recipient organ function testing will include MUGA or Echocardiography, Electrocardiogram, and Pulmonary Function Testing. Donor safety and eligibility assessments and screening for infectious disease markers will be performed according to national marrow donor program (NMDP) guidelines. These include but are not limited to screening for HIV, Hepatitis B and C, HTLV I/II, HSV antibody, Trypanosoma cruzi, west nile virus, syphilis and CMV. The organ function testing may be collected up to 10 weeks prior to enrollment.
2) Laboratory tests include CBC with differential, serum chemistries with creatinine, AST, ALT, and total bilirubin in pre-HCT period. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin will be performed at a minimum on the day of CD24Fc infusion and three times weekly from day 0 until ANC > 500/ul, while hospitalized for HCT. Tacrolimus levels will be monitored per institution clinical practice guidelines. Laboratory testing may be more frequent per standard HCT practice.
3) ECG monitoring will be performed on treatment days (Day -1, Day 14 and Day 28). The ECG should be measured within four hours of the start of study drug infusion and 2 hours ± 15 min after the start of infusion.
4) Per protocol, CD24Fc will be administered on day -1, day 14±4 and day 28±4. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Vital signs will be recorded prior to infusion and after CD24Fc infusion (+/- 30 min).
6) Assessment for acute GVHD will occur weekly through day 100. The weekly visits and the follow up visits can be done through telemedicine to decrease the exposure risk of COVID-19. Following day 100 acute and chronic GVHD assessments will occur monthly. The follow up visits can be done through telemedicine in case of COVID-19. MAGIC acute GVHD grading will be used to report disease severity (APPENDIX C). NIH Consensus chronic GVHD grading will be used to report chronic GVHD (APPENDIX F).
7) The Pre-HCT bone marrow biopsy may be assessed up to 6 weeks prior to enrollment.
8) The follow up of relapse and survival will be up to 3 years after HCT. If a subject withdraws from the study and does not consent to continued follow-up of associated clinical outcome information, a public records search can be performed for survival.

10 PHARMACEUTICAL INFORMATION

10.1 CD24FC OR CD24IGG (ONCOIMMUNE, INC.), STUDY AGENT

CD24Fc (CD24 Ig) is a fusion protein consisting of the extracellular domain of mature human CD24 linked to the human immunoglobulin G1 (IgG1) Fc domain.

10.1.1 Molecular Formula and Formulation

The complete molecular formula of CD24Fc has not been determined at this time. The mature protein is 261 amino acids long and each CD24Fc molecule includes the 30 amino acid CD24 extracellular domain. CD24Fc forms a disulfide-linked homodimer with a predicted mass of 57.7 kilodaltons (kDa) based on the homodimer amino acid sequence. However, the apparent molecular weight of the intact dimer is approximately 80 KDa based on non-reduced SDS-PAGE. The CD24 domain is highly glycosylated with both N-linked and O-linked oligosaccharides, which comprise approximately 80% of the mass of the CD24 domain.

CD24Fc has been formulated as single dose injection solution, at a concentration of 10 mg/mL in phosphate buffered saline at pH 7.2. Each CD24Fc Drug Product vial contains 120 mg of CD24Fc in a volume that allows for extractable 12 ml. Each vial will be labeled according to Title 21 of the U.S. Code of Federal Regulations with product name “CD24Fc” and “Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use”.

10.1.2 Packaging, Ordering, and Inventory Management

CD24Fc Drug Product is supplied in clear borosilicate glass vials with chlorobutyl rubber stoppers and aluminum flip off seals. Vials are further packaged into 8 vial patient kit boxes comprising labeled paperboard boxes outfitted with cardstock box dividers and tamper evident seals. Drug product vials are stored at OncoImmune’s clinical distribution site, Almac Clinical Services, at 25 Fretz Road, Souderton, PA. On site inventory will be managed by Medpace and additional drug will be ordered by Medpace and shipped directly to the drug site from Almac.

10.1.3 Availability, Storage and Stability

CD24Fc is supplied as a sterile, clear, colorless, preservative-free aqueous solution for parenteral administration. CD24Fc is stored at -20° C until use. CD24Fc should be thawed and equilibrated to room temperature prior to administration. CD24Fc Drug Product used in the Phase I and Phase IIa trials (Lot 09MM-036) is stable for at least 66 months at -20^{o}C, for 6 months at 5°C and 3 months at 25^{o}C. New CD24Fc Drug Product has been manufactured as “Lot 0118-002”. Stability studies for Lot 0118-002 are ongoing and it has demonstrated to be stable for 24 months at the intended storage temperature, -20^{o}C, for 6 months at 5^{o}C and 1 month at 25°C.

10.1.4 Administration

CD24Fc at doses 480 mg or 240 mg should be prepared in a diluent comprising 0.9% Sodium Chloride in a volume of 100 ml and be administrated by intravenous infusion over a minimum of 60 minutes.

CD24Fc is intended for use under the guidance and supervision of a physician.

- CD24Fc is formulated as single dose injection solution, at a concentration of 10 mg/mL at pH of 7.2. Each CD24Fc vial contains 120 mg of the fusion protein in 12 mL injection solution.
- CD24Fc is stored at -20° C until use. CD24Fc should be thawed to room temperature prior to administration.
- No precipitation or visible particulates were observed when the CD24Fc Drug Product was formulated with saline for 72 hours at 2 - 8°C or at room temperature.

The constituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.
2. For the first treatment, 4 vials of CD24Fc is required for 480mg, with a total of 48 ml in volume. 52 ml sterile 0.9% Sodium Chloride Injection, USP, is required to reach a final volume of 100 ml for the dose of 480 mg CD24Fc. Using an empty IV bag, add 52 ml sterile 0.9% Sodium Chloride followed by 48 ml CD24Fc solution. Gently mix.
3. For second and third treatments, 2 vials of CD24Fc is required for 240mg, with a total of 24 ml in volume. 76 ml sterile 0.9% Sodium Chloride Injection, USP, is required to reach a final volume of 100 ml for the dose of 240 mg CD24Fc. Using an empty IV bag, add 76 ml sterile 0.9% Sodium Chloride followed by 24 ml CD24Fc solution. Gently mix.
4. The CD24Fc infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 60 minutes (≤ 100 mL/hr). A latex-free DEHP-free infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less) must be used.
5. At the end of infusion, add a small amount of saline (25 ml) according to institution guideline for the flushing of the line to ensure the entire volume of study drug is infused. The 25 ml saline solution flushing should be given at the same infusion rate.

The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.

No physical biochemical compatibility studies have been conducted to evaluate the co-administration of CD24Fc with other agents. CD24Fc should not be infused concomitantly in the same intravenous line with other agents.

10.1.5 Safety in Humans

10.1.5.1 Phase I Safety Data

A Phase I, randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, and PK of CD24Fc in healthy male and female adult subjects was conducted. Details are also provided in section 3.8 A total of 40 subjects were randomized in 5 cohorts of 8 subjects each, and 39 subjects completed the study. CD24Fc was administered via IV infusion over 1 hour. In total, 18 (45.0%) subjects had a treatment-emergent adverse event (TEAE) during the study: 6 (60.0%) subjects in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 3 (50.0%) subjects in the CD24Fc 30 mg group, 2 (33.3%) subjects in the CD24Fc 60 mg group, 3 (50.0%) subjects in the CD24Fc 120 mg group, and 2 (33.3%) subjects in the CD24Fc 240 mg group.

All TEAEs in the study were considered mild to moderate in severity by the Investigator except for 1 subject in the placebo group who experienced a severe headache. The most common TEAEs were headache (6 [15.0%] subjects), burns second degree (3 [7.5%] subjects), non-sustained ventricular tachycardia (2 [5.0%] subjects), and upper respiratory tract infection (2 [5.0%] subjects).

Overall, 5 (12.5%) subjects had a study drug-related TEAE: 1 (10.0%) subject in the placebo group, 2 (33.3%) subjects in the CD24Fc 10 mg group, 1 (16.7%) subject in the CD24Fc 30 mg group, and 1 (16.7%) subject in the CD24Fc 60 mg group. The study drug-related TEAEs during the study were headache (4 [10.0%] subjects) and ventricular tachycardia (1 [2.5%] subject). A drug-related SAE of ventricular tachycardia was experienced by 1 subject in the CD24Fc 60 mg group. This SAE occurred at a rate comparable with normal populations, was considered mild by the Investigator, and did not lead to discontinuation from the study. No subjects died during the study and no subjects discontinued from the study due to an adverse event. There were no clinically meaningful changes from baseline in laboratory parameters, vital signs, ECGs, or physical exams during the study.

10.1.5.2 Phase IIa Safety Data

The number of subjects with TEAEs from Day -1 to 30 or 60 days after the last dosing was the same between all treatment groups: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo experienced TEAEs.

The most common TEAEs were stomatitis (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 6 [100.0%] patients who received placebo); platelet count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 [83.3%] patients who received placebo); white blood cell count decreased (6 [100.0%] patients in the 240 mg CD24Fc single dose cohort, 6 [100.0%] patients in the 480 mg

CD24Fc single dose cohort, 5 [83.3%] patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 4 [66.7%] patients who received placebo). Severe stomatitis (≥ Grade 3) occurred in 3 (50.0%) patients in the 240 mg CD24Fc single dose cohort, 4 (66.7%) patients in the 480 mg CD24Fc single dose cohort, 2 (33.3%) patients in the 480/240/240 mg CD24Fc multiple dose cohort, and 5 (83.3%) patients who received placebo, with a clear inverse correlation between CD24Fc doses and duration of severe stomatitis.

One (16.7%) patient in the 480 mg CD24Fc single dose cohort and 2 (33.3%) patients who received placebo experienced a study drug-related TEAE. The most common study drug-related TEAE was diarrhea (1 [16.7%] patient in the 480 mg CD24Fc single dose cohort and 2 [33.3%] patients who received placebo). No patients in other cohorts experienced a study drug-related TEAE.

The incidence of Grade 3/4/5 TEAEs was the same between all treatments: 6 (100.0%) patients in the 240 mg CD24Fc single dose cohort, 6 (100.0%) patients in the 480 mg single dose cohort, 6 (100.0%) patients in the 480/240/240 mg multiple dose cohort, and 6 (100.0%) patients who received placebo. One (16.7%) patient in the 480 mg CD24Fc single dose cohort experienced hyperglycemia that was considered a study drug-related Grade 3/4/5 TEAE.

No patients receiving CD24Fc experienced a DLT during the study. One dose-limiting toxicity (DLT) was observed in the placebo group

In total, 1 (4.2%) patient died during the study. Patient 103-001 received placebo and experienced Grade 4 pneumomediastinum and Grade 5 pneumonia TEAEs that resulted in death. Per the Investigator, it was considered unlikely that these TEAEs were related to study drug.

