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A Phase II Trial of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplant

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1.0 SYNOPSIS

Overview and Role of GVHD Prevention after HCT:
This is a prospective phase II trial investigating the addition of CD24Fc to standard acute graft-versus-host disease (GVHD) prophylaxis for allogeneic hematopoietic stem cell transplantation (HCT). Despite the rapid expansion and curative potential of HCT for treating hematologic malignancies, recipients remain at significant risk for developing acute GVHD and its morbid sequela.[1, 2] The combination of calcineurin inhibitor (tacrolimus or cyclosporine A) with methotrexate (MTX) is the most common GVHD prophylaxis used worldwide in the context of myeloablative conditioning transplants. This regimen, implemented more than 3 decades ago, demonstrated improved control of acute GVHD[3, 4]. Acute grade III-IV GVHD is the principle contributor to early transplant related mortality (TRM), and develops in approximately 15-25% of recipients receiving unrelated donor HCT despite standard immunosuppressive prophylaxis.[5-8] At same time, leukemia relapse of primary malignancy remains a major risk for mortality after HCT [9-14]. However, the majority of drugs currently available or being developed for the prophylaxis and treatment of acute GVHD are based on general immunosuppression, which can increase the risk for opportunistic infection, contribute to significant morbidity, and increase leukemia relapse by reducing the graft-versus-leukemia (GVL) response [15]. Thus, novel GVHD prophylaxis strategies which successfully attenuate acute GVHD and limit leukemia relapse are urgently needed to improve outcomes after HCT.

Development of Novel Investigational Therapy (CD24Fc) for GVHD Prevention
A CD24 fusion protein (CD24Fc) has been developed by OncoImmune Inc. to selectively target damage associated molecular pattern (DAMP)-induced inflammation inherent to HCT. The protein was studied for its potential role in the prevention of acute GVHD. Following promising results in pre-clinical murine models of GVHD and demonstration of safety in heathy human subjects, a multi-site Phase IIa trial was initiated in 2016 to determine the safety and tolerability, the recommended Phase II dose (RP2D) or maximum tolerated dose (MTD) in the HCT setting. The Phase IIa study consisted of two single ascending dose cohorts (240 mg and 480 mg) and one multi-dose cohort. In the two single dose cohorts, patients received a single administration of CD24Fc at 240 mg or 480 mg at day-1, one day before HCT. In the multi-dosing cohort, patients received 3 biweekly administrations of CD24Fc at 480 mg (day -1), 240 mg (day +14) and 240 mg (day +28). Each cohort enrolled 8 patients, randomized 3:1 (drug:placebo) for a total enrollment of 24 patients, with 18 receiving study drug.

The enrollment of three cohorts of Phase IIa was completed in December 2017 with primary follow up through day 100 post HCT, data-lock and unblinding completed in May 2018. All patients continue to be followed for one year.

Results of Phase IIa Clinical Trial of CD24Fc after HCT:
The study has shown that the single dose of IV administration of CD24Fc up to 480 mg and multi-dosing of 480 mg, 240 mg, and 240 mg are well tolerated in the intent-to-treat

(ITT) population. An MTD was not established. The median follow-up is 10 months (from 6 months to 18 months). Median age for the 18 patients that received study drug is 63 years, with two thirds of the patients over 60 years of age. All patients are undergoing myeloablative allogeneic matched unrelated donor hematopoietic cell transplantation. No infusion toxicities, dose limiting toxicities (DLTs) or serious adverse events (SAEs) attributable or likely attributable to the study drug were observed. All patients achieved primary neutrophil and platelet engraftment.

The incidence of 180 day Grade II-IV acute GVHD was 39%. The incidence of severe Grade III-IV GVHD in the CD24Fc treated cohort was 6% at day 180 with only one subject developing grade III GVHD with lower GI tract involvement. Among patients who developed GVHD there were no instances of steroid resistance. The 180 day Grade III-IV GVHD-free survival is 94% in the CD24Fc-treated group and 50% in the placebo group. One year non-relapse mortality (NRM) is 6% in the CD24Fc treated group and 17% in the placebo group. An unanticipated observation in this Phase IIa study was a lower than anticipated rates of leukemia relapse, with 2 of 18 patients (11%) experiencing recurrence of the primary malignancy compared to 2 of 6 patients (33%) in the placebo group over 16 months (range of 11 - 24 months) of follow up. The respective one-year overall survival (OS) and relapse free survival (RFS) estimates are both at 83% in the CD24Fc group and 50% in the placebo group. These data provide encouraging early evidence that CD24Fc is safe and may improve the HCT outcomes.

Based on the Phase IIa safety results, pharmacokinetic data, promising rates of severe aGVHD and evaluating feedback from the FDA, the study protocol has been amended prior to proceeding to a large randomized trial. The amendment proposes to first perform an open label single arm expansion cohort to further establish safety at the recommended Phase II dose (RP2D) and gain additional data regarding the potential efficacy of this dose in improving grade III-IV acute GVHD free survival at 180 day post HCT. This information that will be used in the development of a subsequent randomized Phase III to assess efficacy of CD24Fc in improving aGVHD-free survival.

Primary Objective(s):

Phase IIa: The primary objective of Phase IIa is to evaluate the safety and tolerability of CD24Fc in subjects undergoing myeloablative allogeneic hematopoietic cell transplantation (HCT), and to define the recommended Phase IIb dose (RP2D) or maximum tolerated dose (MTD) for the addition of CD24Fc to standard GVHD prophylaxis.

Phase IIa – Expansion Cohort:
The primary objective of the expansion cohort is to determine if combining CD24Fc with standard GVHD prophylaxis improves day 180 grade III-IV acute GVHD free survival (AGFS) when compared to matched registered controls with standard GVHD prophylaxis.

Patient Eligibility:
Eligible patients will be those requiring allogeneic HCT for malignant hematologic conditions and receiving a myeloablative conditioning regimen. An unrelated donor is required to match at HLA-A, -B, -C, and –DRB1 loci. Eligibility criteria are defined in Section 4.0.

Study Design:
This is a multicenter prospective randomized Phase IIa with a 20 patient expansion cohort clinical trial designed to determine the RP2D or MTD of CD24Fc for acute GVHD prophylaxis. Phase IIa is a randomized double blind trial comprised of: i) 2 single ascending dose cohorts of 8 patients (3:1 treatment:placebo); and ii) a multi-dosing cohort consisting of 8 patients (3:1 treatment:placebo) that will receive 3 consecutive biweekly administrations of CD24Fc. The multi-dose cohort will be initiated prior to enrolling the highest single dose (960 mg) cohort and the total dose administered will be equal to the highest single dose. The total planned enrollment for the Phase IIa portion is 24 subjects. If CD24Fc demonstrates safety and tolerability in Phase IIa, the trial will proceed to a 20 patient expansion cohort. All other components of the allogeneic HCT process will be according to routine institutional practice. This trial will exclusively utilize unrelated donors that receive myeloablative conditioning regimens and attempt to improve upon standard GVHD prophylaxis with tacrolimus and methotrexate. In the single dose cohorts, the study agent, CD24Fc, will be administered as a single dose on day -1 pre-transplant. In the multi dose cohort the patients CD24Fc will be administered on days -1, 14 and 28.

The amendment to conduct Phase II expansion will utilize unrelated donors that receive pre-defined myeloablative conditioning regimens and attempt to improve upon standard GVHD prophylaxis with tacrolimus and methotrexate. In the Phase II expansion cohort, the study agent, CD24Fc, will be administered on days -1, 14, and 28 at the dose of 480mg, 240 mg and 240mg, respectively, as established in Phase IIa.

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2.0 STUDY OBJECTIVES

The primary goals of this Phase II clinical study are to establish the safety, tolerability and efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT.

The primary goal of the Phase II expansion is to further substantiate the safety and efficacy of CD24Fc in combination with standard prophylaxis for preventing acute GVHD after allogeneic HCT.

We will utilize the following clinical and biologic objectives to accomplish these goals:

2.1 PRIMARY OBJECTIVES

2.1.1 PHASE IIA:

To evaluate the safety, tolerability, dose limiting toxicities (DLT), and to determine the recommended Phase IIb dose (RP2D) or maximum tolerated dose of CD24Fc in subjects undergoing unrelated donor myeloablative allogeneic hematopoietic cell transplantation (HCT)

2.1.2 PHASE IIA – EXPANSION COHORT:

To estimate 180 day grade III-IV acute GVHD free survival (AGFS) after HCT for CD24Fc at the RP2D.

2.2 SECONDARY OBJECTIVES

2.2.1 PHASE IIA

2.2.1.1 To estimate grade II-IV acute GVHD free survival (GFS) at day 180 following HCT

2.2.1.2 To describe incidence of chronic GVHD at one year following HCT

2.2.1.3 To describe incidence of relapse at one year following HCT

2.2.1.4 To describe incidence of transplant-related mortality (TRM) at one year following HCT

2.2.1.5 To describe rates of infection at day 100 following HCT

2.2.1.6 To evaluate overall survival (OS) and absence of grade III-IV GVHD and relapse free survival at one year following HCT

2.2.3 Phase IIA – Expansion Cohort:

2.2.2.1 180 days Grade II-IV acute GVHD Free Survival (AGFS)

2.2.2.2 One Year Disease Free Survival (DFS)

2.2.2.3 One Year Overall Survival (OS)

2.3 EXPLORATORY OBJECTIVES

2.3.1 To describe incidence of chronic GVHD at one year following HCT

2.3.2 To describe incidence of relapse at three years following HCT

2.3.3 To describe incidence of transplant-related mortality (TRM) at one year following HCT

2.3.4 To describe rates of infection at day 100 following HCT

2.3.5 To estimate overall and disease free survival at one and three years following HCT

2.4 CORRELATIVE AND BIOLOGIC STUDIES

2.4.1 To assess the pharmacokinetic (PK) profile of single-dose CD24Fc and anti-drug antibodies in the target patient population.

2.4.2 To examine functional responses of antigen presenting cells and T cells with or without administration of CD24Fc. To examine the biomarkers for T effector cell exhaustion.

2.4.3 To perform phenotyping of T cells, B cells, NK cells and other cellular immune subsets with or without administration of CD24Fc.

2.4.4 To assess plasma concentrations of pro-inflammatory cytokines, damage-associated molecular patterns (DAMPs), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides, Total cholesterol and GVHD biomarkers before and after administration of CD24Fc.

2.4.5: To assess genetic polymorphism of *CD24* and *Siglec10* genes, and microRNAs such as mir29, in both donor and recipients

3.0 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.[16] 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.[6, 17] Because GVHD is the principle contributor to TRM, it poses a fundamental barrier to improving outcomes after HCT.[18, 19]

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.[6] Despite routine administration of immune prophylaxis, clinically significant GVHD (Grade II-IV) occurs in approximately 50 to 80% of patients receiving unrelated donor HCT.[2, 5, 20-22]

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 [23, 24]. Nonetheless, in patients with very severe Grade III-IV GVHD (Figure 1), mortality rates are 50-90%.[18, 25, 26] 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.[27] Survival is significantly diminished for patients who demonstrate steroid refractoriness or who require prolonged treatment.[26, 28, 29] 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.[30, 31] These factors highlight the importance of improving our current approaches for the prevention of grade III-IV acute GVHD.[25-27]

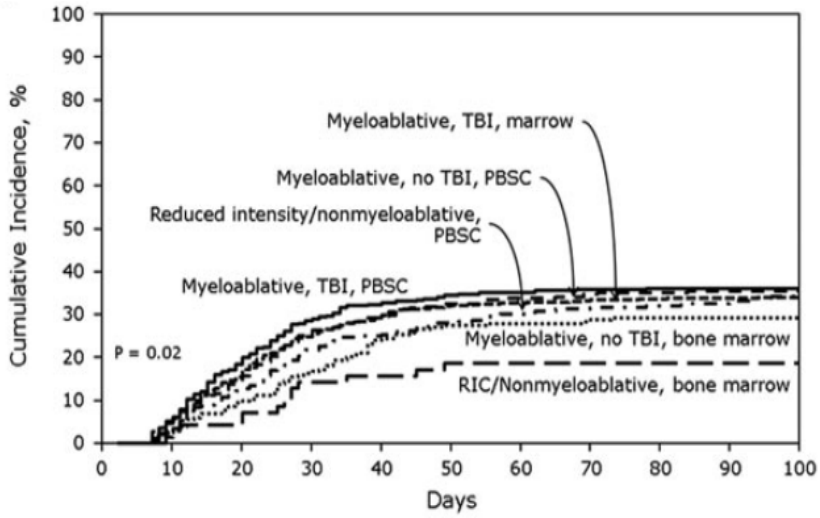


FIGURE 1. INCIDENCE OF GRADE III-IV ACUTE GVHD FOLLOWING UNRELATED DONORS HCT AS REPORTED BY CIBMTR (JAGASIA ET AL: BLOOD 2012, 119: 296-307).

3.2 PATHOGENESIS OF GVHD

Acute GVHD results from immunologically-mediated injury to host tissues.[32] Experimental data have shown that GVHD stems from allogeneic donor lymphocytes responding to host tissues that express polymorphic human leukocyte antigens,[5] 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.[33-35] 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,[36, 37] which are routinely employed for immune-ablation of host immunity and control of primary malignancy. Unfortunately, conditioning

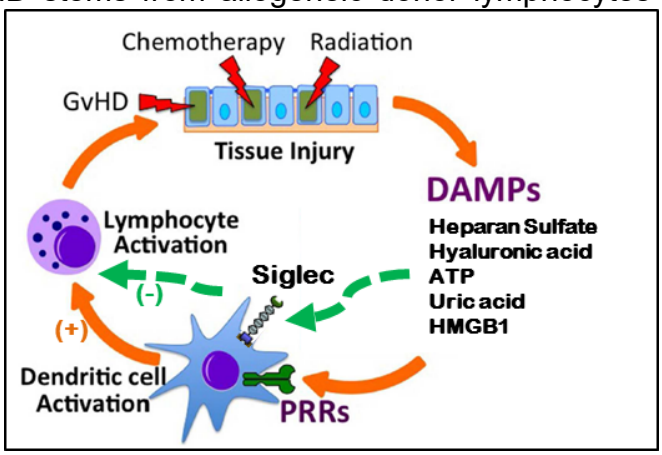


FIGURE 2: TISSUE INJURY AFTER ALLO-HCT. DAMAGE-ASSOCIATED MOLECULAR PATTERNS (DAMPS) INTERACT WITH PATTERN RECOGNITION RECEPTORS (PRRS) TO PROMOTE APC (DENDRITIC CELL) ACTIVATION (+) THAT ACTIVATES DONOR LYMPHOCYTES THAT RESULT IN GVHD. INTERACTIONS OF DAMPS WITH SIGLECS CAN PROMOTE NEGATIVE REGULATION (-) 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)

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 2).