10.1.6 Treatment Emergent SAEs (TESAEs)

In total, 9 (37.5%) patients experienced TESAEs from Day -1 to 30/60 days after the last dosing: 2 (33.3%) patients in the 240 mg CD24Fc single dose cohort (30 days), 1 (16.7%) patient in the 480 mg CD24Fc single dose cohort (30 days), 4 (66.7%) patients in the 480/240/240 mg CD24Fc multiple dose cohort (60 days), and 2 (33.3%) patients who received placebo (30, 30, 60 days). Treatment-emergent SAEs reported for patients who received CD24Fc (some patients had more than one condition) were nausea (2), stomatitis (1), abdominal pain (1), dehydration(1), decreased appetite (1), device related infection (1), pain (1), weight decreased (1), arthritis (1), cognitive disorder (1), and embolism (1).

In total, 1 patient experienced a TEAE that led to discontinuation of study drug: this patient received placebo. Patient 103-001 experienced a Grade 4 pneumonia TEAE that led to discontinuation of study drug (ie, placebo). Per the Investigator, it was considered unlikely that this TEAE was related to study drug.

In Chemistry laboratory tests, the incidence of TEAEs of alanine aminotransferase increased or blood alkaline phosphatase increased were similar between patients who received CD24Fc and patients who received placebo (ALT: 44% vs 50%; ALP 22% vs

17%). The incidence of TEAEs of aspartate aminotransferase increased was higher for patients who received CD24Fc compared to patients who received placebo (28% vs 18%). Treatment-emergent adverse events of blood creatinine increased were only reported by patients who received placebo (33.3%). A TEAE of blood bilirubin increased was reported by 1 (16.7%) patient who received placebo. In general, TEAEs were consistent with toxicities normally associated with HCT conditioning and did not appear associated with investigational therapy or placebo.

Hematologic Effects:

In total, the incidence of TEAEs of white blood cell count decreased, lymphocyte count decreased, and neutrophil count decreased were higher in patients who received CD24Fc compared to patients who received placebo (white blood cells decrease 94% vs 67%, lymphocyte decrease 83% vs 50%, neutrophil decrease 89% vs 50%). The incidence of TEAEs of platelet count decreased was similar between patients who received CD24Fc and patients who received placebo (94% vs 83%).

No patient had a laboratory abnormality that was considered an SAE or resulted in discontinuation of study drug.

No patients who received either single or multiple dosing of CD24Fc had positive ADA results at any time point sampled pre- or post-infusion.

A TEAE of weight increased was reported by 1 (16.7%) patient who received placebo and a TEAE of weight decreased was reported by 3 (16.7%) patients who received CD24Fc. A TEAE of ECG QT prolonged was reported by 1 (16.7%) patient who received placebo.

Donor Cell Engraftment and Chimerism:

In total, 18 (100.0%) patients who received CD24Fc and 6 (100.0%) patients who received placebo experienced neutrophil engraftment. The median time to neutrophil engraftment was 13.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.5 days for patients in the 480 mg CD24Fc single dose cohort, 13.0 days for patients in the 480/240/240 mg CD24Fc multi-dose cohort, and 15.5 days for patients who received placebo.

In total, 18 (100.0%) patients who received CD24Fc and 5 (83.3%) patients who received placebo experienced platelet engraftment. The median time to platelet engraftment was 15.5 days for patients in the 240 mg CD24Fc single dose cohort, 13.0 days for patients in the 480 mg CD24Fc single dose cohort, 12.0 days for patients in 480/240/240 mg CD24Fc multiple dose cohort, and 15.0 days for patients who received placebo. No patients experienced primary engraftment failure.

The mean CD3 cell chimerism on Day 28/Day 30 was 73.0% donor cells for patients who received CD24Fc and 77.4% donor cells for patients who received placebo. The mean CD3 cell chimerism on Day 100 was 80.9% donor cells for patients who received CD24Fc and 73.8% donor cells for patients who received placebo.

The mean CD33 cell chimerism on Day 28/Day 30 was 100.0% donor cells for patients who received CD24Fc and 100.0% donor cells for patients who received placebo. The mean CD33 cell chimerism on Day 100 was 99.4% donor cells for patients who received CD24Fc and 96.6% donor cells for patients who received placebo.

10.1.7 Pharmacokinetics in Humans

10.1.7.1 Phase I PK

The PK of CD24Fc in healthy human subjects was determined from the single dose Phase I study. The mean plasma concentration of CD24Fc increased proportionally to the dose of CD24Fc administered (Figure 14). For all dose groups except 120 mg, the maximum mean plasma concentration of CD24Fc was reached at 1 hour post-dose. The maximum mean plasma concentration of CD24Fc for the 120 mg group was reached at 2 hours post-dose. By Day 42 (984 hours), the mean plasma concentration of CD24Fc for all groups had decreased to between 2% and 4% of the maximum mean plasma concentration. CD24Fc reached Tmax at 1.34 hours. The t½ of plasma CD24Fc range was 280.83 to 327.10 hours.

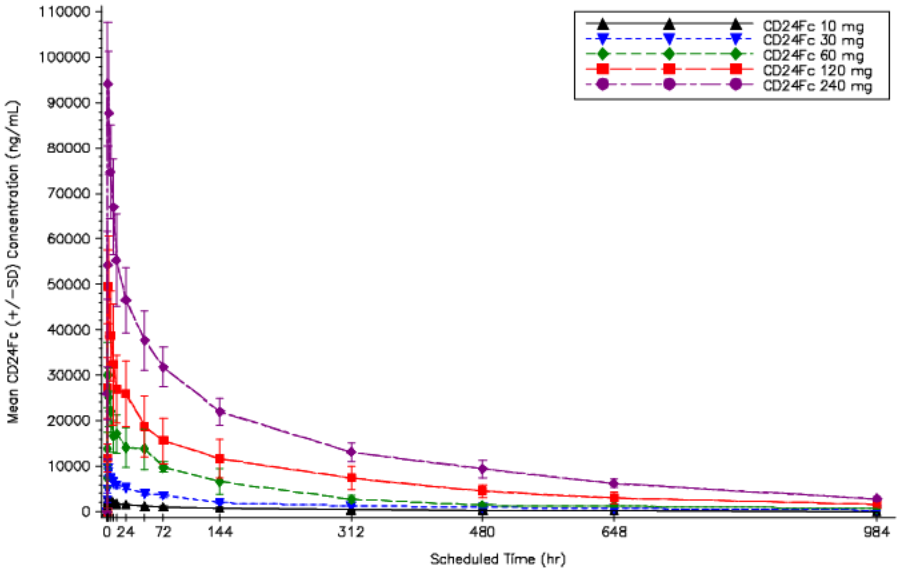

FIGURE 14: PLOT OF MEAN (±SD) PLASMA CD24FC CONCENTRATION BY TREATMENT – PK EVALUABLE POPULATION. PK = PHARMACOKINETIC; SD = STANDARD DEVIATION.

Source: Investigators Brochure.

10.1.7.2 Phase IIa PK

The PK of CD24Fc in human subjects undergoing HCT has been determined from the Phase IIa study from the two single dose cohorts and one multi-dose cohort (Figure 15). With the 240 mg single dose, the mean plasma concentration of CD24Fc is similar to the 120 mg single dose in Phase I human volunteers. The 480 mg dose shows a proportional increase of CD24Fc at all time points. The 480/240/240 mg multi-dose maintains the

CD24Fc plasma concentration over 10,000 ng/ml over the period of Day-1 to Day 42 post-HCT.

Following a single IV administration of CD24Fc (240 and 480 mg CD24Fc single dose cohorts), the geometric mean plasma exposure ($C_{max,-1d}$, AUC_{0-42d}, and AUC_{0-inf}) increased with increasing CD24Fc doses. The mean $t_{½}$ and λ_z were similar between the 240 and 480 mg doses of CD24Fc. The mean values of $t_{½}$ were 414.739 and 406.648 h and the mean values of λ_z were 0.0018 and 0.0017 h^{-1} for the 240 and 480 mg CD24Fc single dose cohorts, respectively. Additionally, there was an increase in the mean V_z and CL between the 240 and 480 mg doses of CD24Fc.

Following multiple IV administrations of CD24Fc (480/240/240 mg CD24Fc multi-dose cohort), the exposure of CD24Fc was sustained over time. Additionally, the mean plasma CD24Fc concentration on Day 100 was higher for the 480/240/240 mg CD24Fc multi-dose cohort (850.84 ng/mL) compared to the single dose cohorts (216.38 ng/mL and 330.96 ng/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively). Furthermore, the geometric mean $AUC_{0-last,overall}$ value was higher for the 480/240/240 mg CD24Fc multi-dose cohort (37,363,953.5 ng·h/mL) compared to the single dose cohorts (10,156,549.9 ng·h/mL and 15,522,686.2 ng·h/mL for the 240 and 480 mg CD24Fc single dose cohorts, respectively).

The median $t_{max,-1d}$ (2.10 h for both the 240 and 480 mg CD24Fc single dose cohorts and 2.13 h for the 480/240/240 mg CD24Fc multiple dose cohort) remained consistent across all of the CD24Fc doses. For the 480/240/240 mg CD24Fc cohort, the median $t_{max,-1d}$ and $t_{max,28d}$ were similar (2.13 and 2.52 h, respectively).