3.3 CURRENT THERAPEUTIC APPROACHES FOR GVHD

To date, treatment and prevention of GVHD has predominantly focused on either pharmacologic inhibition[6, 8] or depletion of T cells through *in vitro*[38] or *in vivo* approaches to limit expansion of alloreactive T cells that mediate tissue injury.[39] 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.[31, 40, 41] 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 [15]. Other large registry analysis have not clearly demonstrated a clinical survival benefit for T cell depleting strategies [63]. 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 .[42, 43] [44, 45]

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.[33-35, 46, 47] 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.[48] Mounting experimental evidence now recognizes innate immune activation via DAMPs as a key initiating, step in promoting allogeneic T cell responses that drive GVHD.[49-51] 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.[52] Recent preclinical data demonstrate Siglec-G expression on hematopoietic APCs mediates significant protective

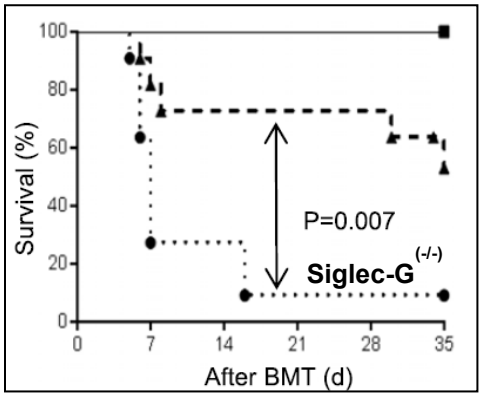


FIGURE 3: **LOSS OF SIGLEC-G SIGNALING RESULTS IN EXACERBATION OF GVHD**. FOLLOWING MYELOABATIVE TBI, SIGLEC-G (-/-) B6 MICE HAD SIGNIFICANT REDUCED SURVIVAL COMPARED TO ALLOGENEIC AND SYNGENEIC CONTROL ANIMALS.

effects against GVHD in multiple models of allogeneic HCT. [53] 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 3). 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.

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[54-56] but also have been shown experimentally in mice to reduce Siglec-G expression.[53] Thus, conditioning therapy may itself limit the capacity of Siglec-G to attenuate inflammatory responses triggered by DAMPs.

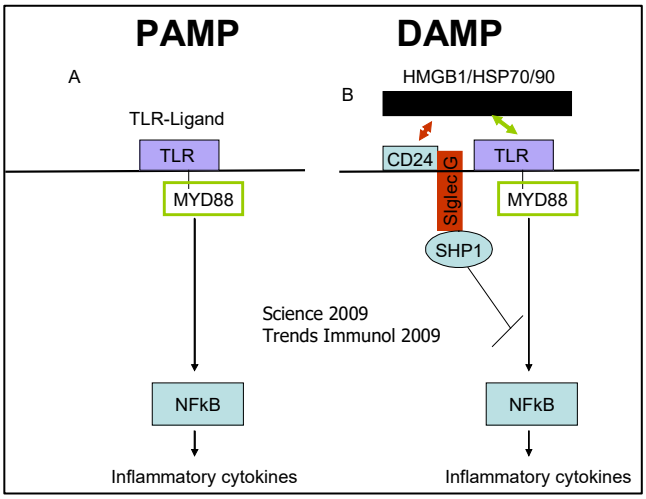


FIGURE 4: CD24-SIGLEC G (10) INTERACTION DISCRIMINATES BETWEEN PATHOGEN ASSOCIATED MOLECULAR PATTERNS (PAMPS) SUCH AS LIPOPOLYSACCHARIDE (LPS) AND DAMPS. A) HOST RESPONSE TO PAMPS WAS UNAFFECTED BY CD24-SIGLEC G(10) INTERACTION. B) CD24-SIGLEC G (10) INTERACTION REPRESSES HOST IMMUNE RESPONSE TO DAMPS. 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.

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 macrophages.[57] When expressed on T cells, CD24 is essential for down-modulating immune stimulation by DAMPs.[58, 59] It has been shown that CD24 directly associates with DAMPs thereby ameliorating their stimulatory activity (Figure 4). 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.[59] 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 vitro* studies demonstrate that CD24Fc binds to murine Siglec-G (and its human orthologue, Siglec 10).[58] 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 5).[53] 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 CD24Fc provides a unique opportunity to target this pathway as an innovative strategy for GVHD prevention.

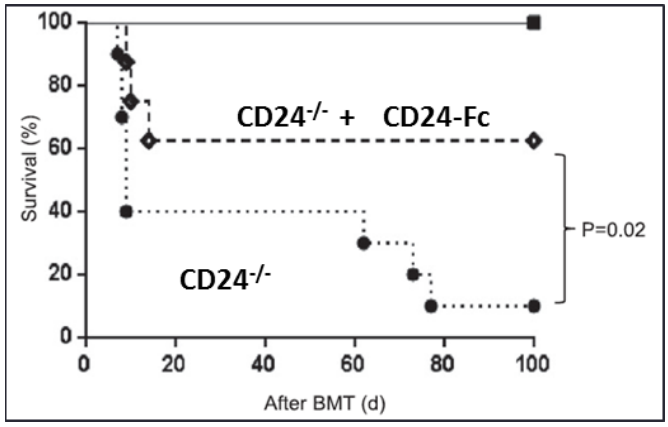


FIGURE 5: **CD24FC PREVENTS EXPERIMENTAL ACUTE GVHD.** B6 MICE WERE ADMINISTERED MYELOABLATIVE XRT FOLLOWED BY INFUSION OF $CD24^{-/-}$T CELLS FROM ALLOGENEIC AND SYNGENEIC DONORS. RECIPIENTS WERE INJECTED WITH CD24FC (5MG/KG) OR PLACEBO ON DAY -1 BEFORE HCT.

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), 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 100 days post-HCT on Apr. 5, 2018. Data was locked and unblinded on May 17, 2018. 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 2A 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 with a Karnofsky performance score $\geq$ 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. Restricting the study to patients receiving HCT from unrelated donors was expected to limit heterogeneity and facilitate statistical estimates of toxicity and aGVHD incidence for subsequent efficacy assessments, given the historically greater incidence of grade II – IV aGVHD (50 – 80%) and grade III-IV aGVHD (20-35%) in this population.

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.

The trial included two ascending single-dose cohorts (240 mg and 480 mg) and a multi-dose cohort (480-240-240 mg in three biweekly doses). In the single dose cohorts CD24Fc was administered as a single dose on day -1 pre-transplant. In the multi dose cohort CD24Fc was administered on days -1, 14 and 28. Eight patients (randomized 3:1 treatment to placebo) were enrolled in each of the 3 cohorts. All patients who signed consent, met eligibility and were enrolled proceed to randomization and study treatment.

3.8.2.2. STUDY RESULTS

3.8.2.2.1. DEMOGRAPHY OF STUDY POPULATION

Subjects were enrolled in the Phase IIa from Sept 2016 to Dec 2017. A total of 18 subjects received CD24Fc in combination with methotrexate and tacrolimus, and 6 subjects in the placebo group received methotrexate and tacrolimus with saline. As of the cutoff date for the data described in this application (May 17, 2018) the median follow-up of Phase IIa subjects was 10 months. The survival data was updated on November 28, 2018, the date of our latest safety monitoring meeting with all surviving subjects surpassing the 6-month follow-up period.

Table 1 lists demography information and clinical characteristics for subjects in the CD24Fc and placebo groups, which were relatively balanced across risk factors such as age, malignancy, and comorbidity. The most common malignancies in both the CD24Fc and placebo groups was AML and MDS (66.7% and 83.3%, respectively). At least half of the subjects in both groups had a comorbidity index of intermediate or high. PBSCs were more frequently used as the graft source as compared to bone marrow in both groups, and Flu/Bu 4 was the most common conditioning regimen across both cohorts. There were four patients in the CD24Fc group that used Cy/TBI conditioning. Patients in the CD24Fc group were also relatively older in age (62 vs. 57 years).

A contemporary control group of 92 adult patients comprising 69% AML/MDS, 26% ALL, 3% CML and 2% CMML was obtained from the University of Michigan and The Ohio State University for comparative analysis given the small size of the placebo group.

TABLE 1. CHARACTERISTICS OF PATIENTS ENROLLED IN THE PHASE IIA

		CD24Fc + TAC/MTX (N = 18)	**Placebo + TAC/MTX** (N = 6)
Age (years)	Median (range)	62 (23-68)	57 (36-66)
Gender (N, %)	Female	7 (38.8)	2 (33.3)
	Male	11 (61.1)	4 (66.7)
Graft Source (N, %)	PBSC	15 (83.3)	4 (66.7)
	BM	3 (16.7)	2 (33.3)
Malignancy (N, %)	AML/MDS	12 (66.7)	5 (83.3)
	CML	2 (11.1)	0 (0)
	CMML	1 (5.6)	1 (16.7)
	ALL	3 (16.7)	0 (0)
Comorbidity Index Score (N, %)	Low (0)	5	3 (50)
	Intermediate (1-2)	9	2 (33.3)
	High (3-4)	4	1 (16.7)
Cytomegalovirus status	D+, R+	5	1
	D+, R–	1	0
	D–, R+	3	1
	D–, R–	8	4
Conditioning regimen (N, %)	Flu/Bu 4	14 (77.8)	6 (100)
	Cy/TBI	4 (22.2)	0 (0)

BM=Bone marrow; Cy/TBI = cyclophosphamide/total body irradiation; D = donor; Flu/Bu = fludarabine/busulfan; R=recipient

All twenty-four subjects had neutrophils successfully engrafted. Neutrophils engrafted a median of 13.0 and 15.5 days after HCT in CD24Fc exposed and placebo subjects, respectively. Except one patient from the placebo group that did not have platelet engraftment before expiring on Day 49, the platelets engrafted a median of 13.0 and 15.0 days after HCT in CD24Fc exposed and placebo subjects, respectively. There were no cases of graft failure. The median CD3 chimerism at day +30 was 82.5% (range 38-100%) in the CD24Fc exposed patients and 82.0% (range, 62%-91%) in the placebo group. The median donor CD3 chimerism increased to 86% (range, 42%-100%) at day 100 in the CD24Fc exposed subjects and 84% (range, 17%-100%) in the placebo group. Donor CD33 chimerism at day 30 and 100 was 100% in both the CD24Fc and placebo groups.

3.8.2.2.2 EFFICACY – CUMULATIVE INCIDENCE OF AGVHD

Acute GVHD was graded according to consensus guidelines utilized by the international CIBMTR registry and Blood and Marrow Transplant Clinical Trials Network and recorded

weekly. Patients were evaluated for aGVHD following receipt of HCT on day 0 until day 100 after HCT. The cumulative incidence of grade II - IV aGVHD is summarized in **Table 2**.

TABLE 2. CUMULATIVE INCIDENCE OF AGVHD DAY 100 AFTER TRANSPLANT

Cohort	aGVHD Day 100 After Transplant
CD24Fc 240mg (N=6)	Gr II: 2 (Skin) Gr III: 0 Gr IV: 0 **Gr II – IV: 33.3%** (95%CI, 3.2, 70.4) **Gr III – IV: 0%**
CD24Fc 480mg (N=6)	Gr II: 2 (Skin and Upper GI) Gr III: 1 (Lower GI) Gr IV: 0 **Gr II – IV: 50.0%** (95%CI, 7.7, 82.9) **Gr III – IV: 16.7%**
CD24Fc 960mg multi-dose (N=6)	Gr II: 2 (Skin and Upper GI) Gr III: 0 Gr IV: 0 **Gr II – IV: 33.3%** (95%CI, 3.2, 70.4) **Gr III – IV: 0%**
CD24Fc all (N=18)	Gr II: 6 Gr III: 1 Gr IV: 0 **Gr II – IV: 38.9%** (95%CI, 16.8, 60.7) **Gr III – IV: 5.6%**
Placebo (N=6)	Gr II: 0 Gr III: 1 (Lower GI) Gr IV: 0 **Gr II – IV: 16.7%** (95%CI, 0.5, 54.9) **Gr III – IV: 16.7%**
Contemporary Control (N=92)	Gr II: 22 Gr III: 16 Gr IV: 3 **Gr II – IV: 50%** (death as competing factor) (95%CI, 39.8, 60.2) **Gr III – IV: 24%** (death as competing factor) (95%CI, 17, 31)

The incidence of grade II – IV aGVHD in CD24Fc exposed subjects was 7 out of 18 (38.9%), 1 out of 6 (16.7%) in the placebo group, and 50% in the contemporary control. The cumulative incidence of grade II GVHD was the same across all CD24Fc cohorts in

the Phase IIa. Four cases of grade II GVHD involved skin only and two cases involved skin and the upper gastrointestinal (GI) tract. There were no cases grade II GVHD in the placebo group.

When evaluating subjects with the more serious aGVHD grade III – IV, only 5.6% (1/18) of subjects in the CD24Fc cohorts experienced grade III GVHD (1 subject in the 480 mg cohort with lower GI involvement) as compared to 16.7% of subjects in the placebo group (1/6, also with lower GI involvement) and 24% in the contemporary control cohort. All patients who developed aGVHD in the trial at the time of the data cutoff have responded to steroid treatment.

After the first one hundred days post HCT, subjects are evaluated quarterly for late onset aGVHD or cGVHD until one year after HCT. No additional aGVHD events have been observed in the CD24Fc cohorts through minimum of 180 days of post-transplant follow-up.

3.8.2.2.3. RELAPSE, TRM AND MORTALITY

The incidence of leukemia relapse in subjects exposed to CD24Fc at Day 180 post HCT is lower as compared to subjects in the placebo group, with 11% (2/18) versus 33% (2/6), respectively, (see **Table 3**). 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 was 23% at day 180.

Regarding details of the relapse events in the current Phase IIa study one subject in the 480 mg CD24Fc cohort experienced relapse of high risk CMML on Day 146 and one subject in the multi-dose 480/240/240 mg CD24Fc cohort experienced relapse of ALL on Day 100 post HCT. The patient with CMML passed away on Day 196 due to leukemia. The patient with ALL relapse was treated with blinatumomab and achieved complete remission. The patient with ALL relapse was treated with blinatumomab and achieved complete remission. The patient experienced ALL relapse again 6 months later, underwent a haploidentical HCT and passed away on Day 357 post first allo-HCT. In the placebo cohort, two subjects experienced relapse of CMML on Day 94 and MDS on Day 146. The patient with CMML passed away on Day 316 and the patient with MDS passed away on Day 184. These preliminary results suggest CD24Fc may suppress GVHD without interfering with the beneficial graft-versus-leukemia (GVL) process, which if confirmed in prospective datasets, would represent a significant advance over available immune suppressive therapy. Relapse has been monitored as of the writing of this report with a median of 16 months of follow up, with no changes in the incidence of relapse in any of the cohorts, up to the Safety Meeting on Nov. 28, 2018.

The incidence of transplantation related mortality (TRM) in the CD24Fc group is also lower than in the placebo group. At Day 180 post HCT, no death occurred in the CD24Fc group, and one death due to pneumonia occurred in the placebo cohort (16.7%). Over

the entire follow up period of 16 months (range 11-23 months) up to the last safety meeting on Nov. 28, 2018, 3 out of 18 patients (17%) in the CD24Fc treated group died, while 3 out 6 in the placebo group died (50%). The one-year overall survival Kaplan-Meier estimate is 83% in CD24Fc vs. 50% in placebo.

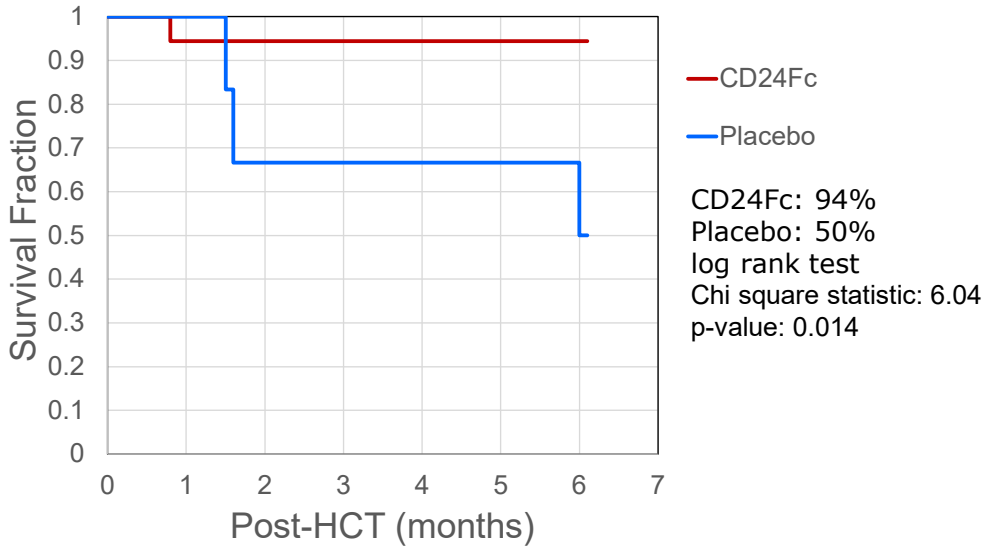
TABLE 3. INCIDENCE OF RELAPSE AND DEATH

Cohort	Relapse (Day 180)	Death (Day 180)
CD24Fc total (N=18)	2/18 (11.1%)	0/18 (0%)
Placebo (N=6)	2/6 (33.3%)	1/6 (16.7%)
Contemporary Control (N=92)	19/92 (23.1%) (Death as competing factor)	22/92 (23.9%)

3.8.2.2.4. 180 DAY GRADE III – IV AGVHD FREE SURVIVAL

Statistically significant improvements in aGVHD grade III-IV-free survival (AGFS) are observed in the CD24Fc cohorts (94%) as compared to the placebo group (50%) at Day 180 post HCT (P=0.014, see **FIGURE 6**).

Figure 6. 180 day grade III-IV GVHD-free survival of patients receiving either CD24Fc or placebo control.



3.8.2.2.5. 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 [65], 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 [63]. 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 7).

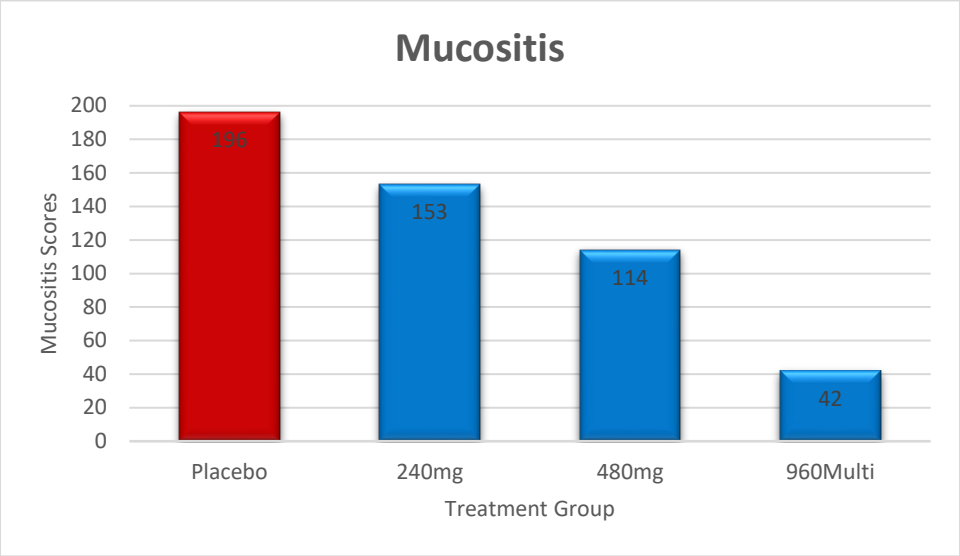


Figure 7. Mucositis scores calculated as multiple of severe mucositis grade ≥3 and duration (person-days).

3.8.2.2.7. 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.

3.8.2.2.8. SAFETY

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 (at least 150 days after the last dosing of CD24Fc). There was one adverse event of pneumonia that led to the death of a subject at Day 48 in the placebo group. One patient in the CD24Fc group died at 7 months after HCT from pneumonia which was determined to be unlikely related to study drug. 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.

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 24% in the contemporary control cohort (methotrexate and tacrolimus alone). These 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, the most serious grades of aGVHD which are associated with increased risk of non-relapse mortality [64]. 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 aGVHD GFS (94% versus 50%, CD24Fc versus placebo, respectively), a dose-dependent reduction in severe mucositis, and a favorable overall safety profile with only one drug-related TEAE (grade III) observed in the study.

Based on these favorable findings and discussions with FDA, sponsor and coordinating institutions, it was deemed beneficial to enroll an expansion cohort of patients to be treated with the CD24FC multidose regimen in accordance with this amended protocol. Estimates of acute GVHD free survival obtained from dose expansion phase will enable further assessment the promising results observed in Phase IIa by increasing available data in patients treated at the RP2D, and optimizing development of sufficiently powered Phase III randomized controlled study. Protocol-defined criteria for patient selection, treatment, data collection, follow-up visit schedule, and safety monitoring will remain substantially unchanged. However, the efficacy endpoints and statistical analysis methods will be updated to describe a more rigorous assessment of clinical outcomes using case-matched historical controls with pre-specified clinical criteria from a large international registry database (CIBMTR).

4.0 PATIENT SELECTION

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:

a. Acute Myeloid Leukemia (AML) or Acute Lymphoblastic Leukemia (ALL) in first or second 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.

b. Chronic Myelogenous Leukemia (CML) in first or subsequent chronic phase failing to respond (or intolerant) to at least two different tyrosine kinase inhibitors. CML in accelerated or blast phase (CML-AP/BP) are eligible without requirement to fail tyrosine kinase inhibitor therapy, but must be in remission at time of enrollment. 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.

c. Myelodysplastic syndrome (MDS) with intermediate or high-risk IPSS or equivalent IPSS-R score with < 10% blasts in the bone marrow.

d. Chronic Myelomonocytic Leukemia (CMML) with < 10% blasts in the bone marrow.

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 21 days of beginning conditioning are listed in Table 4 below:

TABLE 4: Eligibility According to Pre HCT Organ Function

Total bilirubin	≤2.5 mg% (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 6 weeks prior to the date of enrollment

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. Sorafinib).

4.2.3 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.

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

4.2.9 Prior HCT (allograft or prior autograft).

4.2.10 Use of T cell depletion either *ex vivo* or *in vivo* (i.e. ATG, alemtuzumab) is prohibited.

4.2.11 Current or prior diagnosis of antecedent Myelofibrosis is excluded.

5.0 TREATMENT SCHEDULE

5.1 REGISTRATION PROCEDURES

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 additional sites. The University of Michigan will serve as the coordinating center. 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 underlying disease, donor type, 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.

Patient Characteristics to be Collected at Registration for Cohort Matching.

The patient's age, gender, the CIBMTR CRID number, underlying disease, disease risk index (DRI) [66], disease remission status, conditioning regimen, cell source, donor/recipient CMV status, HCT-CI, KPS, transplant center and donor age/gender will be recorded and reported to University of Michigan O-CTSU as part of patient enrollment. These pre-specified parameters will be utilized to assemble an external database of registered case matched controls from the CIBMTR.

5.2 OVERVIEW

This is a prospective Phase II clinical trial designed to assess the safety, tolerability, and preliminary efficacy of the addition of CD24Fc to standard tacrolimus and methotrexate GVHD prophylaxis. This trial employs a sequential design. The initial Phase IIa portion is a randomized double blind study to establish the recommended Phase II dose (RP2D) or the maximum tolerated dose (MTD) of CD24Fc and is comprised of: i) two single ascending dose cohorts (240 mg and 480 mg CD24Fc administered on day -1) of 8 patients (3:1 treatment:placebo); and ii) a multi-dosing cohort consisting of 8 patients (3:1 treatment:placebo) that will receive 3 consecutive biweekly administrations of CD24Fc on day -1 (480 mg), day 14 (240 mg) and day 28 (240 mg). The total planned enrollment for the Phase IIa portion is 24 subjects.

This is a prospective Phase II clinical trial designed to assess the safety, tolerability, and preliminary efficacy of the addition of CD24Fc to standard tacrolimus and methotrexate GVHD prophylaxis. The Phase II dose expansion will further examine CD24Fc at the

RP2D with standard immune prophylaxis to determine if this combination reduces the incidence of acute GVHD after HCT compared to standard prophylaxis alone. The aim of this portion of the trial is to investigate the ability of this new regimen for GVHD prevention to improve AGFS. Since the potential efficacy of CD24Fc in GVHD prevention is not established, this will enable assessment of initial efficacy in improving AGFS, which will be determined in a subsequent randomized placebo controlled trial.

All patients will undergo HLA matched unrelated donor allogeneic HCT according to standard institutional practice. This trial will exclusively focus on HLA matched unrelated donors given the historically greater incidence of grade II-IV acute GVHD in this population. Restricting the study to unrelated donors receiving myeloablative conditioning will limit heterogeneity in Phase IIa to best assess potential toxicity and facilitate statistical estimates of GVHD and relapse incidence for subsequent efficacy assessments. The preparative regimen will employ standard doses of myeloablative conditioning, with suggested regimens outlined in section 5.6.

5.3 TREATMENT SCHEMA

For the single dose escalation cohorts of the study, the investigational agent (CD24Fc) will be given intravenously as a single dose on day -1 before HCT (Figure 8A). In the Phase IIa portion of the study a dose level will be assigned at enrollment.

For the multi-dosing cohort, the investigational agent (CD24Fc) will be given intravenously on day -1 (480 mg) before HCT, and on day 14 (240 mg) and day 28 (240 mg) post HCT (Figure 8B).

Based on the Phase IIa clinical safety results and the pharmacokinetic data, the recommended Phase III dose was determined to be multi-dose 480-240-240 mg administered on day -1, day 14 and day 28. The Phase II expansion cohort will use the same multi-dose 480-240-240 mg regimen. This regimen will provide biologically active levels of CD24Fc through the peak period of DAMP exposure and acute GVHD (median 30 days). The Phase II expansion study schema is shown in Figure 8C.

Dosing is based on a fixed amount and not based on weight or BSA.

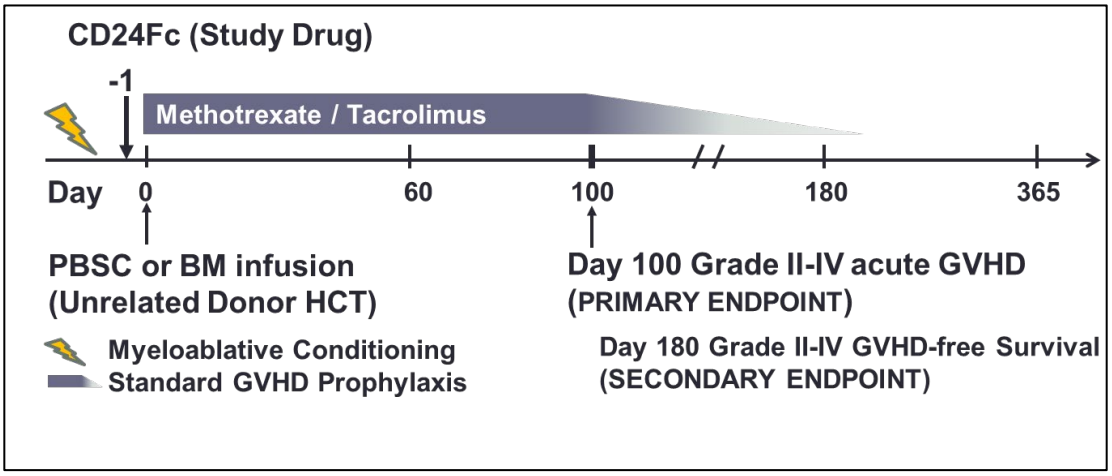


Figure 8A: Single dose escalation Study Schema of CD24Fc for GVHD Prevention.