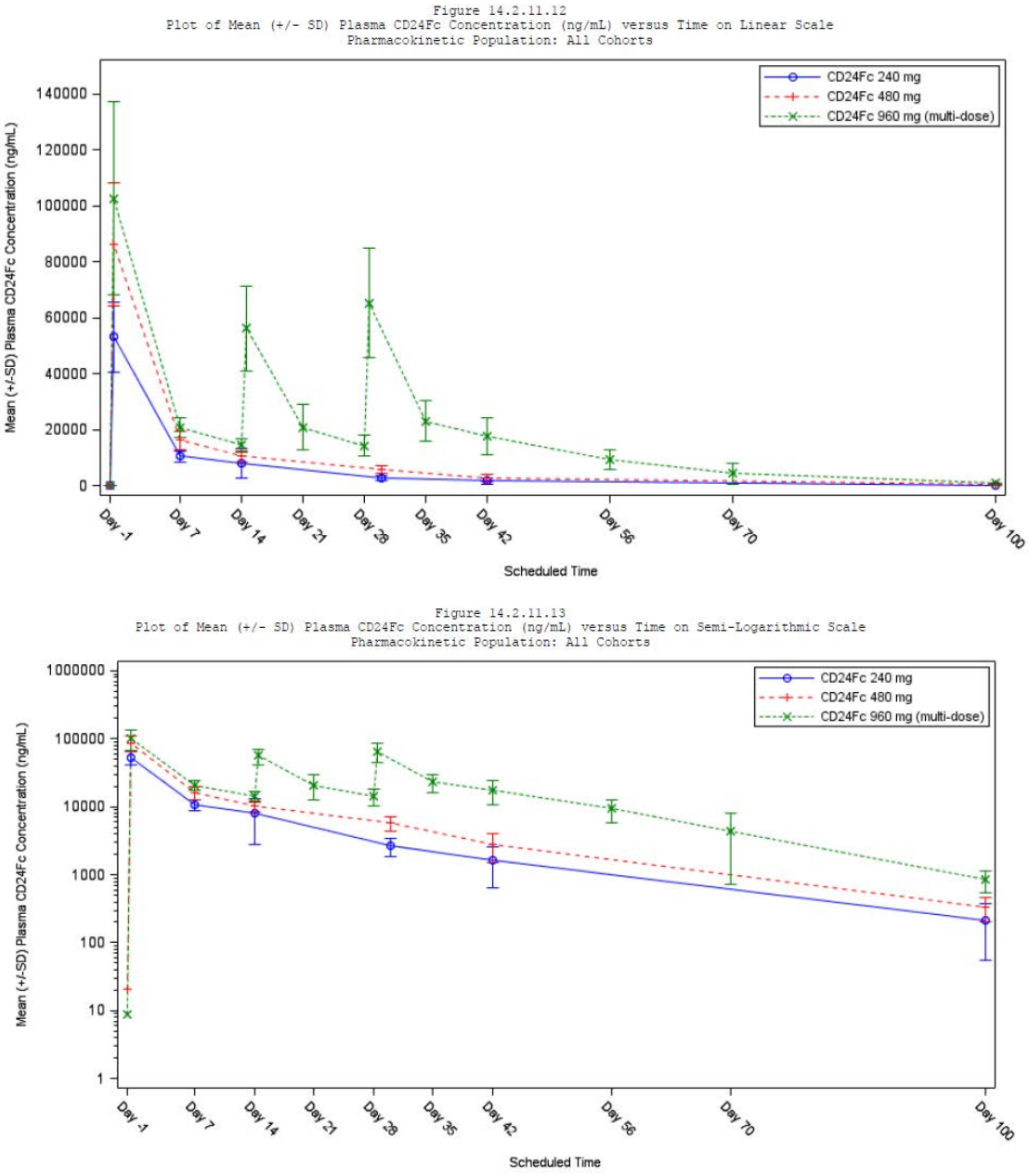

FIGURE 15: PLOT OF MEAN (±SD) PLASMA CD24FC CONCENTRATION BY TREATMENT – PK EVALUABLE POPULATION.
UPPER PANEL: PK IN LINEAR SCALE. LOWER PANEL: PK IN SEMI-LOG SCALE. SINGLE DOSE COHORTS, 240MG (N=6); 480MG (N=6); MULTI-DOSE COHORT, 480-240-240MG (N=6).

10.1.8 Immunogenicity in Humans

10.1.8.1 Phase I ADA

Serum samples in the Phase I study were screened for anti-drug antibodies. Anti-CD24Fc antibodies were detectable at Day 28 and Day 42 in 1 subject in each of the 5 dose cohorts; however, for the subject in the CD24Fc 120 mg group and the subject in the CD24Fc 240 mg group, anti-CD24Fc antibodies were also detectable pre-dose at levels higher than post-dose levels. Except for those subjects with significant pre-dose anti-CD24Fc antibody levels, all post-dose anti-CD24Fc antibody levels were modest. No deviations in PK were found in any subjects with detectable anti-CD24Fc antibody levels.

10.1.8.2 Phase IIa ADA

In the Phase IIa allogeneic HCT context, given the immunoablation and immunosuppression of host immunity at time of CD24Fc administration, ADA responses were monitored but unlikely to be elicited.

For the two single dose cohorts, the samples were collected at 7 time points from Day-1 to Day 100. For the multi-dose cohort, the samples were collected at 13 time points from Day-1 to Day 100. As expected, all samples are negative for ADA in the Phase IIa study.

10.2 PLACEBO

The placebo will consist of 100 ml of 0.9% Sodium Chloride.

CD24Fc is supplied as a sterile, clear, colorless, preservative-free aqueous, solution and thus is indistinguishable from placebo (saline). Since CD24Fc has not been associated with infusion reactions and is a clear, colorless liquid, saline should be an effective placebo.

The study drug (CD24Fc or placebo) will be labeled anonymously in order to maintain the study blind.

The Phase III study will randomize patient in 1:1 ratio to receive either CD24Fc or Placebo.

10.3 METHOTREXATE

10.3.1 Formulation

Methotrexate: N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid, is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, adult rheumatoid arthritis, and prevention of acute GVHD. Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication.

10.3.2 Availability and administration

Methotrexate sodium for injection is available in 25 mg/ml solution. The appropriate amount is drawn into a syringe for administration. Store at controlled room temperature, 20°-25° C (68°-77° F); excursions permitted to 15°-30° C (59°-86° F). Protect from light.

10.3.3 Potential Side Effects

The most frequently reported adverse reactions associated with methotrexate use as GVHD prophylaxis include ulcerative stomatitis, leucopenia and suppressed hematopoiesis, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Methotrexate may be associated with increased rates of pulmonary complications after transplantation. The risk of infections is due to the suppression of hematopoiesis after transplantation.

10.3.4 Potential Drug Interactions

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored. Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

10.4 TACROLIMUS (PROGRAF, FK506)

10.4.1 Formulation

Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. 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. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the generation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

10.4.2 Availability and administration

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 1-mg capsule shell contains gelatin and titanium dioxide, and the 0.5 mg and 5-mg capsules shell contains gelatin, titanium dioxide and ferric oxide. Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection before use. Intravenous administration will be given by continuous infusion. Oral preparation will be administered on empty stomach every 12 hours.

10.4.3 Potential Side Effects

a. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

b. Nephrotoxicity has been noted in 40% and 33% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein - Barr virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to Prograf following long-term immunosuppression therapy.

c. Mild to severe hyperkalemia has been noted in 44% and 10% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials and may require treatment.

d. Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf. Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

e. Hypertension is a common adverse effect of Prograf therapy. Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus can cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

f. Hyperglycemia was associated with the use of Prograf in 47% and 29% of liver transplant recipients in the U.S. and European randomized studies, respectively and may require treatment.

10.5 CYCLOSPORINE (SANDIMMUNE, NEORAL)

NOTE: Per protocol Cyclosporine will only be administered as a second line agent in cases where tacrolimus is no longer indicated due to intolerance (i.e. CNS toxicity) or unavailable commercially. Cyclosporine is a cyclic polypeptide immunosuppressant agent produced by the fungus species Beauveria nivea. While the molecular structure of cyclosporine is distinct from tacrolimus, their mechanism of action is almost indistinguishable and involves inhibition of calcineurin and the resulting activation cascade leads to inhibition of T cell signaling. Cyclophilin is the cytosolic binding protein for cyclosporine that is distinct from FK binding protein. Refer to the FDA-approved package insert for more information

10.5.1 Oral or Intravenous Availability

a. Cyclosporine is most commonly prescribed as soft gelatin capsules (neoral) or modified oral solution (Neoral Oral Solution) that have increased bioavailability in comparison to the less commonly used Sandimmune formulations. Neoral and Sandimmune cannot be used interchangeably and care must be exercised when converting from high doses of Sandimmune to Neoral. Neoral capsules are available in two strengths: 25 mg (oval, blue-gray) or 100 mg (oblong, blue-gray) imprinted in red. Neoral Oral solution is available in 50 mL bottles of yellow liquid containing 100 mg/mL of cyclosporine. Both neural formulations contain 11.9% v/v alcohol. Sandimmune capsules are available in two strengths: 25 mg (oblong, pink) or 100 mg (oblong, dusty rose), in unit dose packages of 30 capsules that should be stored at 25°C (77°F). Sandimmune Oral solution is available in 50 mL bottles of yellow liquid containing 100 mg/mL of cyclosporine. Both Sandimmune formulations contain ~12.5% v/v alcohol.

b. Sandimmune IV solution is supplied in 5 mL ampoules that contain 50 mg of cyclosporine per mL, Cremaphor and 32.9% alcohol v/v.

c. Neoral or Sandimmune is available through the hospital pharmacy during all inpatient admissions and through the local pharmacy for outpatient management.

10.5.2 Storage and Handling

Sandimmune should be stored in the original container below 25°C (77°F). Neural capsules and oral solution should be stored at 20°C-25°C (68°F-77°F) and not in the refrigerator. Sandimmune intravenous solution should be stored at temperatures below 30°C (86°F) but not in the refrigerator and should be protected from light.

Oral or Intravenous Administration

a. Do not administer liquid from plastic or Styrofoam cup. May dilute Neoral oral solution with orange juice or apple juice. May dilute Sandimmune oral solution with milk, chocolate milk, or orange juice. Avoid changing diluents frequently. Mix thoroughly and drink at

once. Use syringe provided to measure dose. Mix in a glass container and rinse container with more diluent to ensure total dose is taken. Do not rinse syringe before or after use (may cause dose variation).

b. Intravenous administration will be given by continuous infusion. Discard solution after 24 hours. Anaphylaxis has been reported with intravenous use; reserve for patients who cannot take oral form. Patients should be under continuous observation for at least the first 30 minutes of the infusion, and should be monitored frequently thereafter. Maintain patient airway; other supportive measures and agents for treating anaphylaxis should be present when intravenous drug is given.

10.5.3 Sirolimus or other prevention regimen

If patient cannot tolerant either Tacrolimus or Cyclosporine, Sirolimus or other GVHD prevention regimen should be given per institution practice guideline. The change of GVHD prophylaxis regimen should get approval by the PI and protocol chair.

10.5.4 Potential drug interactions

Cyclosporine is extensively metabolized by the cytochrome P450 (CYP3A4) system. Drugs that may increase cyclosporine blood concentrations include: calcium channel blockers (e.g., diltiazem, nicardipine, nifedipine, verapamil), antifungal agents (e.g., ketoconazole, clotrimazole, fluconazole, itraconazole, voriconazole, pozaconazole), macrolide antibiotics (e.g., clarithromycin, erythromycin, troleandomycin), gastrointestinal prokinetic agents (e.g., cisapride, metoclopramide), and/or other drugs (e.g., bromocriptine, cimetidine, tacrolimus, danazol, ethinyl estradiol, omeprazole, nefazodone, HIV-protease inhibitors. Drugs that may decrease cyclosporine concentrations include: anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin), antibiotics (e.g., rifabutin, rifapentine), and/or herbal preparations (e.g., St. John's Wort [hypericum perforatum]). Refer to http://medicine.iupu.edu/clinpharm/ddis/table.aspx for current information about drug interactions with calcineurin inhibitors.

10.5.5 Excretion

The absorption of cyclosporine after oral administration is incompletely dependent on the individual patient, patient population and the formulation. Cyclosporine is extensively metabolized by CYP3A4 and to a lesser extent in the gastrointestinal tract and kidney. At least 25 metabolites have been identified in bile, feces, blood and urine but the parent compound is primarily responsible for the immunosuppressive activity. Elimination is primarily biliary with only 6% of the dose excreted in urine. The mean terminal elimination half-life (T1/2) of cyclosporine is 8.4 hours (range 5-18 hours). The mean T1/2 was reduced by 2-3 fold in patients with impaired hepatic function. Dosage reduction is recommended for patients with mild to moderate hepatic impairment.

11 ADVERSE EVENTS AND REPORTING CRITERIA

11.1 DEFINITION OF ADVERSE EVENTS

Adverse Event (AE): An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease temporarily associated with or occurring during the use of an investigational product whether or not considered related to the investigational product. As such, the AEs will be continuously followed and reported after the study subjects have been started on the investigational drug and recorded on the appropriate electronic case report form (eCRF).