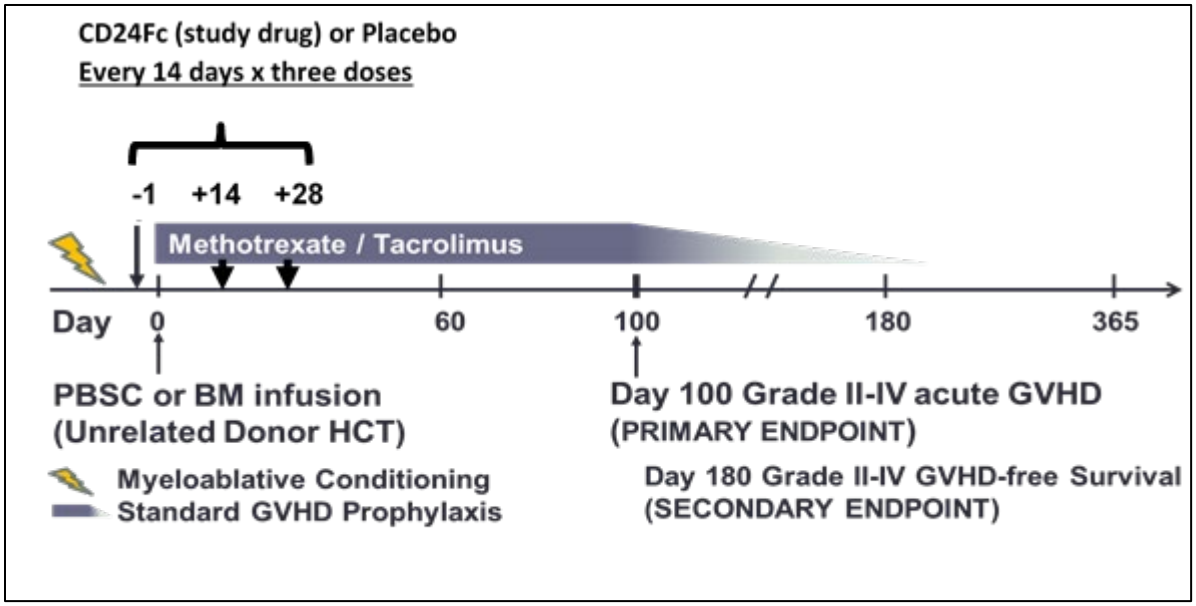


Figure 8B: Multi-Dosing Cohort Study Schema of CD24Fc for GVHD Prevention

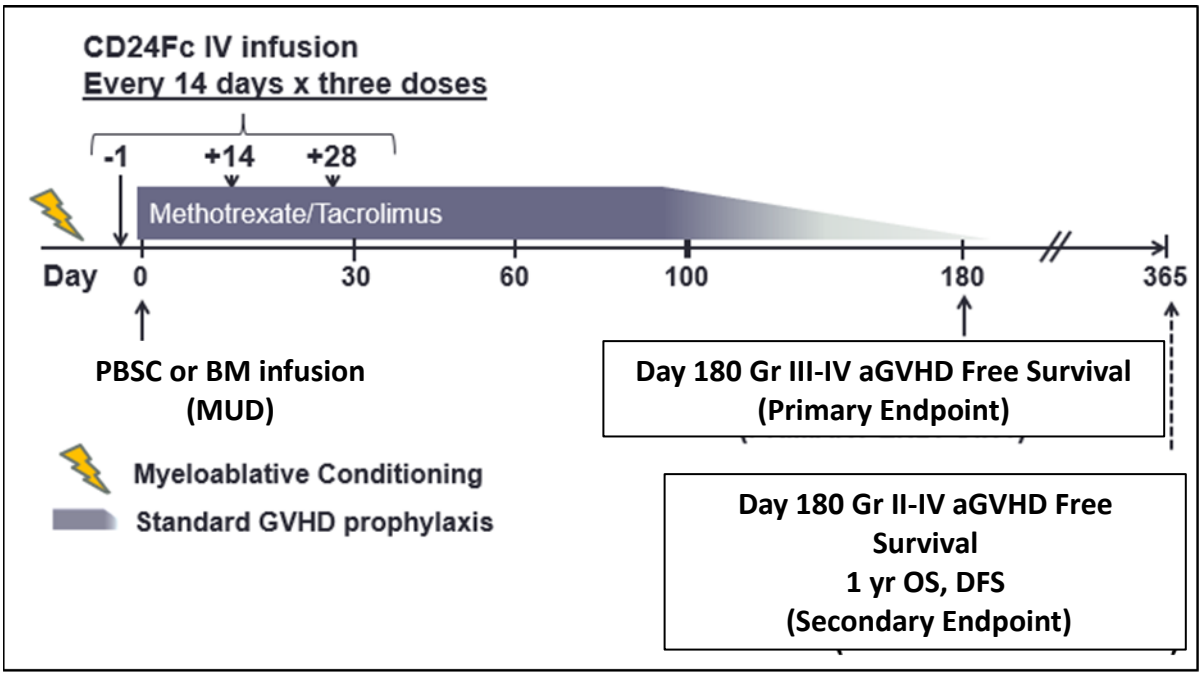


Figure 8C. Phase IIa – expansion cohort Study Schema of CD24Fc for GVHD Prevention.

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

For the single dose escalation cohorts, CD24Fc (study agent) will be administered intravenously as a single dose on day -1 prior to HCT. Subjects will also receive standard of care GVHD prophylaxis with methotrexate and tacrolimus. Attempts should be made

to administer the CD24Fc on schedule. The dose may be delayed up to 2 days after its intended administration (i.e. up to day 1 post HCT) for unanticipated events such as toxicity from preceding conditioning chemotherapy or infection. Administration of CD24Fc on a delayed schedule will not be a deviation but will be recorded and require approval from study PI or protocol chair.

For the multi-dose cohort and the Phase IIa expansion cohort, 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. Administration of CD24Fc on a delayed schedule on day -1 will not be a deviation but will be recorded and require approval from study PI or protocol chair.

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.

g. Patients who are unable to initiate standard or alternative prophylaxis (calcineurin inhibitor) will be removed from the study and replaced.

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 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.

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/m2/day; total dose of 12.8 mg/kg or 520 mg/m2, respectively).
Days -5 to -2: Flu (30 to 45 mg/m2/day, total dose of 120 - 180 mg/m2)

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

5.6.4 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* (i.e. ATG, alemtuzumab) 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 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.

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).

PBSC should be infused into the patient on the same day of collection whenever possible. However, given logistics of unrelated donor collections, unrelated PBSC may be infused within 48h of collection.

For PBSC: The recommended stem cells dose is ≥ 5.0 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 participants 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 60 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.

5.8.5.4 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 Lyphocyte Infusions – Viral-specific cytotoxic T-Lyphocytes (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.

5.8.7 Intravenous Immune Globulin (IVIG).

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

6.0 STUDY DEFINITIONS

a. 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.

b. Enrolled. 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 multi-site coordinator confirms these data. The date of enrollment will be documented as date of notification from the multi-site coordinator.

c. Treatment Period. The "Treatment Period" is defined as the first day of treatment with CD24Fc until 30 days after HCT for the single-dosing cohorts or 60 days after HCT for the multi-dose and expansion cohort. 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 30 or day 60 post HCT. Based upon PK data for CD24Fc this time period will allow for passage of greater than two half-lives.

d. 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 31 or day 61) until the subject comes off study. The follow-up period can be up to 4 years post HCT. During this time subjects will be followed for GVHD (acute and chronic), 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.

e. On Study: 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.

f. Off Treatment: The "Off Treatment" period is generally defined as the time period where the patient completes the study drug treatment period (Day 30 for the single-dosing cohorts or Day 60 for the multi-dosing cohort) or if one or more of the following criteria are met:

- Death
- Lost to follow up
- Entry on to a competing trial
- Withdrawal of consent by the patient or 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 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).

g. 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/uL. Engraftment for platelets is defined as the first of three consecutive days in which the platelet count is > 20,000/uL, without transfusion support.

Primary engraftment failure: will be defined as ongoing ANC <500/uL by day 28 post HCT. Failure to attain platelet count ≥ 20,000/uL will not be considered engraftment failure. Patients who engraft prior to day 28 and later have ANC < 500/uL or platelet transfusion requirements, as frequently occurs in HCT patients due to infection and other complications will not be considered to have engraftment failure.

7.0 MANAGING TOXICITIES

7.1 MANAGING INFUSION REACTIONS

Infusion reactions were not observed in the Phase 1 and Phase IIa clinical trials. 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. Patient 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 an infusion-related reaction. If an infusion reaction is deemed severe (e.g. severe hypotension, hypoxemia) the infusion should be stopped.

3) Supportive care will be provided as clinically indicated and commiserate with the intensity of the infusion reaction. These measures may include supplemental oxygen, diphenhydramine, acetaminophen, ibuprofen, IV corticosteroids (i.e. hydrocortisone) and iv fluids.

4) 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 at the bedside during CD24Fc administration.

7.2 MANAGING ACUTE GVHD

a. Acute GVHD will be graded and recorded according to consensus guidelines utilized by international CIBMTR registry and Blood and Marrow Transplant Clinical Trials Network (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 according to consensus guidelines until day 180 after HCT.

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 [67]. 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 month from Day 100 to Day 180 with quarterly thereafter. 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. **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.**

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. 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).

e. 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.

8.0 DOSE MODIFICATIONS BASED ON LABORATORY VALUES

8.1 RENAL FUNCTION

If estimated GFR is less than 30 mL/min dosing will be held. If GFR recovers to greater than 30 mL/min within the protocol defined treatment period window then CD24Fc may be resumed.

8.2 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.

9.0 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 for the single-dose cohorts (Table 5A), the multi-dosing cohort (Table 5B), and the expansion cohort (Table 5C). These procedures will be conducted as required observations for study unless indicated otherwise.

Table 5A. Study Calendar for Single Dose Cohorts

	PRE-HCT								
Observations	Day -28 to -7 (enrollment)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 3)	Weekly from + 0 to + 29 (± 3)	+ 30 (± 5)
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			x	x	x	x	x
Laboratory testing[2]	x	x			x	x	x	x	x
ECG monitoring[3]		x		x					
CD24Fc (Study Agent)[4]			x						
Hematopoietic Stem Cell Transplant (HCT)					x				
Vital Sign monitoring[5]		x	x	x					
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
Toxicity Assessment (NCI Criteria)			x		x	x	x	x	x
Assess Engraftment									x
Bone marrow aspirate & biopsy	x								
Chimerism									x
Anti-drug-antibody/PK samples		x		x		x	x		x
hs-CRP		x					x		x
Fasting Lipid Panel including LDL		x					x		x
Research samples (Subject)[7]	x	x					x		x
Research sample (Donors)[8]					x				
Survival Follow-Up									

Table 5A. Study Calendar Cont.

				FOLLOW-UP PERIOD				SURVIVAL FOLLOW-UP
Observations	Weekly from +30 to +100 (± 5)	Every other week from +30 to +100 (± 5)	+ 42 (± 5)	+ 100 (± 7)	Quarterly: Day +180 and Day +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	x			x	x	x	x	
Laboratory testing[2]		x		x				
ECG monitoring[3]			x					
CD24Fc (Study Agent)[4]								
Vital Sign monitoring[5]								
Acute GVHD assessment[6]	x			x	x		x	
Chronic GVHD assessment				x	x	x		
Concomitant Medications	x			x	x	x	x	
Toxicity Assessment (NCI Criteria)	x			x				
Assess Engraftment								
Bone marrow aspirate & biopsy				x				
Chimerism				x				
Anti-drug-antibody/PK samples			x	x			x	
hs-CRP				x			x	
Fasting Lipid Panel including LDL				x			x	
Research samples (Subject)[7]				x			x	
Research sample (Donors)[8]								
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 30, ± 5 days for observations from day 31 until day 100, and ± 7 to 14 days for observations from day 100 to day 365. Collection windows do not apply to early PK studies which should be collected around the time of CD24Fc infusion.**

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 Pulmonary Function Test may be assessed up to 6 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 at a minimum of three times (e.g. every 48-72 hours) for the first week post CD24fc infusion (day 0 to day 7) and then per institution clinical practice guidelines. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin then performed weekly through day 29 and performed every other week through day 100 post HCT. Laboratory testing may be more frequent per standard HCT practice.
3) 12 lead ECG monitoring will be performed at 3 time points to assess cardiac safety signals. On Day -1, the ECG should be measured within four hours of start of study drug infusion and 2 hours (± 15 minutes) post drug (i.e. 2 hours after the start of infusion). ECG should be measured 3 hours (± 15 min) post drug in the 960mg dosing cohort due to prolonged infusion time (i.e. 3 hours after the start of infusion).
4) Per protocol, CD24Fc will be administered on day -1. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Frequent vital sign monitoring is required following CD24Fc infusion. Vital signs will be recorded prior to infusion and at approximately 15, 30, 60, and 120 minutes from the start of the CD24Fc infusion.
6) Assessment for acute GVHD will occur weekly through day 100. Following day 100 acute and chronic GVHD assessments will occur approximately at a quarterly schedule (day 180 and day 270 ± 14 days). Consensus acute GVHD grading will be used to report disease severity (APPENDIX C)
7) Research samples include PBSC and serum from subjects at indicated time points to be cyropreserved for correlative immunologic studies.
8) In the pre-HCT period, a research sample from the donor HCT product will also be cryopreserved prior to infusion.

Table 5B. Study Calendar for Multi-Dose Cohort

	PRE-HCT	POST-HCT							
Observations	Day -28 to -7 (enrollment)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 4)	+ 28 (± 4)	Weekly from + 0 to +60 (± 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			x	x	x	x	x
Laboratory testing[2]	x	x			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	x	
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
Toxicity Assessment (NCI Criteria)			x		x	x	x	x	x
Assess Engraftment								x	
Bone marrow aspirate & biopsy	x								
Chimerism								x	
Anti-drug-antibody/PK samples[7]		x		x		x	X (see note 7)	X (see note 7)	(see note 7)
hs-CRP		x					x	x	
Fasting Lipid Panel including LDL		x					x	x	
Research samples (Subject)[8]	x	x					x	x	
Research sample (Donors)[9]					x				
Survival Follow-Up									

Table 5B. Study Calendar Cont.

					FOLLOW-UP PERIOD				SURVIVAL FOLLOW-UP
Observations	Weekly from +60 to +100 (± 5)	Every other week from +60 to +100 (± 5)	+ 42 (± 5)	+60 (±5)	+ 100 (± 7)	Quarterly: Day +180 and Day +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	x	x	
Pre-HCT organ function and infectious disease testing[1]									
Pregnancy test (if applicable)									
Karnofsky Performance Status	x		x	x	x	x	x	x	
Laboratory testing[2]		x	x	x	x				
ECG monitoring[3]			x	x					
CD24Fc (Study Agent)[4]									
Vital Sign monitoring[5]									
Acute GVHD assessment[6]	x				x	x		x	
Chronic GVHD assessment					x	x	x		
Concomitant Medications	x				x	x	x	x	
Toxicity Assessment (NCI Criteria)	x				x				
Assess Engraftment									
Bone marrow aspirate & biopsy					x				
Chimerism					x				
Anti-drug-antibody/PK samples[7]			x	x (see note 7)	x			x	
hs-CRP					x			x	
Fasting Lipid Panel including LDL			x	x	x			x	
Research samples (Subject)[8]			x	x (see note 8)	x			x	
Research sample (Donors)[9]									
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. Collection windows do not apply to early PK studies which should be collected around the time of CD24Fc infusion.**

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 Pulmonary Function Test may be collected up to 6 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. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin then performed weekly through day 59 and performed every other week through day 100 post HCT. Laboratory testing may be more frequent per standard HCT practice.
3) 12 lead ECG monitoring will be performed at 8 time points to assess cardiac safety signals. On Day -1, Day 14 and Day 28, the ECG should be measured within four hours of start of study drug infusion and 2 hours (± 15 minutes) post drug (i.e. 2 hours after the start of infusion).
4) Per protocol, CD24Fc will be administered on day -1, day 14 and day 28. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Frequent vital sign monitoring is required following CD24Fc infusion. Vital signs will be recorded prior to infusion and at approximately 15, 30, 60, and 120 minutes from the start of the CD24Fc infusion.
6) Assessment for acute GVHD will occur weekly through day 100. Following day 100 acute and chronic GVHD assessments will occur approximately at a quarterly schedule (day 180 and day 270 ± 14 days). Consensus acute GVHD grading will be used to report disease severity (APPENDIX C).
7) Anti-drug-antibody / PK samples: Blood samples should be taken before infusion and 2 hours after completing the CD24Fc infusion (on day -1, day 14, and day 28). Additional ADA/PK samples to be drawn on day 7, day 21, day 35, day 42, day 56, day 70, and day 100.
8) Research samples include PBSC and serum from subjects. Research samples should be taken at the following time points to be cyropreserved for correlative immunologic studies: Baseline (Day -7, prior to initiating conditioning), prior to infusion on Day -1, Day 14, and Day 28, Day 42, Day 56 and Day 100.
9) In the pre-HCT period, a research sample from the donor HCT product will also be cryopreserved prior to infusion.

Table 5C. Study Calendar for Phase IIa – Expansion Cohort

	PRE-HCT	POST-HCT							
Observations	Day -28 to -7 (enrollment)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 4)	+ 28 (± 4)	Weekly from + 0 to +60 (± 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	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	x	
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
Toxicity Assessment (NCI Criteria)			x		x	x	x	x	x
Assess Engraftment								x	
Bone marrow aspirate & biopsy[10]	x								
Chimerism								x	
Fasting Lipid Panel including LDL		x					x		
Research samples (Subject)[7]	x	x					x	x	
Survival Follow-Up									

Table 5C. Study Calendar for Phase IIA – Expansion Cohort Continued.

	POST-HCT		FOLLOW-UP PERIOD					SURVIVAL FOLLOW-UP
Observations	+ 42 (± 5)	+60 (±5)	+ 100 (± 7)	+ 180 (± 7)	Quarterly: Day +180 and Day +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	x	x	
Pre-HCT organ function and infectious disease testing[1]								
Pregnancy test (if applicable)								
Karnofsky Performance Status								
Laboratory testing[2]	x	x	x	x				
ECG monitoring[3]	x	x						
CD24Fc (Study Agent)[4]								
Vital Sign monitoring[5]								
Acute GVHD assessment[6]	x	x	x	x	x		x	
Chronic GVHD assessment			x	x	x	x		
Concomitant Medications	x	x	x	x	x	x	x	
Toxicity Assessment (NCI Criteria)	x	x	x	x				
Assess Engraftment								
Bone marrow aspirate & biopsy[8]			x					
Chimerism			x					
Fasting Lipid Panel including LDL								
Research samples (Subject)[7]	x	x	x	x			x	
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 6 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) 12 lead ECG monitoring will be performed at 8 time points to assess cardiac safety signals. On Day -1, Day 14 and Day 28, the ECG should be measured within four hours of start of study drug infusion and 2 hours (± 15 minutes) post drug (i.e. 2 hours after the start of infusion).
4) Per protocol, CD24Fc will be administered on day -1, day 14 and day 28. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Frequent vital sign monitoring is required following CD24Fc infusion. Vital signs will be recorded prior to infusion and at approximately 15, 30, 60, and 120 minutes from the start of the CD24Fc infusion.
6) Assessment for acute GVHD will occur weekly through day 100. Following day 100 acute and chronic GVHD assessments will occur monthly. Consensus acute GVHD grading will be used to report disease severity (APPENDIX C).
7) Research samples include PBSC and serum from subjects. Research samples should be taken at the following time points to be cyropreserved for correlative immunologic studies: Baseline (Day -7, prior to initiating conditioning), prior to infusion on Day -1, Day 14, and Day 28, Day 42, Day 60, Day 100 and Day 180.
8) The Pre-HCT bone marrow biopsy may be assessed up to 6 weeks prior to enrollment.

10.0 RESEARCH SAMPLES

10.1 RESEARCH BLOOD SAMPLES

10.1.1 PHASE IIA - SINGLE DOSE AND MULTI-DOSE COHORTS

Research samples (approximately 28 ml) and PK/ADA samples (approximately 8 ml) will be obtained from the peripheral blood per time point (up to approximately 36 mL total) from each patient at 5 (single dose) or 7 (multi-dose) and 7 (single dose) or 13 (multi-dose) planned time points, respectively, during the course of the study. An additional sample will be drawn at time of GVHD onset, if applicable. Samples will be collected coincident with routine blood draws on the patients. In addition, one heparinized blood sample (approximately 2 mL) will be taken from the donor stem cell grafts once prior to administration to the recipient (Day 0).

Research samples will be obtained at the following time points for the single dose cohorts: at baseline on day -7 (±5) prior to initiating conditioning and then prior to study drug infusion on day -1, day +14 (±3), day +30 (±5) and day +100 (±7). Research samples will be obtained at the following time points for the multi-dose cohort: at baseline on day -7 (±5) prior to initiating conditioning, prior to study drug infusion on day -1, day 14 (±4), day 28 (±4), day 42 (±5), day 56 (±5) and day +100 (±7). PBMCs and serum will be isolated and frozen for future analysis. All samples will be processed, frozen, and banked in the Immunology Core Lab at the University of Michigan.

For PK and anti-drug antibody (ADA) analysis in the single dose cohorts, blood samples will be collected prior to study drug infusion and 2 hours (±30 minutes) after completing the CD24Fc infusion on day -1 and on days +7 (±2), +14 (±3), +30 (±5), +42 (±5), and +100 (±7). For the multi-dose cohort, PK/ADA samples will be collected prior to study drug infusion and 2 hours after completing study drug infusion on day -1, day +14 and day +28 (Note: these days should be adjusted to the precise day of infusion if the CD24Fc is delayed for any reason). Samples will also be collected days +7 (±2), +21 (±3), +35 (±5), +42 (±5), +56 (±5), +70 (±5) and +100 (±7) after HCT. ADA will be tested on the samples from pre-infusion (-1 day), day 60 and day 100. PK and ADA will be measured using validated assays in a GLP-compliant laboratory that performed these analyses for the Phase I study. Pharmacokinetic parameters will be calculated using actual collection times. The PK parameters for CD24Fc (Cmax, Tmax, kel, t½, AUC0-42d, AUC0-inf, AUCextr, CL, and Vd) will be calculated from the individual plasma concentrations profile by non-compartmental approaches. In patients with pre-existing or induced ADA, we will determine whether the ADA affects PK of the drug, although the results from the Phase I study demonstrated that a small number of patients with either pre-existing or induced ADA have similar PK to subjects without ADA.

10.1.2 – PHASE IIA – EXPANSION COHORT

Research samples (approximately 28 ml) will be obtained from the peripheral blood per time point from each patient at the time points marked in Table 5C.

10.2 CORRELATIVE STUDIES

10.2.1 OVERVIEW OF EXPERIMENTAL DESIGN:

The aims of the correlative studies will be to explore the pharmacokinetics, pharmacodynamics (PD) and immunologic impact of CD24Fc administration on human immune subsets following allogeneic HCT. For these studies, samples will be obtained before infusion into the patient and at time points after infusion in the presence of CD24Fc, such that each patient serves as their own internal control. These data will then be aggregated and used for comparisons to time matched controls not receiving CD24Fc available within the University of Michigan biorepository (HUM#48783). Additionally, the randomized, double blind, placebo controlled, component of the trial will facilitate contemporaneous comparisons between subjects receiving standard GVHD prophylaxis with or without CD24Fc. This design will enable robust intra-patient comparisons. Correlative experiments will be designed and conducted by the laboratory of Dr. Pavan Reddy (Univ. of Michigan) and OncoImmune, or at a designated contract research organization. Any human samples sent for analysis by external collaborators including OncoImmune, Inc. and their designated CRO will be de-identified by coding to protect subject personal health information.

10.2.2 PD AND IMMUNOLOGIC STUDIES:

Cryopreserved specimens will be utilized as indicated for exploratory PD and immunologic studies to evaluate the effects of CD24Fc which includes but is not limited to the following analysis:

PD studies: will evaluate Siglec-10 intracellular phosphorylation status of SHP-1, and activation status of Nuclear Factor kappa B (NF-kB) components within immune subsets, namely APCs and T cells.

Cellular immunology correlatives: will examine a) *Ex vivo* T cell responses (cytokine release, proliferation) to DCs from patients treated with and without CD24Fc; b) T cell phenotyping, to assess expression of CD44, CD62L, CD25, PD-1, PDL-1, CD127 and intracellular staining of Foxp3, IFN-γ, and IL-17 to identify $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs, naïve (CD45RA+), memory (CD45RO+) T cells and additional T cell subsets; c) NK cell subsets; d) B-cell subsets; e) Treg and conventional T cell functional responses to nominal and specific antigens and f) anti-drug antibody levels.

Inflammatory mediators and biomarkers of GVHD: will include a) pro-inflammatory cytokines (TNFα, IL-1, IL-6, IL-8, others); b) previously established plasma GVHD biomarkers[62] and c) DAMPs (HMGB1, uric acid, ATP, etc.).

Lipids: Lipid panel, Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides, and Total cholesterol.

The laboratory of Dr. Pavan Reddy has extensive experience in successfully completing these immunologic assays.

10.3 ADDITIONAL RESEARCH SAMPLES

Additional samples will be collected with a suspected new diagnosis of acute GVHD. Attempts will be made to obtain samples in a timely fashion before treatment is initiated. However, treatment will not be delayed while awaiting sample procurement. Obtaining samples for research purposes are secondary, not primary objective of this study. As such, failure to have a research sample drawn at any time point will not be considered a protocol violation.

11.0 PHARMACEUTICAL INFORMATION

11.1 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.

11.1.1 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 20 mL CD24Fc Drug Product vial contains 160 mg of CD24Fc in 16 mL ± 0.2 mL (Lot 09MM-036) or 120 mg of CD24Fc in 12 mL ± 0.2 mL (Lot 0118-002).

11.1.2 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 of Lot 0118-002 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 the multi-site coordinator, MedPace, and additional drug

will be ordered by OncoImmune or CRO and shipped directly to the drug site from the CRO.

11.1.3 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°C, for 6 months at 5°C and 3 months at 25°C. New CD24Fc Drug Product has been manufactured for the Phase IIa - Expansion trial (Lot 0118-002). Stability studies for Lot 0118-002 are ongoing and it has demonstrated to be stable for six months at the intended storage temperature, -20°C, for 6 months at 5°C and 1 month at 25°C.

11.1.4 Administration

CD24Fc at doses up to 480 mg (i.e. dose levels -1, 0, 1 and 2; see Section 17.2.1) will 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.

11.1.5 Preclinical Safety Pharmacology

The safety pharmacology assessments were included as part of the toxicity studies performed in mice and monkeys. The mouse study was performed by JOINN Laboratory at Beijing, China, while the cynomolgus monkey study was carried out by Charles River Laboratory at Reno, Nevada, USA. Both studies are in compliance with the Good Laboratory Practices (GLP) and the final reports were audited.