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

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

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

These events may be:

- *Related:* clearly or likely associated with study drug/treatment
- *Not related: unlikely or definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as related to the study drug if the Investigator believes that at least one of the Number 1 or Number 2 criteria plus at least one of the Number 3 or Number 4 criteria are met:

1. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
2. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.

3. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
4. A potential alternative cause does not exist.

Serious Adverse Experience (SAE): Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening adverse drug experience,
  Note: An adverse event or adverse reaction is considered 'life-threatening' if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization,
  Note: Any hospital admission that is >24 hours is considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (e.g. no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- a persistent or significant disability/incapacity,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Expected Events*:* - An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section for the list of expected adverse events related to the drug under study.

Unexpected adverse events: - An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

11.2 DEFINITION OF AE SEVERITY

The severity or grade of an adverse event may be measured using the following definitions:

Event grading: The NCI Common Terminology Criteria (CTCAE Version 5.0) will be used to grade intensity of adverse events and assist in reporting adverse events.

Mild: Noticeable to the subject, but does not interfere with the subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study. In the transplant setting CTCAE version 5.0 grades 1 and 2.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study. In the transplant setting using the CTCAE version 5.0 some grade 2 and most grade 3.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve. In the transplant setting using the CTCAE version 5.0 some grades 3 and all grade 4.

11.3 AE AND SAE REPORTING REQUIREMENTS

11.3.1 AE Reporting

Reports of AEs and SAEs will be sent by the clinical site PI or PI designated clinical coordinator directly to the CRO, which will be disseminated to the Sponsor, PI, IRB, FDA and other regulatory bodies, as appropriate.

In order to maintain the safety of subjects, the following study specific AE / SAE reporting plan has been devised.

Reporting to Sponsor:

As the expectation of a high rate of low grade adverse events associated with conditioning regimen and HCT procedure, only Grade 3 to 5 AEs (regardless attribution) will be recorded in the patient's source and entered into the electronic data capture system from the time of CD24Fc or placebo infusion through day 100 post HCT.

All grade AE will be recorded only within 24 hours of start of an infusion of CD24Fc/placebo.

The acute GVHD is the study primary endpoint. Infections and leukemia relapse are study endpoints. The CMV reactivation, myeloablative conditioning regimen associated myelosuppression, anemia, thrombocytopenia, mucositis will not be considered as AE as these are expected events in HCT. The post-HCT hospital re-admission due to these conditions will be recorded.

Reporting of SAEs to the IRB

The Investigator must comply with the applicable regulatory requirements related to the report of SAEs to their Institutional Review Board (IRB). The IRB must be informed in a

timely manner by the Investigator, or their designee, of SAEs occurring at their study site during the study, as required. The Investigator must also submit safety reports provided by the Sponsor to their IRB, as required.

Reporting of SAES to the FDA

In accordance with FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312): In this trial, serious, unexpected adverse events believed to be related to the study treatment will be reported to the FDA as applicable.

SAE Reporting-Procedures for Investigators

Initial Reports

All SAEs occurring from the time of CD24Fc or placebo infusion up to and including 100 days post HCT must be reported to the CRO within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the investigator considers related to study drug occurring after 100 days post HCT must be reported to the CRO.

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

The CRO will disseminate information regarding SAEs to the participating sites within 15 days of review of the information by the CRO only in the case that the event(s) is believed to be unexpected and related to the study drug.

Follow-up Reports

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

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

Safety Contact Information:

Medpace Clinical Safety
Telephone: PPD
Facsimile: PPD
E-mail: PPD

11.3.2 Pregnancy Reporting

If the subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the CRO within 24 hours of being notified.

A subject becoming pregnant prior to administration of study drug will immediately be withdrawn from the study.

A subject becoming pregnant within the treatment period drug should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the CRO. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

11.3.3 Emergency Unblinding

In situations where the Investigator believes that knowledge of the Subject's treatment assignment is required to select appropriate continuing therapy for the disease under study, the Investigator may unblind the Subject's treatment assignment. The Investigator should make every effort to contact the Medical Monitor before unblinding a Subject's treatment assignment unless the urgency of the case requires immediate action. All other members of the study team should remain blinded to treatment assignment. If a Subject's treatment assignment is unblinded, the CRO must be notified within 24 hours as outlined in the Site Blinding Plan.

The procedure for emergency unblinding and associated reporting is provided in the Site Blinding Plan located in the investigator site file (ISF) and pharmacy binder.

12 DATA SAFETY MONITORING PLAN (DSMP)

The CRO Medpace will collect the data and provide the data to an independent DMC at the planned safety monitoring meetings and the pre-specified interim analysis. This is to ensure the safety of subjects, the validity of research data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. This protocol will conduct a data and safety monitoring process as described in the plan below.

12.1 TRAINED AND CERTIFIED PERSONNEL

All of the research protocol personnel who will work with study subjects, study subject data or subjects' research samples have completed training in the protection of human research subjects per guidelines issued by the U. S. Department of Health and Human Services, Office of Human Research Protections. The investigator and designated associates have attended an IRB sponsored HIPAA research presentation in accordance with the policy of the study site. Each participant in this research trial will be listed by study specific numbers, without initials or date of birth; however, the date of transplant may be included when corresponding with the IRB or outside agencies.

Designation of Responsibilities: The Clinical Principal Investigator(s) are solely responsible for the implementation, conduct and safety of human subjects enrolled in this trial. The Clinical Principal Investigator has however, designated associates to assist with the protocol implementation which includes but is not limited to the following:

1. BMT Physicians – have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation, AE assessment and reporting, adherence to all regulations.

2. BMT Research Nurse(s) - have been designated to assist with participant education, informed consent process, study implementation and compliance, recording of primary source documentation and adherence to all regulations.

3. BMT Data Manager(s) - have been designated to assist with patient enrollment/eligibility, verification of protocol compliance, all data collection and recording from primary source, AE reporting, DSM reports and adherence to all regulations.

4. BMT Clinical Team - The members of the BMT clinical team that have been designated to assist the investigator in any aspect of this protocol will be listed on the protocol specific designation log.

12.2 STORAGE AND DISSEMINATION OF REPORTS

Medpace is responsible for collecting all safety data in the electronic Case Report Forms (eCRFs) from all participating institutions and providing the data to the independent DMC.

12.3 CLINICAL MONITORING PROCEDURES

Clinical studies must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices and in compliance with other applicable regulatory requirements. The following measures have been taken to ensure the safe conduct of this clinical trial:

This study will be continuously monitored by medical monitor from Sponsor and from the CRO. Monitoring visits will be made during the conduct of the study and at study close-out. Monitoring visits can be conducted remotely.

Prior to subject recruitment, a site initiation meeting will be conducted by the Sponsor or the CRO through teleconference. The PI and the study staff should make every effort to attend the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed by the appropriate personnel until they have been answered and resolved.

Monitoring of the study site will be performed by the CRO. The purpose is to verify:

a. Adherence to the protocol
b. Completeness and accuracy of study data and samples collected
c. Proper storage, dispensing, and inventory of study medication
d. Compliance with regulations

Monitoring may be in the form of a site visit or a remote review of the documents. During a monitoring visit, access to relevant hospital and clinical records must be given by the clinical site PI to the CRO representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The CRO expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated and are expected to be resolved in a timely manner.

At close-out visit will occur upon completion, termination, or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and the clinical site PI will be informed of his / her ongoing responsibilities.

12.4 INDEPENDENT DATA MONITORING COMMITTEE (DMC)

An independent DMC has been convened for the Phase III study. The purpose of the DMC is to safeguard the interests of study subjects, assess the safety of the interventions, and monitor the overall conduct of the study. The DMC acts as an advisory to the clinical study leadership team of OncoImmune. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The leadership team will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the trial, and for determining whether amendments to the protocol or changes to the study conduct are required.

13 QUALITY ASSURANCE AND AUDITS

Audits provide assurance that trials are conducted in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in

compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. All audit findings are reported to the DMC and the sponsor. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the CRO and Sponsor that such a request has been made.

14 REMOVAL FROM STUDY

Patients have the right to withdraw from the study at any time for any reason. The clinical site PI also has the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a patient (or a patient's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation should be made at the time of the patient's withdrawal with an explanation of why the patient is withdrawing. Patients may be removed from the study treatment if one or more of the following events occur:

- Significant protocol violation or noncompliance, either on the part of the patient or the clinical site PI.
- Refusal of the patient to continue treatment and / or observations.
- Unacceptable or dose-limiting toxicity.
- Decision by the clinical site PI that removal from the study is in the patient's medical interest.
- Unrelated medical illness or complication.
- Lost to follow-up.
- Disease relapse or progression.

In the event a subject fails to appear for a scheduled follow-up visit, Institution and/or Principal Investigator shall use reasonable efforts contact the subject within ten (10) days after the date of the scheduled visit regarding the failure to keep the appointment. If a subject withdraws from the Study, Institution and Principal Investigator shall use reasonable measures to follow up with the subject in person or by telephone (if possible), otherwise by certified mail, to determine the reason for the discontinuance.

15 STATISTICAL CONSIDERATIONS

15.1 STUDY DESIGN

The study is designed as a Phase III randomized, double blind, placebo controlled, multicenter trial to compare CD24Fc/Tac/MTX with Placebo/Tac/MTX in the setting of myeloablative conditioning (MAC), matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplantation (HCT) in patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).

The primary endpoint is 180 day grade III-IV acute GVHD-free survival (aGFS). An event for this time-to-event outcome is defined as grade III-IV aGVHD, or death by any cause, whichever occurs first.

The target enrollment is 180 patients in total, with 90 patients on each of the two treatment arms.

15.2 ACCRUAL

It is estimated that 24 months of accrual will be necessary to enroll the targeted sample size with an accrual rate of approximately 8 patients per month. Approximately 15 clinical sites will enroll patients on this study. Accrual will be reported by race, ethnicity, gender, and age.

15.3 RANDOMIZATION AND STRATIFICATION

All patients will be randomized within 48 hours prior to the first dosing of either CD24Fc or placebo at Day -1 of HCT.

Randomization will be performed in a 1:1 ratio using permuted block randomization stratified by disease type: AML vs. ALL.

15.4 PRIMARY ENDPOINT

The primary endpoint is time to grade III-IV acute GVHD or death (aGFS) in 180 days after HCT. This endpoint is chosen based on large retrospective analyses showing that grade II acute GVHD does not affect the overall survival in HCT patients [58, 59].

The primary endpoint is aGFS from the HCT, treated as a time to event variable. All transplanted patients will be followed for the primary endpoint for 180 days after transplantation. The aGFS will be compared between groups in the ITT population using the stratified log-rank test, with the randomization factor of disease type (AML or ALL) used as stratification variables.

The aGFS event is defined as Grade III-IV acute GVHD, or the death by any cause. Since leukemia relapse leads to treatment that can induce GVHD, the subject will be censored at relapse.