11.1.6 A 4-Week Intravenous Toxicity Study of CD24Fc in Mice with A 4-Week Recovery Period

The objectives of this study were to evaluate the toxicity and systemic exposure of CD24Fc when intravenously administered to mice once weekly for four weeks and the reversibility of toxicity following a four-week recovery period. A total of 320 male and female mice were assigned to Groups 1-4 for evaluation of the toxicity (20/sex/group) and reversibility (20/sex/group). All of these mice were treated intravenously with either PBS buffer or CD24Fc at doses of 12.5, 35, or 125 mg/kg once weekly for 4 weeks. A total of 360 mice were assigned to Groups 5-8 for evaluation of the systemic exposure of CD24Fc following the first dose (3/sex in Group 5 and 27/sex/group in Groups 6-8) and the last dose (6/sex in Group 5 and 30/sex/group in Groups 6-8.). All of these mice were treated

intravenously with either PBS buffer or CD24Fc at doses of 12.5, 35, or 125 mg/kg once on Day 1 or once weekly for 4 weeks.

No morbidity or mortality were found in all mice treated with either PBS buffer or CD24Fc with the exception that one male mouse treated with 35 mg/kg of CD24Fc in Group 7 was found dead on Day 21. This death occurred in 1/680 of mice and did not appear to be associated with the treatment. No treatment-related changes were noted in clinical observations, body weights, food consumption, ophthalmology, hematology, coagulation, clinical chemistry, organ weights, and organ-to-body or to-brain weight ratios. No treatment-related macroscopic and microscopic findings were observed in all examined animals.

Anti-CD24Fc antibody was detected in 10/30 of mice on Day 30 and 12/30 of mice on Day 57, which appeared to be dose dependent with no difference between male and female mice. Higher systemic exposure following the first dose and last dose in male animals were observed than in female animals. An approximately linear increase in AUC value was observed when mice treated with CD24Fc from 12.5 mg/kg to 125 mg/kg. An accumulation of CD24Fc in mice was observed after dosing once weekly for four weeks.

In summary, no observed adverse effects were noted in mice treated with CD24Fc at doses of 12.5, 35 or 125 mg/kg once weekly for 4 weeks with a 4 week recovery period. The NOAEL was considered to be equal to or greater than 125 mg/kg.

11.1.7 A 4-Week Toxicity Study of CD24Fc Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 10-Week Recovery Period

The objectives of this study were to examine the pharmacokinetics and potential toxicity, acquired immunity, and immunogenicity following administration of CD24Fc administered by intravenous infusion once weekly for four weeks, and to evaluate recovery from any effects of the test article over a dose-free period of at least 10 weeks. The test article, CD24Fc and the control article, 1X phosphate-buffered saline (PBS), pH 7.2 were supplied by the Sponsor as a clear, colorless, preformulated aqueous solution and by the Testing Facility as a preformulated aqueous solution, respectively. The test article formulation provided by the Sponsor was used as received for dose administration.

Forty experimentally naive cynomolgus monkeys (20 males and 20 females), 2.9 to 4.7 years of age for the males and 2.9 to 5.0 years of age for the females, and weighing 2.1 to 3.2 kg for the males and 2.2 to 2.9 kg for the females at the outset (Day -1) of the study. All animals were dosed via 1-hour intravenous infusion once weekly for 4 consecutive weeks. The first day of dosing was designated Day 1 (04 and 05 Sep 2009, Sets A and B, respectively). The animals were evaluated for changes in clinical signs (evaluations of morbidity and/or mortality [twice daily] and cage side observations [once daily], body weight (Weeks -2 and –1, and weekly thereafter), electrocardiography (prestudy and Day

28), ophthalmology (prestudy and Day 28), and clinical pathology indices (including serum chemistry, hematology, and coagulation (three prestudy and Days 28 and 98), and urinalysis [via cystocentesis on Days 28 and 98]). Blood samples were collected for toxicokinetic analysis predose, 15 minutes, and 6, 24, and 72 hours in relation to dose administration on Days 1 and 22, predose on Day 8, and on Day 29 (at the same time of day as Day 22 end of infusion). Blood samples for flow cytometry were collected prestudy (three time points), and on Days 28 and 98. Blood samples for anti-drug antibodies (ADA) were collected prestudy and on Days 28 and 98. At termination, a full necropsy was conducted on all animals, and tissues were collected, preserved, processed, and examined microscopically by a Study Pathologist certified by the American College of Veterinary Pathologists (ACVP).

The results showed that CD24Fc administered via 1-hour intravenous infusion once weekly for 4 consecutive weeks at 12.5 mg/kg/week (Group 2), 35 mg/kg/week (Group 3), or 125 mg/kg/week (Group 4) was generally well tolerated in male and female cynomolgus monkeys through a 4-week dosing period, followed by a 10 week recovery period. There were no CD24Fc-related changes in clinical observations, food consumption, body weights, electrocardiographic measurements, ophthalmic examinations, serum chemistry (one exception noted below), coagulation, urinalysis parameters, macroscopic findings, or organ weights or organ weight ratios. There were no CD24Fc-related changes in peripheral blood mononuclear cell subset counts obtained by flow cytometry, or anti-KLH immunoglobulin G (IgG) responses to KLH challenge.

There was a possible CD24Fc-related approximately 2-fold increase in alkaline phosphatase (ALP), an indicator of liver function, for one male administered 35 mg/kg/week at Day 98 compared to predose and Day 28 values.

There was a possible CD24Fc-related slight decrease in hemoglobin at Day 28 for 35 mg/kg/week males. The magnitude and/or nature of these changes were not considered adverse in this study.

On Day 28, one male administered 35 mg/kg/week had an approximate 13% decrease in hemoglobin concentration. On Day 98 (76 days after the last dose), changes in hematology for this animal included a 21% decrease in hemoglobin, a 16% increase in red blood cell counts, a 21% decrease in mean cell volume (MCV), a 32% decrease in mean cell hemoglobin (MCH), a 14% decrease in mean cell hemoglobin concentration (MCHC), a 24% increase in red cell distribution width (RDW), and an approximately 2-fold increase in platelet and reticulocyte counts compared to prestudy (Day -2) levels. Day 98 blood smear analysis documented hypochromic red blood cells, microcytosis, anisocytosis, schistocytes, poikilocytes, and spherocytes, as well as an apparent increase in platelet numbers. These hematology changes are not considered typical findings in cynomolgus monkeys at this Testing Facility. However, no corresponding histopathology abnormalities were identified, and these hematology findings were not observed in any other animals in the mid-dose (35 mg/kg/week) or high-dose (125 mg/kg/week) groups.

At recovery necropsy, histopathologic analysis of the following subset of tissues was performed based on clinical pathology or gross findings: all tissues except for mammary glands from a male administered 35 mg/kg/week, the duodenum from another male administered 35 mg/kg/week, and testes from one male administered 125 mg/kg/week. No microscopic findings were found related to the administration of CD24Fc.

CD24Fc was detected in serum samples from all dosed animals. No measurable amount of CD24Fc was detected in control or predose serum samples. Incurred sample reanalysis (ISR) was performed, and the results met the acceptance criteria.

Serum was screened for the presence of anti-CD24Fc antibody. Seven animals out of the 40 total were identified as positive at the prestudy time point (17.5%). This rate of positive samples prior to test article administration is similar to the rate observed in the validation (12.5%) which demonstrated a subpopulation of animals with pre-existing anti-CD24Fc antibodies. Three animals were identified as positive during the dosing period of the study, two of which were positive at the prestudy timepoint. The validation experiment also demonstrated that 10 µg/mL of CD24Fc inhibited the measurement of anti-CD24Fc antibodies in reference to the positive control, and all dose groups at the Day 29 toxicokinetic time point had concentrations greater than 10 µg/mL measured in serum. Only one animal (125 mg/kg/week dose group) screened positive for anti-CD24Fc antibodies within the recovery interval.

Based on the hematology findings, the no-observed-adverse-effect level (NOAEL) for CD24Fc was considered to be 12.5 mg/kg/week under the conditions of this study when administered once weekly for four weeks.

11.1.8 SAFETY IN HUMANS

11.1.8.1 PHASE 1 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 (16.7%) 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.

11.1.8.2 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 PPD 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.

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). No patients experienced a study drug-related treatment-emergent SAE.

In total, 1 patient experienced a TEAE that led to discontinuation of study drug: this patient received placebo. Patient PPD 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%). TEAEs of blood cholesterol increased were only reported by patients in the 480/240/240 mg CD24Fc multiple dose cohort (11%). 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.

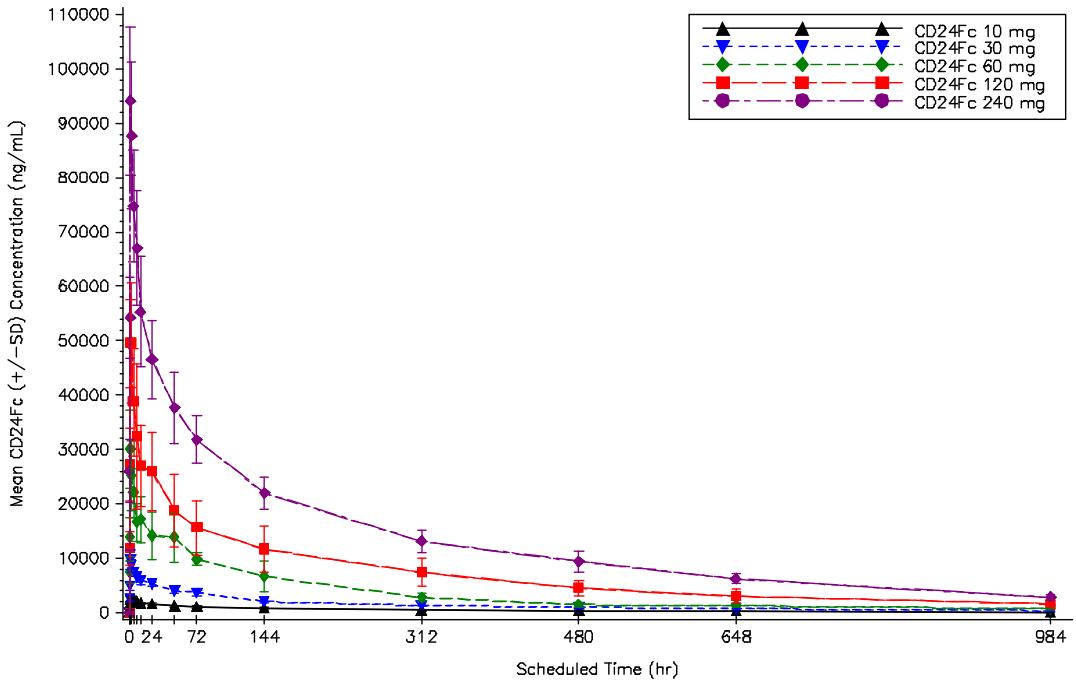
The mean CD33 cell chimerism on Day 28/Day 30 was 100.0% donor cells for patients who received CD24Fc and 100.0% donor cells for patients who received placebo. The mean CD33 cell chimerism on Day 100 was 99.4% donor cells for patients who received CD24Fc and 96.6% donor cells for patients who received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

11.1.9 PHARMACOKINETICS IN HUMANS

11.1.9.1 PHASE I PK

The PK of CD24Fc in healthy human subjects was determined from the single dose Phase 1 study. The mean plasma concentration of CD24Fc increased proportionally to the dose of CD24Fc administered (Figure 9). 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. The plasma CD24Fc reached Tmax at 1.34 hours. The t½ of plasma CD24Fc range was 280.83 to 327.10 hours.

FIGURE 9. PLOT OF MEAN (±SD) PLASMA CD24FC CONCENTRATION BY TREATMENT – PK EVALUABLE POPULATION



PK = pharmacokinetic; SD = standard deviation.
Source: Investigators Brochure.

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11.1.9.2 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. 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 (Figure 10, upper panel). 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 (Figure 10, lower panel).

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).

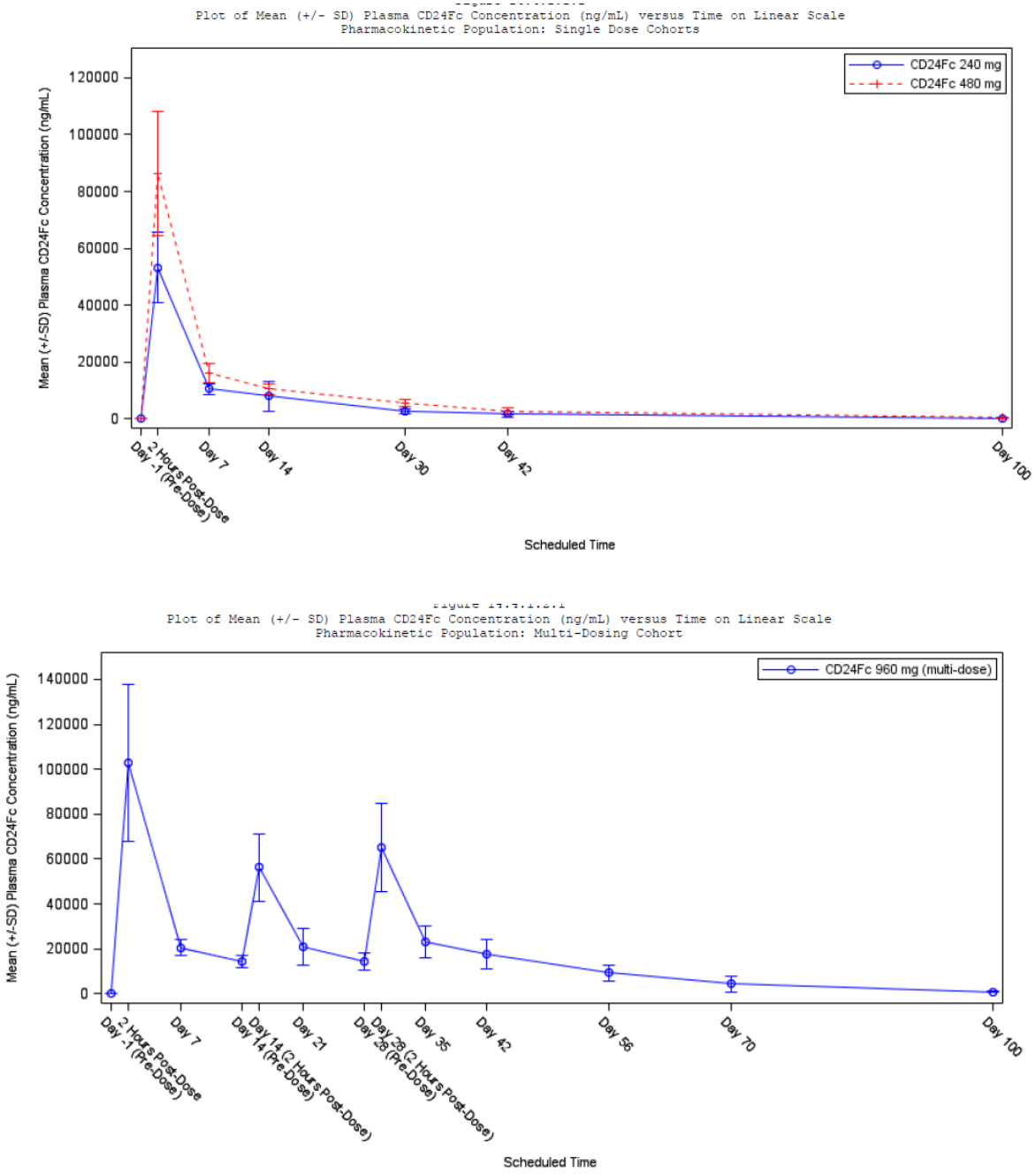

FIGURE 10. PLOT OF MEAN (±SD) PLASMA CD24FC CONCENTRATION BY TREATMENT – PK EVALUABLE POPULATION. (UPPER). SINGLE DOSE COHORTS, 240MG (N=6); 480MG (N=6). (LOWER). MULTI-DOSE COHORT. 480-240-240MG (N=6).