The primary estimation of aGFS event rate at 180 days based on the Kaplan-Meier estimates will be accompanied by the corresponding two-sided 95% confidence interval calculated using Greenwood's formula.

The primary test null hypothesis of

$$H_0: HR = 1.0$$

will be rejected in favor of

$$H_a: HR < 1.0$$

if the p-value based on the stratified log-rank test (two sided) with stratification factor of disease type is less than the significance level of 5%.

15.5 SAMPLE SIZE AND POWER CONSIDERATIONS

15.5.1 Power Calculation for the Primary Endpoint

Sample size and power considerations are based on an accrual period of 24 months and a 6-month follow-up period with a 5% drop-out rate. We further assume that the drop-out and time-to-event are exponentially distributed.

From our preliminary study (Figure 8), we assume that the rate of 180 days aGFS for the CD24Fc group is set at 84.2% (10.2% lower that the Phase IIa CD24Fc aGFS of 94.4%) while the rate for placebo group is 68%, i.e., HR=0.446. A total of 65 aGFS events will be required to maintain a two-sided type I error of 5% while providing about 90% statistical power which corresponds to approximately 180 patients (90 per arm). There will be a sample size re-estimation at the planned interim analysis.

15.5.2 Power Calculation for the Secondary Endpoints

The sample size of the Phase III trial is based on the primary endpoint. The sample size allows adequate power for most secondary endpoints, as detailed below.

DFS The proposed trial period has two years of enrollment period and 1 year of follow up for the last patient. The relapse will be observed over 3 years period. Our Phase IIA data suggest an HR=0.39 (0.18-0.81) when CD24Fc-dosed patients were compared to 68 matched control patients from CIBMTR. Assuming 10% drop out and HR of 0.5 for the Phase III trial, the pre-specific sample size of 180 is sufficient to achieve 83% power for DFS.

OS The proposed trial period has two years of enrollment period and 1 year of follow up for the last patient. The relapse will be observed over 3 years period. Our Phase IIA data suggest an HR=0.42 (0.19-0.96) when CD24Fc-dosed patients were compared to 68 matched control patients from CIBMTR. Assuming 10% drop out and HR of 0.5 for the Phase III trial, the pre-specific sample size of 180 is sufficient to achieve 81% power for OS.

180 day Grade II-IV GVHD-free survival. Our Phase IIA data suggest an HR=0.538 (0.284-0.102) when CD24Fc-dosed patients were compared to 68 matched control patients from CIBMTR. Using the same HR of 0.5, pre-specific sample size of 180 is insufficient to achieve 80% power for 180 day Grade II-IV GVHD-free survival.

180 day Grade III-IV GVHD-free, Relapse-free survival. Our Phase IIA data suggest an HR=0.434 (0.196-0.964) when CD24Fc-dosed patients were compared to 68 matched control patients from CIBMTR. Using the same HR of 0.446, pre-specific sample size of 180 is sufficient to achieve 91% power for 180 day Grade II-IV GVHD-free survival.

15.6 INTERIM ANALYSIS AND STOPPING GUIDELINES

The study will consist of one interim analysis for efficacy after observing a total of 46 events, at a 70% information fraction. The final analysis will be conducted when the targeted number of events of 65 occurs.

A sample size re-estimation will be performed at this interim analysis by the DMC to support a decision to increase the target number of aGFS events. Except for the DMC, there are no other parties who will have access to unblinded data. The DMC has been contracted by another CRO, ACI, that is completely independent from the clinical CRO, Medpace. A Reporting Statistician has been appointed for the DMC and the Reporting Statistician will have access to the clinical database and to the randomization code. The Reporting Statistician will report to the DMC Chair and will support presentation of the data during sessions that are closed to anyone else associated with the study. The Reporting Statistician is permitted and empowered to disclose unblinded study data to the DMC members. The method based on Chen et al. [60] will be used for the sample size re-estimation. If the conditional power is < 50% or >85%, the trial will continue without a sample size increase; whereas if the conditional power is between 50% to 85%, the sample size will be re-calculated to have 85% power. To maintain trial integrity, the DMC will pick a sample size in a nearest interval with 5 patients. For example, if the re-estimated sample size is 240, the DMC could pick any number in the interval of 237 to 242. Also, the maximum increased sample size will not be more than 70 patients above what is needed to observe 65 events. No new sites will be added after sample size is adjusted.

15.6.1 Interim Analysis for Efficacy

Analyses will be performed as described below for the primary endpoint. At the interim analysis time point, a Z test for comparing the two treatments will be compared to the critical values with non-binding boundary for efficacy as shown in Table 7. All patients with follow-up post randomization prior to the time of the interim analyses will be used to compute this statistic. If the test statistic is outside the continuation range, the DMC will discuss the continuation of the trial.

Efficacy stopping rules are based on *O'Brien-Fleming-type error spending function*. A P-value less than 0.0147 at the interim analysis would indicate a statistically significant result.

TABLE 7: EFFICACY STOPPING THRESHOLDS WITH TYPE I ERROR 0.05, AND AN EFFECT SIZE OF HAZARD RATIO 0.446

Analysis Time	Information Fraction	Cumulative Sample Size Under Alternative	Cumulative Events Under Alternative	Cumulative Alpha
Interim	0.7	126	46	0.0147
Final	1	180	65	0.045

15.6.2 Operating Characteristics of the Design

The statistical power to reject the null hypothesis under various hazard ratio treatment effect sizes using the Z test for comparing treatments is shown in Table 8. This table shows that the target sample size of 180 patients has 90% power (unstratified) or 81% (stratified) power to detect a hazard ratio of 0.446.

TABLE 8: SUMMARY OF OPERATING CHARACTERISTICS

Hazard Ratio	Expected Events	Overall Cumulative Power
0.4	63	0.952
0.446	65	0.9
0.5	67	0.807
0.6	71	0.572
0.7	75	0.336
1	83	0.05

15.7 GUIDELINES FOR SAFETY MONITORING

Monitoring of the safety endpoint will be conducted by the Sponsor and CRO in a blinded fashion The CRO will collect the data and share this with the DMC at the planned interim analysis or call a meeting with the DMC at other times if needed. In the trial, the most important safety factors are acute GVHD events and death, which are collected as the primary efficacy endpoint. Since there are no other adverse events of special interest in the trial, the CRO will monitor adverse events, and other safety endpoints and call a meeting with DMC as soon as there are safety concerns.

15.8 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, disease-specific risk categories, DRI, hematopoietic cell transplant comorbidity index (HCT CI), donor type and HLA matching, donor/recipient CMV status, donor/recipient sex match, donor/recipient ABO match, and conditioning regimen. Between group comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test.

Subgroup analyses by age, gender, race, region and other baseline disease characteristics will be performed for the primary and key secondary endpoints.

15.9 ANALYSIS POPULATIONS

15.9.1 Primary Population

The intention-to-treat population will serve as the population for the primary analysis. All randomized patients will be included in this population. Patients will be included in the treatment group to which they are randomized. Intention-to-treat population consists of all randomized patients whether or not treatment was administered.

15.9.2 Safety Population

The safety analysis population in this study will comprise of all patients “as treated” in the study. This population will be used for the analysis of safety data. The “as treated” population consists of all randomized patients who received a HCT with one of the two randomized GVHD prophylaxis regimens. Patients will be included in the treatment group corresponding to the study treatment (GVHD prophylaxis) they actually received for the analysis of safety data using the “as treated” population. For most patients this will be the treatment group to which they are randomized.

15.9.3 Transplant Population

The transplant population will include all patients who have received a transplant after randomization.

15.10 ANALYSIS OF THE PRIMARY ENDPOINT: 180 DAY AGFS

Kaplan-Meier curves along with 95% confidence intervals will be constructed to estimate grade III-IV aGFS probabilities at 180 days for each treatment group. The primary analysis will be a stratified log-rank test with stratification factor of disease type: AML vs. ALL. . A significance level of 0.05 (two-sided, appropriately adjusted for an interim analysis) will be used to test the null hypothesis of no difference between the treatments. 95% confidence intervals for the hazard ratio of the CD24Fc vs placebo treatment will also be constructed using a stratified Cox proportional hazard model with exact method of tie handling.

15.10.1 Censoring rules for time to event efficacy endpoints

For the primary endpoint, subjects who have not dropped out or experienced the event (grade III-IV GVHD or death) will be censored at the time of leukemia relapse or Day 180 after HCT. Subjects going off study drug without prior documentation of an event will continue to be followed for acute GVHD or death, and this additional follow-up will be included in the primary analysis. Subjects without an event but lost to follow-up will be censored at last date of follow-up.

15.11 ANALYSIS OF SECONDARY ENDPOINTS

15.11.1 The secondary endpoints (1) Disease (Relapse) Free Survival; (2) Overall Survival; (3) 180 days grade II-IV acute GVHD free survival will be included in a formal testing procedure after the primary analysis is statistically significant and (4) 180 Day Grade III-IV acute GVHD and Relapse-free survival. The multiplicity adjustment will be a gate-keeping method in the order described above. Disease-free Survival

Kaplan-Meier curves will be constructed to estimate disease free survival probabilities for each treatment group. The efficacy analysis will be a stratified log-rank test with stratification factor of disease type, and a stratified Cox proportional hazard model with exact method of tie handling will be used to estimate HR and its 95% CI.

15.11.2 Overall Survival

Kaplan-Meier curves will be constructed to estimate overall survival probabilities for each treatment group. The efficacy analysis will be a stratified log-rank test with stratification factor of disease type, and a stratified Cox proportional hazard model with exact method of tie handling will be used to estimate HR and its 95% CI.

15.11.3 180 Day Grade II-IV GVHD-Free Survival

Kaplan-Meier curves along with 95% confidence intervals will be constructed to estimate grade II-IV aGFS probabilities at 180 days for each treatment group. The efficacy analysis will be a stratified log-rank test with stratification factor of disease type, and a stratified Cox proportional hazard model with exact method of tie handling will be used to estimate HR and its 95% CI.

15.11.4 180 Day Grade III-IV GVHD and Relapse-Free Survival (aGRFS)

Kaplan-Meier curves along with 95% confidence intervals will be constructed to estimate aGRFS at 180 days for each treatment group. The efficacy analysis will be a stratified log-rank test with stratification factor of disease type, and a stratified Cox proportional hazard model with exact method of tie handling will be used to estimate HR and its 95% CI.

15.12 ANALYSIS OF EXPLORATORY ENDPOINTS

15.12.1 Chronic GVHD

Incidence of chronic GVHD at 1 year will be estimated with 95% confidence intervals for each treatment group using the cumulative incidence estimate, treating death prior to chronic GVHD as a competing event. Comparison of cumulative incidence will be done using Gray's test. A multivariate Cox regression model for the cause-specific hazard of chronic GVHD will be used to compare the treatment groups, after adjustment for baseline characteristics as described for the primary endpoint.

15.12.2 Disease Relapse or Progression

Incidence of disease relapse at 1 year will be estimated with 95% confidence intervals for each treatment group using the cumulative incidence estimate, treating death prior to disease relapse as a competing event. A multivariate Cox regression model for the cause-specific hazard of relapse will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

15.12.3 Non-relapse Mortality

Incidence of non-relapse mortality (NRM) at 1 year will be estimated for each treatment group using the cumulative incidence estimate, treating disease relapse or progression as a competing event. A multivariate Cox regression model for the cause-specific hazard of TRM will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

15.12.4 Mucositis

All Grade mucositis will be tabulated by grade for each randomized treatment arm, by duration of mucositis as well as the grade. Mucositis will be scored up to 28 days.

15.12.5 Infections

The number of infections and the number of patients experiencing infections will be monitored and tabulated for each randomized treatment arm by type of infection, severity, site and through 100 days after transplant.

15.12.6 Safety Analysis

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 5.0.

15.13 MISSING DATA AND SENSITIVITY ANALYSIS

For our primary analysis, we will use the following rules to deal with missing data:

Subjects who have not dropped out or experienced the event (grade III-IV GVHD or death) will be censored at the end of the trial. Subjects going off study drug without prior documentation of an event will continue to be followed for acute GVHD or death until the end of the trial, and this additional follow-up will be included in the primary analysis. Subjects without an event but lost to follow-up will be censored at last date of follow-up.

As a supplemental analysis, a Restricted Mean Survival Time (RMST) method will be used to estimate hazard ratio in case the proportionality assumptions do not hold. The pre-specified cutoff point to evaluate the RMST will be minimum of a) 2 times expected median GVHD survival time for the experimental arm, b) the largest observed GVHD survival time for the experimental arm, and c) the largest observed GVHD survival time for control arm.

As another supplemental analysis, the primary endpoint will be defined as time from transplantation to acute GVHD of grade III or IV severity, treatment for acute GVHD with

systemic agents other than corticosteroids, or death, whichever occurs first, up to day 180.

For key secondary endpoints, we will use the same rules to deal with missing data.

We will perform three more analyses on the following sets for the purpose of sensitivity analysis:

First: Subjects who have not dropped out or experienced the event are censored at the end of the trial. Subjects going off study drug without prior documentation of an event will be censored at the last disease assessment before going off treatment. Subjects without an event but lost to follow-up will be censored at last date of follow-up. When the event is documented, the time to the event is the length of time from the randomization to the event observed if at most one missed disease assessment before the event is documented. If more than one missed disease assessment before the event is documented, it censors at the last disease assessment without acute GVHD.

Second: Subjects who have not dropped out or experienced the event and are followed at the end of the trial will be included. Subjects going off study drug will be excluded. Subjects who have documented the event and no missing disease assessment(s) will be included.

Third, we will use time from randomization instead of time from HCT for analysis of primary and secondary endpoints. We will compare the results of primary analysis with the results from sensitivity tests. The impact of missing data and robustness of the primary analysis will be evaluated.

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17 APPENDIX A: KARNOFSKY PERFORMANCE SCALE

%	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor symptoms of disease
80	Normal activity with effort, some signs of symptoms of disease
70	Cares for self (consistent with age), unable to carry on normal activity or do active work/school/play
60	Requires occasional assistance (beyond age-appropriate care), but is able to care for most of their needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active support treatment is necessary
10	Moribund, fatal processes progressing rapidly

18 APPENDIX B: CIBMTR OPERATIONAL GUIDELINES

EXAMPLES OF MYELOABLATIVE, REDUCED INTENSITY, AND NON – MYELOABLATIVE REGIMENS.

Myeloablative Regimens	Reduced Intensity and Non-Myeloablative Regimens
• TBI > 500 cGy (single) or > 800 cGy (fractionated) • Cyclophosphamide + TBI (> 500 cGy (single) or > 800 cGy (fractionated)) • Cyclophosphamide + Etoposide + TBI (> 500 cGy (single) or > 800 cGy (fractionated)) • Busulfan > 7.2 mg/kg IV or >9.0mg/kg orally • Busulfan >300 mg/m2 IV or >375 mg/m^2 orally • Busulfan (> 7.2 mg/kg IV or >9.0mg/kg orally) + Cyclophosphamide • Busulfan (>7.2 mg/kg IV or >9.0 mg/kg orally) + Melphalan >150 mg/m^2 • Melphalan >150 mg/m^2 • Thiotepa ≥ 10 mg/kg • Treosulfan > 30,000 mg/m^2 or > 30 g/m^2	• TBI ≤ 500 cGy (single) or ≤ 800 cGy (fractionated) • ATG + Cyclophosphamide • BEAM (Carmustine [BCNU], Etoposide, Cytarabine [Ara-C], Melphalan) • Busulfan ≤ 7.2 mg/kg IV or ≤ 9.0mg/kg orally • Busulfan ≤ 300 mg/m^2 IV or ≤ 375 mg/m^2 orally • Melphalan ≤ 150 mg/m^2 • Fludarabine + Cytarabine • Fludarabine + Cyclophosphamide • Fludarabine + TBI ≤ 500 cGy (single) or ≤ 800 cGy (fractionated) • Thiotepa < 10 mg/kg • Treosulfan ≤ 30,000 mg/m^2 or ≤ 30 g/m^2 • Etoposide + Cyclophosphamide

19 APPENDIX C: ORGAN STAGING OF ACUTE GVHD

GVHD Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

From Harris AC, et al: BBMT 22:4-10, 2016.

20 APPENDIX D: DISEASE RISK INDEX FOR AML/ALL

(Armand P, et al. Blood, 2014, 123:3664-3671)

Disease	Stage	DRI Group	HR[1]
AML favorable cytogenetics[2] CR		Low	0.64
AML intermediate cytogenetics[2] CR		Int	Ref (1.00)
ALL CR1		Int	1.00
AML favorable cytogenetics[2]	Advanced[3]	high	1.42
ALL CR2		high	1.58
AML adverse cytogenetics[2] CR		high	1.59
ALL CR3		high	1.70
AML intermediate cytogenetics[2]	Advanced[3]	high	1.89
ALL	Advanced[3]	Very high	2.23
AML adverse cytogenetics[2]	Advanced[3]	Very high	2.83

1. Hazard ratio for mortality compared with AML intermediate cytogenetics in CR1.
2. For AML, t(8;21), inv(16), and t(15;17) were classified as favorable, complex karyotype (4 or more abnormalities) as adverse, and all others as intermediate.
3. Advanced stage refers to induction failure or active relapse in AML or ALL.

21 APPENDIX E: HCT-SPECIFIC COMORBIDITY INDEX SCORE

HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		0
Osteoporosis		0
Osteoarthritis		0
Hypertension		0
Gastrointestinal	Including inflammatory bowel disease	0
Mild pulmonary	DLCo and/or FEV_1 >80% or Dyspnea on moderate activity	0
Mild renal	Serum creatinine 1.2-2 mg/dl	0
Endocrine		0
Bleeding		0
Coagulopathy	Deep venous thrombosis or pulmonary embolism	0
Asthma		0
Arrhythmia		1
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EF≤50%	1
Mild hepatic	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	1
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	1
Morbid obesity		1
Diabetes	Requiring treatment	1
Depression/anxiety		1
Infection	Requiring continuation of treatment after Day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary	DLCo and/or FEV_1 66-80% or Dyspnea on slight activity	2
Peptic ulcer	Patients who have required treatment	2
Moderate-severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	2
Valvular heart disease	Except mitral valve prolapse	3
# Prior solid tumor	Requiring treatment with chemotherapy	3
Moderate-severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN	3
Severe pulmonary	DLCo and/or FEV_1 ≤65% or Dyspnea at rest or requiring oxygen	3

Total score is the sum of all comorbidities present at time of transplantation.

#The "Prior solid tumor" "requiring treatment with chemotherapy" (HCI-CI score=3) is modified to "Prior solid tumor" "requiring treatment with chemotherapy, if the solid tumor chemotherapy is documented to be complete and the tumor has not progressed in the two years before the HCT, the BMT physician may take this into consideration and adjust the HCI-CI score to < 3."

22 APPENDIX F: CHRONIC GVHD ASSESSMENT

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD) ASSESSMENT AND SCORING FORM **Page 1 of 2**

Name:_____ **Date of birth:**_____ **Assessment date:**_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐ Rodnan score: ☐	☐ No Symptoms/ Manifestation	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
☐ *Abnormality present but NOT thought to represent GVHD*				
MOUTH *Diagnostic/Distinctive features* ☐ Present ☐ Absent	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but NOT thought to represent GVHD*				
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
☐ *Abnormality present but NOT thought to represent GVHD*				
GI TRACT	☐ No symptoms	☐ Symptoms such as nausea, vomiting,anorexia,dysphagia, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
☐ *Abnormality present but NOT thought to represent GVHD*				

(continued) **CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD) ASSESSMENT AND SCORING FORM** **Page 2 of 2**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN
☐ *Abnormality present but NOT thought to represent GVHD*				
LUNGS † ☐ PFTs not done **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
☐ *Abnormality present but NOT thought to represent GVHD*				
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but NOT thought to represent GVHD*				
GENITAL TRACT *Diagnostic/ Distinctive features* ☐ Present ☐ Absent ☐ Not examined	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum
☐ *Abnormality present but NOT thought to represent GVHD*				

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply):

☐ Weight loss	☐ Bronchiolitis obliterans	☐ Bronchiolitis obliterans with organizing pneumonia	
☐ Esophageal stricture or web	☐ Pericardial Effusion	☐ Pleural Effusion(s)	☐ Ascites (serositis)
☐ Nephrotic syndrome	☐ Peripheral Neuropathy	☐ Myasthenia Gravis	☐ Polymyositis
☐ Malabsorption	☐ Cardiac conduction defects	☐ Coronary artery involvement	☐ Cardiomyopathy
☐ Eosinophilia >500/microliter	☐ Other: _____		☐ **None**

Biopsy obtained: ☐**Yes** ☐**No** **Organ system(s) biopsied**:_____ **GVHD confirmed by histology**: ☐**Yes** ☐**No**

OVERALL severity of GVHD: ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by:_____ **Date form completed**:_____

† Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO (carbon monoxide diffusion capacity corrected for hemoglobin) is not available, grading using FEV1 (forced expiratory volume) should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established.[28] The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: > 80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; < 40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); AST (aspartate aminotransferase); ULN (upper limit of normal); LFS (Lung Function Score); N/A (not applicable).

23 SUMMARY OF CHANGES

Substantive changes to the Protocol are outlined in the Table below. In cases where the change involves the insertion or deletion of one or a few words, the text may be underlined for ease of reviewing. Additional typographical corrections or edits may also be made throughout the Protocol but not detailed in the Table.