11.1.10 IMMUNOGENICITY IN HUMANS

11.1.10.1 PHASE 1 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.

11.1.10.2. 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.

11.2 PLACEBO

The placebo will consist of 100 ml of 0.9% Sodium Chloride for dose levels -1, 0, 1 and 2 and will be administrated by intravenous infusion over a minimum of 60 minutes. The placebo will consist of 200 ml of 0.9% Sodium Chloride for dose level 3 and will be administrated by intravenous infusion over a minimum of 120 minutes.

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 IIa expansion cohort is open label and will not utilize placebo.

11.3 METHOTREXATE

11.3.1 FORMULATION

Chemically methotrexate is N - [4 - [(2, 4 – diamino – 6 – pteridinyl) methyl] methylaminolbenzoyl] – L - glutamic acid. Methotrexate 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.

11.3.2 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.

11.3.3 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.

11.3.4 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.

11.4 TACROLIMUS (PROGRAF, FK506)

11.4.1 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).

11.4.2 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.

11.4.3 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.

11.5 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). 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

11.5.1 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.

11.5.2 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.

11.5.3 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 drug interactions with calcineurin inhibitors.

11.5.4 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.

12.0 ADVERSE EVENTS AND REPORTING CRITERIA

12.1 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:

- *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 following criteria are met:

- There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
- There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
- 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 Event**:* - 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 3.7 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.

12.2 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 4.0) 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 4.0 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 4.0 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 4.0 some grades 3 and all grade 4.

12.3 AE AND SAE REPORTING REQUIREMENTS

12.3.1 AE REPORTING

Reporting of AEs and SAEs will occur directly to the Multi-Site study coordinator, which will be disseminated to the Sponsor, CRO, 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/CRO:

- 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 30 post HCT for single dose cohorts and through day 60 post HCT for the multi-dosing and expansion cohorts (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/CRO 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 indicated in Section 12.3.2) 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.

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.

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.

SAE Reporting-Procedures for Investigators

Initial Reports

All SAEs occurring from the time of CD24Fc infusion up to and including 30 days post HCT for the single-dosing cohorts or 60 days post HCT for the multi-dosing and expansion cohorts must be reported to the Principal Investigator and Coordinating Center 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 30 days post HCT for the single-dosing cohorts or 60 days post HCT for the multi-dosing and expansion cohorts must be reported to the Principal Investigator and Coordinating Center

Events should be reported using the Coordinating Center's SAE form as available in the study database. A copy of SAE form should be sent to the Coordinating Center via email to PPD 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 Coordinating Center/CRO will disseminate information regarding SAEs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) 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 Coordinating Center will be responsible for reporting of events to the Sponsor and CRO, as outlined below:

Safety Contact Information:

Medpace Clinical Safety

Facsimile: PPD

e-mail: PPD

Anticipated SAEs occurring within the treatment period that will not be reported by the Coordinating Center to the Sponsor, CRO and FDA in an expedited manner are listed in section 12.3.2 below.

12.3.2 Events Not Reported:

The following events will not be reported to the Sponsor, CRO, IRB or FDA in an expedited manner because they are anticipated to occur in the study population independent of study drug exposure.

Anticipated events include hematologic AEs (i.e. anemia, thrombocytopenia, leukopenia, neutropenia), infections, electrolyte abnormalities, and some organ toxicities if they can be directly related to components of the HCT procedure (e.g. conditioning regimen, immunosuppressant medications, blood transfusion reactions). Events directly related to progression of the underlying malignancy or condition under investigation (e.g. acute GVHD) will not require expedited reporting. NOTE: see section 17.5 for formal stopping rules for excessive GVHD.

Given the frequency with which these occur in transplant patients, we will record but not report events that typically occur during the pre and post-transplant related therapy unless they otherwise meet the criteria for reporting as detailed above and below. An event is regarded as typical if it is specified in BMT Program transplant consent and / or it occurs in more than 5% of transplant patients.

12.3.3 Events Reported as Adverse Events Routinely in Tabular Format:

In addition to the reporting guidelines above, all serious adverse events will be reported to the University of Michigan Rogel Cancer Center DSMC and Sponsor with each routine report (monthly) and in the annual IRB report.

Events not meeting criteria for SAE will also be recorded and compiled in tabular format, but will not be routinely reported to the DSMC, oversight bodies or Sponsor unless observed to be more frequent in nature or specifically requested.

12.3.4 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 Principal Investigator and Coordinating Center within 24 hours of being notified. The Coordinating Center will be responsible for notifying the Sponsor and CRO 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.

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 Principal Investigator and Coordinating Center. 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.

13.0 DATA SAFETY MONITORING PLAN (DSMP)

The following are the procedures for data and safety monitoring of this clinical trial to be coordinated by the University of Michigan Blood and Marrow Transplant program 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.

13.1 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 participants per guidelines issued by the U. S. Department of Health and Human Services, Office of Human Research Protections. The documentation of completion of the certification is maintained in the University of Michigan Rogel Cancer Center Oncology Clinical Trials Support Unit office. 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 Principal investigator(s) are solely responsible for the implementation, conduct and safety of human subjects enrolled in this trial. The 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.
5. The BMT program's internal Data and Safety Monitoring Committee (BMT DSMC) will meet monthly to review the data, safety and monitoring reports and all SAEs that have been filed.

13.2 STORAGE AND DISSEMINATION OF REPORTS

The multisite coordinator at the Coordinating Center at the University of Michigan is responsible for collating all the Data and Safety Monitoring Reports from all participating institutions and providing this information to Data Safety Monitoring Committee. The Coordinating Center will coordinate the reporting process between the Investigators, the Sponsor, the IRB and University of Michigan Rogel Cancer Center DSMC as well as other applicable reporting agencies (FDA and study sponsors). Copies of all related correspondence and reporting documents will be maintained by the Coordinating Center and the research data file will be maintained in a file by the BMT data management team.

13.3 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:

Monthly teleconferences will be conducted among investigators from participating study sites, the multisite coordinator from University of Michigan, 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 Coordinating Center will also be submitted to the University of Michigan Rogel Cancer Center Data Safety Monitoring Committee (DSMC) and the medical monitor from the sponsor monthly. The DSMC 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).

If the protocol advances to Phase IIa – expansion cohort the DSMC will review reports in a similar fashion on a monthly basis. Evidence of DSMC review will be provided to the study team for submission to the University of Michigan IRBMED monthly during Phase IIa and Phase IIa – expansion cohort.

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.

This study will be continuously monitored by a Coordinating Center representative of the University of Michigan Rogel Cancer Center in addition to a clinical research organization (CRO) to be determined by the sponsor. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a site initiation meeting will be conducted by the Coordinating Center. 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 University of Michigan Rogel Cancer Center personnel until they have been answered and resolved.

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. 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 review of the documents at the Coordinating Center. During a monitoring visit, access to relevant hospital and clinical records must be given by the PI to the Coordinating Center 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 Coordinating Center 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 time manner.

At close-out upon completion, termination, or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study will occur, and the PI will be informed of his / her ongoing responsibilities. In general, close-out is conducted during a site visit. However, a site close-out can occur without a site visit.

14.0 QUALITY ASSURANCE AND AUDITS

The Quality Assurance Review Committee (QARC) of the University of Michigan Rogel Cancer Center performs quality assurance audits of investigator-initiated clinical trials. 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. A QARC audit of each clinical trial is conducted annually. All audit findings are reported by QARC to the DSMC and the sponsor. The DSMC can also request QARC for 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 Coordinating Center that such a request has been made. Audits of conduct of the clinical trial will also be conducted by the CRO to be determined by the sponsor.

15.0 REMOVAL FROM STUDY

Patients have the right to withdraw from the study at any time for any reason. The 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 and every effort should be made to perform follow-up evaluations. 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 PI.
- Refusal of the patient to continue treatment and / or observations.
- Unacceptable or dose-limiting toxicity.
- Decision by the 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 single dose cohorts patients removed from the study prior to receiving their CD24Fc dose maybe replaced. In the multi-dose cohort subjects who receive < 2 dosages may be replaced. Additionally, subjects who die of causes that are unrelated to study drug toxicity (i.e. documented progression of underlying malignancy) during the treatment period may be replaced. The number of patients removed from the study prior to being fully evaluable will be monitored regularly by the study's DSMC in order to identify and address problems that may develop with respect to patient accrual. We estimate that <10% of subjects may need to be replaced because they encounter relapse / progression or toxicity related to HCT conditioning therapy. Patients who are enrolled but are replaced will still be counted in an intention to treat analysis.

16.0 OPERATIONS AS A MULTI-CENTER STUDY

16.1 MULTI-CENTER COORDINATION

This is a multi-center Phase II randomized, double blinded, dose escalation study followed by an open label dose expansion at the RP2D. The University of Michigan will be the coordinating center.

16.2 SUBJECT SCREENING AND REGISTRATION PROCEDURE

Patient registration for this trial will be centrally managed by the Coordinating Center of the University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log. It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to:

PPD

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar, will be emailed back to the requesting site registrar. Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

CONTACT INFORMATION:

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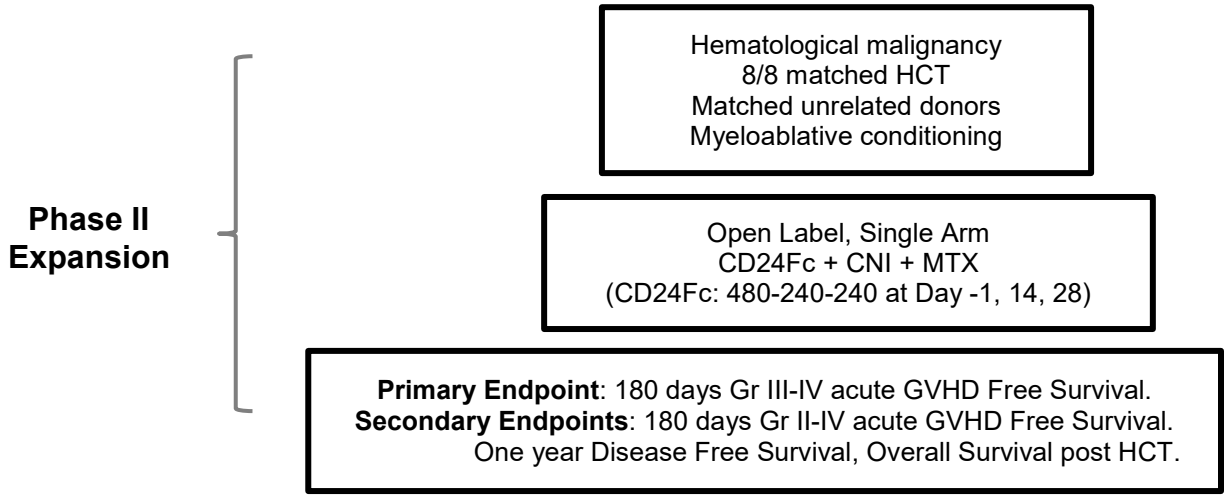
17.0 STATISTICAL CONSIDERATIONS

17.1 OVERVIEW

As the Phase IIa part of the study has completed, the statistical considerations of this section will be focused on the Phase II open label single arm expansion and the registered control matching method.

Given that there is sufficient evidence for safety in Phase IIa, the Phase II expansion study will enroll an additional 20 subjects in order to further evaluate the efficacy of the

multi-dose regimen as RP2D. The primary objective is to determine whether the addition of CD24Fc to standard GVHD prophylaxis improves 180 day grade III-IV acute GVHD free survival (AGFS) when compared to registered controls receiving standard GVHD prophylaxis.



17.2. PRELIMINARY EFFICACY RESULTS FROM PHASE IIA STUDY

Placebo-Controlled Comparison

The Phase IIa portion of the study was carried out in 24 patients with 3 dosing cohorts. The first cohort received a single dose of 240 mg CD24Fc at Day -1 (one day before transplantation). The second cohort received a single dose of 480 mg CD24Fc at Day -1. The third cohort received three doses of CD24Fc in a schedule of 480 mg at Day -1, 240 mg at Day 14 and 240 mg at Day 28. The patients were randomized into CD24Fc or placebo group at 3:1 ratio in a double blind fashion so that each dose level consisted of 6 patients receiving CD24Fc and 2 receiving placebo. Overall, a total of 18 patients received CD24Fc (combined dose levels) and 6 received placebo. When the data from 18 CD24Fc-treated patients were compared with the 6 placebo controls, the data demonstrated that CD24Fc provided a statistically significant improvement in severe acute GVHD-free (AGRS) survival at day 180 post HCT.