Section of the document	**Revision and Justification**
Title page and footer (all pages)	Protocol version number updated to 1.5, dated August 17, 2020
Title page	Multi-site coordinator information updated. Clinical Sites and Principal Investigators information removed. Study Statistician information updated.
Study Synopsis: Primary Objective (Page 2)	Primary Objective changed from: The primary objective of the trial is to compare the rate of 180 days grade III-IV acute GVHD-free survival (aGFS) between the two GVHD prophylaxis regimens. An event for this time-to-event outcome is defined as grade III-IV aGVHD, or death by any cause, whichever occurs first. To: To establish the efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT.
Study Synopsis: Secondary Objectives (Page 2)	Secondary Objectives changed from: Secondary objectives are to compare, for each treatment arm, rates of disease free survival (DFS), overall survival (OS), and 180 days grade II-IV aGVHD free survival (aGFS). Other exploratory evaluations will be rates of chronic GVHD at 1 year, relapse rate at 1 year, non-relapse mortality (NRM) at 1 year, incidence and rate of infections at 100 days, and mucositis rate at 28 days. To: To improve the relapse free survival (RFS) and overall survival (OS) in leukemia patients after allogeneic HCT through (1) reduction of the myeloablative conditioning toxicity; (2) reduction of severe acute GVHD; and (3) reduction of relapse
Study Synopsis: Study Endpoints: (Page 2)	Primary Endpoint added: 180 day grade III-IV acute GVHD free survival (aGFS), event defined as the earlier time of GVHD or death within 180 days of HCT. Secondary Endpoints added:

Section 2.3.1 Primary Efficacy Endpoints (Page 15) Section 2.3.2 Secondary Efficacy Endpoints (Page 15)	Disease Free Survival (DFS), event defined as the earlier time of leukemia relapse or death after HCT. Overall Survival (OS), event defined as time of all-cause mortality after HCT. 180 day grade II-IV acute GVHD free survival (aGFS), the earlier time of event defined as Grade II-IV GVHD or death within 180 days of HCT. 180 day grade III-IV acute GVHD relapse-free survival (aGRFS), the earlier time of event defined as GVHD, relapse or death within 180 days of HCT.
Study Synopsis: Data Monitoring Committee: (Page 3)	Stopping Guidelines language removed and replaced with Data Monitoring Committee language: The DMC consists of experts outside of the Sponsor will be responsible for the planned interim analyses.
Study Synopsis: (Page 4)	Figures 1 and 2 showing the Study Diagram and Randomization scheme, respectively, added.
Study Synopsis: (Pages 5-7)	Phase III Study Calendar added.
CD24Fc Protocol Signature page (Page 8)	Signature line for Sponsor representative added.
Table 4 (Page 27)	Data for the following outcomes added: Grade II-IV acute GVHD-free survival at 180 days Grade III-IV acute GVHD-free relapse free survival at 180 days
Figure 9 (Pages 28 and 29)	Figure showing 180 days probability of grade II-IV acute GVHD-free survival and description added.
Figure 12 (Pages 30 and 31)	Figure showing 180 days probability of grade III-IV acute GVHD and relapse-free survival and description added.
Table 5 (Page 34)	Eligibility criteria for Total Bilirubin changed from ≤2.5 mg% to ≤2.0 x ULN

Section 4.2 Exclusion Criteria (Pages 35 and 36)	4.2.7 changed from: Uncontrolled infections. Patients still under therapy for presumed or proven infection are eligible provided there is clear evidence (radiologic, clinical and/or culture) that the infection is well controlled. To: Uncontrolled infections. Patients still under therapy for presumed or proven infection are eligible provided there is clear evidence (radiologic, clinical and/or culture) that the infection is well controlled. Patients testing positive for SARS-CoV-2, whether symptomatic or asymptomatic, are excluded. Patients recovering from COVID-19 and viral testing negative for SARS-CoV-2 are eligible. 4.2.8 changed from: Patients seropositive or PCR positive for the human immunodeficiency virus (HIV). Patients with evidence of Hepatitis B or Hepatitis C PCR positivity. To: Patients seropositive or PCR positive for the human immunodeficiency virus (HIV). Patients with evidence of active Hepatitis B or Hepatitis C PCR positivity. 4.2.10 changed from: Use of T cell depletion either *ex vivo* or *in vivo* (i.e.ATG, alemtuzumab) is prohibited. To: Use of T cell depletion either *ex vivo* or *in vivo* (such as ATG or alemtuzumab or ex vivo $CD34^+$ selected HCT) is prohibited.
Section 5.2 Screening Procedures (Page 36)	The following language was deleted and the CRO is identified as Medpace: This multi-site study will be conducted at the University of Michigan, The Ohio State University, Karmanos Cancer Institute and Indiana University with the potential to recruit 10-15 additional sites.
Section 5.3 Treatment Schema (Page 36)	Figure 10 moved to Study Synopsis section as Figure 1.
Section 5.5.2 Tacrolimus (Page 37)	The following language is deleted: g. Patients who are unable to initiate standard or alternative prophylaxis (calcineurin inhibitor) will be removed from the study and replaced.
Section 5.5.3 Methotrexate	Language changed from:

(Pages 37 and 38)	Methotrexate will be used in combination with tacrolimus for standard GVHD prophylaxis. Methotrexate will be given intravenously at a dose of 15 mg/m^2/dose once daily on Day 1 after HCT, and at a dose of 10 mg/m^2/dose on days 3, 6, and 11 after HCT. Attempts should be made to deliver all four doses, however, methotrexate may be omitted at the discretion of the treating physician. Missed doses of methotrexate will be recorded as a deviation, but will not constitute a protocol violation. Leucovorin rescue may also be administered according to local institutional practice guidelines. Reduced Methotrexate per institutional practice guidelines is allowed, but should inform the study PI. To: Methotrexate will be used in combination with tacrolimus for standard GVHD prophylaxis. Methotrexate will be given intravenously at a dose of 15 mg/m^2/dose once daily on Day 1 after HCT, and at a dose of 10 mg/m^2/dose on days 3, 6, and 11 after HCT. Attempts should be made to deliver all four doses, however, methotrexate may be omitted or reduced doses at the discretion of the treating physician according to institutional guidelines. Leucovorin rescue may also be administered according to local institutional practice guidelines. Reduced Methotrexate per institutional practice guidelines is allowed, but should inform the study PI.
Section 5.6.5 Other Myeloablative Conditioning (Page 38)	Prohibited T cell depletion changed from: i.e.ATG, alemtuzumab. To: such as ATG or alemtuzumab or *ex vivo* CD34$^+$ selected HCT.
Section 5.7 Donor Eligibility, Selection, and Related Procedures (Page 39)	The following language was added: Due to the COVID-19 situation, the NMDP strongly recommends cryopreservation of all donor products as far in advance of the initiation of patient conditioning as is feasible, dictated by the clinical situation of the patient.
Section 5.8.4.2 Cytomegalovirus (CMV) (Page 40)	Monitoring period changed from Day 60 to Day 100.
Section 6.2 Randomization (Page 41)	Language changed from: A patient is considered to be “Enrolled” onto the study once they have signed consent and have successfully met all screening criteria, as documented by the

	inclusion/exclusion document, and the CRO confirms these data. The date of enrollment will be documented as date of notification from the CRO. To: A patient is considered to be "Randomized" onto the study once they have been assigned to one of the treatment arms through randomization process. All patients will be randomized within 48 hours prior to the treatment of first dosing of either CD24Fc or placebo at day -1 (one day before transplantation).
Section 6.3 Treatment Period (Page 41)	Language changed from: The "Treatment Period" is defined as the first day of treatment with CD24Fc until 60 days after HCT. The exact days may vary depending on the last day of administration of study drug without constituting a deviation. The assessment and reporting period for adverse events (AE) including dose limiting toxicities potentially related to the study drug (CD24Fc) will extend through day 60 post HCT. Based upon PK data for CD24Fc this time period will allow for passage of greater than two half-lives. To: The "Treatment Period" is defined as the first day of treatment with CD24Fc until 60 days after HCT. The assessment and reporting period for adverse events (AE) potentially related to the study drug (CD24Fc) extend through day 100 post HCT. Based upon PK data for CD24Fc this time period will allow for passage of greater than two half-lives.
Section 6.4 Follow up Period (Pages 41 and 42)	Language changed from: The "Follow Up" period is defined as the first day the patient is no longer within the treatment period (i.e. day 61) until the subject comes off study. The follow-up period can be up to 3 years post HCT. During this time subjects will be followed for acute or chronic GVHD, relapse, and survival. Data collection after one year post HCT will be minimal and can be an office visit, phone contact or review of the subject's medical chart. Outcome information collected on other BMT program clinical research studies may be analyzed in relation to patients participating in this study. To: The "Follow Up" period is defined as the first day the patient is no longer within the treatment period (i.e. day 101) until the subject comes off study. The follow-up period can be up to 3 years post HCT. During this time subjects will be followed for acute or chronic GVHD, relapse, and survival. Data collection after one year post HCT will be minimal and can be an office visit, phone contact or review of the subject's medical chart.
Section 6.5 On Study (Page 42)	Language changed from: The "On Study" period is defined as the day the patient signs the protocol consent document and meets the protocol eligibility criteria ("Enrolled"), until the

	subject comes off study. Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. To: The "On Study" period is defined as the day the patient signs the protocol consent document, meets the protocol eligibility criteria and is randomized to a study arm, until the subject comes off study. Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons.
Section 6.6 Off Treatment (Page 426)	The treatment period is changed from Day 60 to Day 100. Language changed from: Note: Subjects will be continuously monitored for adverse events per local institutional guidelines through day 60 post-HCT (e.g. for routine post HCT care and measurement of primary clinical endpoint of acute GVHD) and then at minimum quarterly through one year. Adverse events occurring beyond day 60 post-HCT will be evaluated, monitored and recorded but not be reported unless related (probably or definitely) to the study drug (CD24Fc). The survival and disease relapse status will be followed for up to 3 years. To: Note: Subjects will be continuously monitored for all grade adverse events per local institutional guidelines within 24 hours and severe grade 3 to 5 adverse events through 100 days post-HCT (e.g. for routine post HCT care and measurement of primary clinical endpoint of acute GVHD) and then at minimum quarterly through one year. Severe adverse events occurring beyond day 100 post-HCT will be evaluated, monitored and recorded but not be reported unless related (probably or definitely) to the study drug (CD24Fc). The survival and disease relapse status will be followed for up to 3 years.
Section 7.1 Managing Infusion Reactions (Page 43)	Specific language relating to the management of infusion reactions added: nfusion reactions were not observed in the Phase I and Phase IIa clinical trials which involved 84 patients. Infusion reactions were not observed in an ongoing Phase III clinical trial in COVID-19 treatment which more than 180 patients have been dosed. Premedications do not need to be administered prior to the infusion of CD24Fc to prevent infusion reactions Patients who develop a grade 3 or higher infusion reaction will be taken off study drug but continued on study follow up. The grade 2 or above infusion reaction can be treated following NCI CTEP guidelines

Section 7.2 Managing Acute GVHD (Pages 43 and 44)	The language was changed from: Overall acute GVHD will be assessed and graded weekly through day +60 after transplant, then at minimum monthly from Day 60 to Day 180 with quarterly thereafter. To: Overall acute GVHD will be assessed and graded weekly through day +100 after transplant, then at minimum monthly from Day 100 to Day 180 with quarterly thereafter. The following language was added: However the study primary endpoint analysis will not include the acute GVHD secondary to the treatment to leukemia relapse. The following language was deleted: **Diagnosis of Stage I GVHD of the gut (grade II overall) that involves the upper GI tract (e.g. with stool volumes < 500ml/day) requires biopsy with histologic evidence of GVHD for confirmation.** d. Discrepant GVHD scores will be reviewed by at least 1 investigator who will resolve the discrepancies (which may/may not include the use of a third, independent evaluation adjudication committee).
Section 8.1 Renal Function	Section deleted - dose modification based on renal function removed.
Section 9.1 Special Considerations for COVID-19 (Page 45)	New section added.
Table 5 Study Calendar for Phase III Study (Pages 46-48)	A number of changes were made to the Table and footnotes reflect changes in the protocol, most notably the following: Assessment period for GVHD and AEs changed from weekly through Day 60 to weekly through Day 100, and monthly from Day 100 to Day 180. Concomitant Medications not assessed beyond Day 100. Frequency of Vital Signs monitoring reduced to prior to infusion and after infusion (+/- 30 min). Telemedicine visits allowed to minimize COVID-19 exposure. If a subject withdraws from the study and does not consent to continued follow-up of associated clinical outcome information, a public records search can be performed for survival.

Section 10.1 Pharmaceutical Information (Page 49)	Reference to a specific lot number removed as this may change. CRO identified as Medpace.
Section 10.1.4 Administration (Pages 49 and 50)	Specific information relating the preparation, storage and administration of the drug product added.
Section 11.1 Definition of Adverse Events (Page 62)	Language changed from: These events may be: • *Definitely related:* clearly associated with study drug/treatment • *Probably related*: likely associated with study drug/treatment • *Possibly related*: may be associated with study drug or other treatment • *Unlikely to be related*, or • *Definitely not related* to the study drug/treatment For reporting purposes, an AE should be regarded as definitely or probably related to the study drug if the Investigator believes that at least one of the Number 1 or Number 2 criteria plus at least one of the Number 3 or Number 4 criteria are met: To: These events may be: • *Related:* clearly or likely associated with study drug/treatment • *Not related: unlikely or definitely not related* to the study drug/treatment For reporting purposes, an AE should be regarded as related to the study drug if the Investigator believes that at least one of the Number 1 or Number 2 criteria plus at least one of the Number 3 or Number 4 criteria are met:
Section 11.3.1 AE Reporting (Page 64)	Language changed from: **Reporting to Sponsor:** All AEs (regardless of grade and attribution) will be recorded in the patient's source and entered into the electronic data capture system from the time of CD24Fc infusion through day 60 post HCT (the treatment period). Any AE that is reported after the treatment period has ended and is considered related to treatment (possibly, probably, definitely) should also be entered in the electronic data capture system.

	Expedited Reporting ***(the following need to be added into the electronic data capture system and reported to the Sponsor within 24 hours of knowledge)***: • All AEs (regardless of grade) from time of CD24Fc infusion through 24 hours after CD24Fc infusion including subjects receiving blinded placebo. • All grade 3-5 AEs (except as defined in Section 11.1 Expected Events) occurring after the 24 hour post CD24Fc infusion period has elapsed on day 0 through the treatment period will be recorded and reported to the Sponsor and CRO. Note: this duration allows for over two half-lives of CD24Fc to elapse ($t_{1/2}$ is 11 -14 days). • Events resulting in death during the treatment period. To: As the expectation of a high rate of low grade adverse events associated with conditioning regimen and HCT procedure, only Grade 3 to 5 AEs (regardless attribution) will be recorded in the patient's source and entered into the electronic data capture system from the time of CD24Fc or placebo infusion through day 100 post HCT. All grade AE will be recorded only within 24 hours of start of an infusion of CD24Fc/placebo. The acute GVHD is the study primary endpoint. Infections and leukemia relapse are study endpoints. The CMV reactivation, myeloablative conditioning regimen associated myelosuppression, anemia, thrombocytopenia, mucositis will not be considered as AE as these are expected events in HCT. The post-HCT hospital re-admission due to these conditions will be recorded.
Section 11.3.1 AE Reporting (Page 65)	Language changed from: **Reporting of SAES to the FDA** In accordance with FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312): In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the FDA. To: In accordance with FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312): In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the FDA as applicable.
Section 11.3.1 AE Reporting	Language changed from: **SAE Reporting-Procedures for Investigators**

(Pages 65 and 66)	Initial Reports All SAEs occurring from the time of CD24Fc infusion up to and including 60 days post HCT must be reported to the Principal Investigator and CRO within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the investigator considers related to study drug occurring after 60 days post HCT must be reported to the Principal Investigator and CRO. Events should be reported using the CRO's SAE form as available in the study database. A copy of SAE form should be sent to the CRO via email within 24 hours of the site's knowledge of the event. **Contact information for Principal Investigator SAE Reporting:** • Name: John Magenau, MD • Email: PPD The CRO will disseminate information regarding SAEs to the participating sites within 5 days of review of the information by the CRO only in the case that the event(s) is believed to be unexpected and related (i.e., possibly, probably, or definitely) to the study drug. The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. Follow-up information must also be reported within 24 hours of receipt of the information by the Investigator. The CRO will be responsible for reporting of events to the Sponsor, as outlined below: Safety Contact Information: CRO (TBD) Facsimile: e-mail: Anticipated SAEs occurring within the treatment period that will not be reported by the CRO to the Sponsor and FDA in an expedited manner are listed below. To: **SAE Reporting-Procedures for Investigators** Initial Reports All SAEs occurring from the time of CD24Fc or placebo infusion up to and including 100 days post HCT must be reported to the CRO within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the investigator considers

		related to study drug occurring after 100 days post HCT must be reported to the CRO. To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at PPD or call the Medpace SAE hotline (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. The CRO will disseminate information regarding SAEs to the participating sites within 15 days of review of the information by the CRO only in the case that the event(s) is believed to be unexpected and related to the study drug. <u>Follow-up Reports</u> The investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs. <u>Safety Contact Information</u>: Medpace Clinical Safety Telephone: PPD Facsimile: PPD E-mail: PPD
Section 11.3.2 Events Not Reported		Section deleted
Section 11.3.2 Pregnancy Reporting (Page 66)		Language changed from: If the subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the <u>Principal Investigator and</u> CRO within 24 hours of being notified.

	The CRO will be responsible for notifying the Sponsor within 24 hours of knowledge. A subject becoming pregnant prior to administration of study drug will immediately be withdrawn from the study and early termination study procedures will be performed. To: If the subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the CRO within 24 hours of being notified. A subject becoming pregnant prior to administration of study drug will immediately be withdrawn from the study.
Section 11.3.3 Events reports as Adverse Events Routinely in Tabular Format	Section deleted
Section 11.3.3 Emergency Unblinding (Page 66)	New section added
Section 12 Data Safety Monitoring Plan (DSMP) (Page 66)	Language changed from: The following are the procedures for data and safety monitoring of this clinical trial to be coordinated by the CRO and sponsored by OncoImmune, Inc. This is to ensure the safety of participants, the validity of research data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. This protocol will conduct a data and safety monitoring process as described in the plan below. To: The CRO Medpace will collect the data and provide the data to an independent DMC at the planned safety monitoring meetings and the pre-specified interim analysis. . This is to ensure the safety of subjects, the validity of research data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. This protocol will conduct a data and safety monitoring process as described in the plan below.

Section 12.2 Storage and Dissemination of Reports (Page 67)	Language changed form: The CRO is responsible for collating all the Data and Safety Monitoring Reports from all participating institutions and providing this information to independent DSMB. The CRO will coordinate the reporting process between the Investigators, the Sponsor, the IRB, as well as other applicable reporting agencies (FDA and study sponsors). Copies of all related correspondence and reporting documents will be maintained by the CRO and the research data file will be maintained in a file by the BMT data management team. To: Medpace is responsible for collecting all safety data in the electronic Case Report Forms (eCRFs) from all participating institutions and providing the data to the independent DMC.
Section 12.3 Clinical Monitoring Procedures (Pages 67 and 68)	Language added to allow remote monitoring and site initiation through teleconference. The following language was deleted: The first monitoring visit at each site should occur after the first subject enrolled completes the Day 30 visit. At a minimum, a central and/or on-site monitoring visit will be done at least quarterly. And replaced with: Monitoring of the study site will be performed by the CRO. The following language was deleted: Weekly teleconferences will be conducted among investigators from participating study sites, the CRO, the principal investigator (PI), study statistician and medical monitor from the sponsor and / or its designee (i.e. CRO). At these meetings safety events, DLTs, withdrawals, subjects' progress and other relevant events on trial will be reviewed and appropriate actions will be taken including amending or suspending the trial. Safety reports generated by the CRO will also be submitted to the DSMB and the medical monitor from the sponsor monthly. The DSMB and Sponsor will both be responsible for reviewing these reports monthly and if necessary taking appropriate steps to ensure the safety of subjects and compliance with this protocol (i.e. inquiries, suspension, or termination of trial). Finally, whenever an unanticipated data, safety and monitoring board meeting takes place or when a new development occurs the medical monitor from the sponsor and / or its designee (i.e. CRO) and IRB will be notified of the occurrence. In general, close-out is conducted during a site visit. However, a site close-out can occur without a site visit.

Section 13 Quality Assurance and Audits (Pages 68 and 69)	Language changed from: The CRO will perform quality assurance audits. Audits provide assurance that trials are conducted in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. All audit findings are reported to the DSMB and the sponsor. The DSMB can also request a 'for cause' quality audit of the trial if the Committee identifies a need for a more rigorous evaluation of study-related issues. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the CRO and Sponsor that such a request has been made. To: Audits provide assurance that trials are conducted in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. All audit findings are reported to the DMC and the sponsor. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the CRO and Sponsor that such a request has been made.
Section 14 Removal from Study (Page 69)	The following language was deleted: and every effort should be made to perform follow-up evaluations The following language was added: In the event a subject fails to appear for a scheduled follow-up visit, Institution and/or Principal Investigator shall use reasonable efforts contact the subject within ten (10) days after the date of the scheduled visit regarding the failure to keep the appointment. If a subject withdraws from the Study, Institution and Principal Investigator shall use reasonable measures to follow up with the subject in person or by telephone (if possible), otherwise by certified mail, to determine the reason for the discontinuance.
Section 15	Section deleted
Section 15 Statistical Considerations (Pages 69 to 77)	Substantial changes were made to this section to reflect changes in the study analyses. The most notable changes include: Patients will be randomized with 48 hours prior to the first dosing. Power calculations for the Secondary Endpoints were added. The Interim Analysis will test for efficacy (not futility) when 46 events (70%) of information occurs (previously 39 events and 60%). Details regarding the sample size re-estimation process are added. 180 Day Grade III-IV acute GVHD and Relapse-free survival added as a secondary endpoint.

	Supplement analyses were added including (1) a Restricted Mean Survival Time (RMST) method used to estimate hazard ratio in case the proportionality assumptions do not hold, and (2) defining the primary endpoint as time from transplantation to acute GVHD of grade III or IV severity, treatment for acute GVHD with systemic agents other than corticosteroids, or death, whichever occurs first, up to day 180.