These results are promising and suggest that CD24Fc, when added to methotrexate and tacrolimus prophylaxis, reduces the risk of developing grade III and IV aGVHD in patients undergoing HCT after receiving myeloablative conditioning. However, due to the small sample size, it is not possible to rule out potential baseline imbalances that might explain the improved outcome for CD24Fc-treated patients. To address this concern, OncoImmune intends to collect additional clinical data to confirm the apparent treatment effect.

Comparison with contemporary controls

Clinical outcomes of the 18 CD24Fc-treated patients in the Phase IIa study were compared with data from a cohort of 92 consecutive transplant cases admitted at two of the study sites over the same period of time. The controls were chosen based on the following pre-specified criteria:

a. Myeloablative conditioning
b. Patients having leukemia indicated for HCT
c. HCT performed using 8/8 matched unrelated donor bone marrow or peripheral blood hematopoietic stem cells.
d. Age between 18-70 years old.
e. Transplantation were performed between 2012 and 2017.
f. The GVHD prophylaxis is Tac/MTX.

Data from 92 consecutive patients that met these inclusion criteria were included for comparison.

Results of this analysis showed a significantly improvement of 180 day severe aGVHD-free survival (see section 3.8.2). In addition, further follow up since data lock showed an encouraging trend for better 18-month relapse free survival and overall survival in patients treated with CD24Fc as compared to the cohort of contemporary controls.

These data are encouraging as they suggest that better outcomes in CD24Fc-treated HCT patients. However, OncoImmune recognizes two key limitations of this comparison: (1) the disease and disease status were not included in selection criteria for the controls, and (2) a number of baseline factors were missing for the 92 patients, such as disease risk group, KPS score, HCT-CI score and the CMV status. As a result, it is not possible to ensure baseline comparability on factors known to affect clinical outcomes. We have requested matched historical control samples from CIBMTR using pre-specified criteria to ensure baseline compatibility.

To further address these limitations and provide more evidence that CD24Fc has a significant impact on 180 day severe GVHD-free survival following HCT, the sponsor proposes to: (1) conduct a cohort-expansion study of 20 additional patients to evaluate CD24Fc at the multi-dose regimen (480-240-240 mg administered on days -1, +14, and + 28 days of HCT). These data will be combined with the 6 patients previously treated at this dose level in Phase IIa (total 26 patients) and (2) match these treated patients to historical controls obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR).

Data from this new cohort of cases and matched historical control comparisons are expected to support findings from the previous Phase IIa study and fully justify breakthrough therapy designation for CD24Fc.

17.3 PHASE II COHORT EXPANSION (PLANNED)

An additional 20 patients will be enrolled in this prospective single-arm, open-label Phase II cohort expansion study of CD24Fc for the prevention of acute GVHD following myeloablative allogeneic HCT. Clinical outcomes in this patient cohort will be compared to clinical outcomes of matched historical controls extracted from an international transplant registry.

After interim analysis of data from phase IIa, a discussion between the sponsor and study investigators was held to determine the RP2D. The 480/240/24/0 mg multi-dose was selected based on combination of factors including no discernable difference in toxicity between single dose or placebo, apparent lowering of mucositis and optimal PK data.

This case-matched control comparison will focus on several measures of clinical outcome, including: time to first onset of grade III-IV acute GVHD or death within 180 days, time to first onset of grade II-IV acute GVHD or death within 180 days, overall survival, time to disease progression, and treatment-related mortality. Individuals with unobserved event times will be censored at the time of last follow-up. The primary goal is to develop a more robust efficacy database and confirm the RP2D.

17.4. MATCHING CRITERIA FOR PLANNED MATCHED HISTORICAL CONTROLS COHORT

Individual subjects in the cohort receiving multi-dose CD24Fc (including the 6 multi-dose cases from Phase IIa) will be matched 1:4 with controls in the CIBMT registry based on a set of prognostic factors known to potentially influence GVHD or survival after HCT. Each of the 26 cases will be paired with up to 4 control subjects (all available controls in the registry that satisfy matching criteria), thus avoiding the need to select controls using a model-based covariate score.

Directly matching covariate values of each treated patient with all available registry controls having identical values will ensure comparability of case/control groups and provide a reliable test of the treatment effect, without imposing model assumptions or matching algorithms to select the control subjects.

The following prognostic variables will be used for matching:

1. Age (within 5 years);
2. Gender;
3. Performance score (KPS ≥90 *vs*. <90);
4. HCT-CI (≥3 *vs*. <3);
5. Myeloablative conditioning regimen (Flu/Bu4 or Cy/TBI);
6. 8/8 matched unrelated donor;

7. Disease;
8. Disease status;
9. Disease risk group;
10. Stem cell source (BM or PBSCT)
11. TAC/MTX as GVHD prophylaxis method.

Up to four matches per case will be selected whenever possible; when more controls are available, preference will be given to controls who are closest in age to the patient. The follow up for control patients will be administratively censored at the time corresponding to the longest follow up of the trial patients.

17.5 SAMPLE SIZE JUSTIFICATION

The Phase IIa dose escalation portion of the study enrolled 24 patients (18 CD24Fc, 6 placebo). An additional 20 patients will participate in the Phase II cohort expansion portion of the trial, yielding a total of 38 patients exposed to the active product for safety analysis. Data from all 26 patients treated with the multi-dose CD24Fc regimen (20 patients in the expansion cohort plus 6 patients from Phase IIa) will be used for the primary efficacy analysis. A sensitivity analysis will also be performed for the 20-patient expansion cohort.

The sample size for the expansion cohort was derived on the basis of feasibility as well as clinical and statistical considerations. A total of 20 patients matched with 80 historical controls from the CIBMTR will provide approximately 80% power to detect a hazard ratio of 5.0 (corresponding to an improvement in the 180 day GFS-free survival rate from 0.75 to 0.945), using a 2-sided logrank test at the 5% significance level. This calculation assumes proportional hazards and an event rate of 1/18, or 0.055 in the CD24Fc-treated patients (as observed in Phase IIa study). The event rate in the control is conservatively projected at 75%, even though it was 50% is placebo control and <60% in contemporary controls.

17.6. DATA ANALYSIS METHODS

Endpoints will be defined as follows:

Primary endpoint:
AGFS: Time from transplant to the earliest of aGVHD (Grade III-IV), death, or the last day of GVHD evaluation at 180+/-4 days.

Secondary endpoints:
(1) Overall Survival (OS): Time from transplant to the earlier of death or last follow-up;
(2) Disease Progression-Free Survival (DFS): Time from transplant to the earliest of progression/relapse, death, or last follow-up.

(3) aGVHD (Grade II-IV)-free Survival (GFS): Time from transplant to occurrence of aGVHD (Grade II-IV) or death or last follow up at 180+/-4 days, whichever comes first;

The probabilities of AGFS, OS, GFS and DFS will be calculated using the Kaplan-Meier estimator. Outcomes will be compared between groups using a stratified two-sided log-rank test. Stratified Cox or Fine-Gray regression will be used to obtain hazard ratios with 95% confidence intervals.

To account for multiple significance testing, the secondary endpoints will be evaluated using Hochberg's procedure to control the overall Type 1 error rate at 0.05.

Specific details will be provided in the full statistical analysis plan for the study.

17.7 PROPENSITY SCORE MATCHING (PSM)

For the analysis of primary and secondary efficacy endpoints, individual subjects in the cohort receiving experiment treatment will be matched 1:4 with registry controls in the CIBMTR registry based on a set of known prognostic factors. The 6 subjects in multi-dose cohort with CD24Fc treatment in Phase IIa will be combined with 20 subjects in Phase II expansion study to make a total of 26 cases. It is expected that approximately 104 registered controls will be selected from CIBMTR database. Note that propensity scores may be potentially limited in this setting because of the small number of CD24Fc-treated cases and the large size of the registry database, which allows an exact match on the full set of covariates.

To adjust for any potential biases due to imbalances in pretreatment factors between the case and control groups, a logistic regression model will be used to determine the vector of pretreatment characteristics that best discriminates between the treated and control populations. The following 7 independent pretreatment factors will be included in the binary logistic regression model for calculation of propensity score: age, remission status, diagnosis, cytogenetic risk group (adverse-risk versus favorable/intermediate), donor type, HCT-CI, and period effect. Then each case will be matched and paired to another patient from the registry control group with the smallest differences in propensity score.

Following the advice of Rosenbaum and Rubin [68], the log of the odds of the probability of exposure will be used as a basis for matching. This is preferred to the propensity score itself because it is a linear function of the baseline variables (or of transformations of the baseline variables if the association between the variable and the log-odds of exposure is found to be nonlinear) and generally follows a reasonably normal distribution. Matching will be based on the magnitude of the difference, not the direction. A narrow caliper

(maximum permitted difference between matched subjects) will be used to improve performance of propensity score matching. To ensure that all treated subjects have at least one matched control, controls will be selected in order of the best available matches (in descending order), without increasing or decreasing the propensity score.

Stated formally, the propensity score e(x) is the conditional probability of belonging to the treatment group given the observed pretreatment variables, x, denoted as

$e(x) = Pr(z = 1|x)$,

where z = 1 for subjects in the treatment group and z = 0 for the registry control subjects.

Covariate balance between the case and control subjects will be checked by (a) regressing each covariate and the logit of the propensity score on the treatment assignment, controlling for S-1 dummy indicators for the S propensity strata and their interactions with treatment assignment, and (b) conducting 2 × S (Conditions × Strata) ANOVAs, using both the propensity score and each predictor individually as dependent variables. Rosenbaum and Rubin [68] present three criteria for assessing the adequacy of the regression adjustment: (a) the difference in the means of the propensity scores in the groups being compared must be small, (b) the ratio of the variances of the propensity score in the treatment and comparison groups must be close to one, and (c) the ratio of the variances of the residuals of the covariates after adjusting for the propensity scores must be close to one.

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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

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

APPENDIX C: CONSENSUS ACUTE GVHD GRADING

Organ Staging of Acute GVHD

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dl	Adult: < 500 ml/day Child: < 10 ml/kg/day
1	Maculopapular rash < 25% BSA	2-3 mg/dl	Adult: 500–999 ml/day Child: 10 -19.9 ml/kg/day Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy.
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dl	Adult: 1000-1500 ml/day Child: 20 – 30 ml/kg/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dl	Adult: >1500 ml/day Child: > 30 ml/kg/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).

- For GI staging: The "adult" stool output values should be used for patients ≥ 50 kg in weight.
- Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is estimated to be 50% of total stool/urine mix.
- For stage 4 GI: the term "severe abdominal pain" will be defined as:
  (a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
  (b) Pain that significantly impacts performance status, as determined by the treating MD.
- If colon or rectal biopsy is +, but stool output is <500 ml/day (<10 ml/kg/day), then consider as GI stage 0.
- There is no modification of liver staging for other causes of hyperbilirubinemia (see appendix A).

Overall Clinical Grade:

Grade 0	No stage 1-4 of any organ
Grade I	Stage 1-2 rash and no liver or gut involvement
Grade II	Stage 3 rash, or Stage 1 liver involvement, or Stage 1 GI
Grade III	Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
Grade IV	Stage 4 skin, liver or GI involvement

Adapted from Thomas et al. NEJM, 1975, p 895-890 and and Bone Marrow Transplant. 1995 Jun;15(6):825-8.

APPENDIX D: PHASE II EXPANSION STUDY SAMPLE SIZE CALCULATIONS

Assuming a 4:1 matching ratio, the proportion of subjects in Group 1 (the CD24Fc-treated group) will be 0.20 (q1) and the proportion of subjects in Group 0 (control group) will be 0.80 (q0). Setting power = 0.80 (1-beta) and a two-sided significance level of 0.05 (alpha), the required number of events to detect a hazard ratio of 5.0 would be 19.

The total of 34 events (acute Grade III-IV GVHD or death within 180 days) are required to meet power specifications.

Based on the phase IIa trial, 1 event occurred in 18 patients in 180 days (which is defined as 1.000 unit), so the Baseline Event Rate (BER0) = 1/18 = 0.055. All event-free patients will be followed for 180 days with a censoring rate (CR)=0.000. Calculator 2 indicates the same size required to achieve the required number of events:

Group 1, matched controls = 75

Group 0, CD24Fc treated subjects = 19

An additional patient will be included in the treatment arm to allow for one case of patient withdrawal or loss to follow up.

The sample size for an unmatched logrank test (80% power; 2-sided alpha=0.05) would be 260 subjects (52 CD24Fc versus 208 control) to detect a difference of 0.1914 between 0.9450 and 0.7536--the proportions alive and free of aGVHD by day 180. This corresponds to a hazard ratio of 5.0. The calculation assumes proportional hazard rates, with no loss to follow-up.

With 1:4 matching, a total of 245 subjects (49 CD24Fc versus 196 controls) provides 81% power to detect a difference of at least 0.206 between the proportions surviving in the treated group 1 (0.734) and control group 2 (0.940). This corresponds to a hazard ratio of 0.2000. The intracluster correlation coefficient is 0.000. The power calculation is based on a two-sided logrank test (alpha=0.05) and assumes hazard rates are proportional. The design requires 11 events in treated group and 44 events in the matched controls.

Two calculators for two-group survival analysis.

Calculator 1: Number of events, given relative hazard.

Instructions: Enter parameters in the red cells. Answers will appear in blue below.

α (two-tailed) =	0.050	*Threshold probability for rejecting the null hypothesis. Type I error rate.*
β =	0.200	*Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate.*
q_1 =	0.800	*Proportion of subjects that are in Group 1 (exposed)*
q_0 =	0.200	*Proportion of subjects that are in Group 0 (unexposed); 1-q_1*
RH =	5.000	*Relative hazard (Group 1/Group 0)*

Calculate events

The standard normal deviate for α = Z_α = 1.960
The standard normal deviate for β = Z_β = 0.842
A = $(Z_\alpha+Z_\beta)^2$ = 7.849
B = $(\log(RH))^2 q_0 q_1$ = 0.414

Total events needed = A/B = 19

Calculator 2: Sample size, given number of events.

This calculator will calculate the number of subjects needed in each group to achieve the number of events calculated above.

q_1 = 0.800
q_0 = 0.200
RH = 5.000
Total events = 19

Note: If you change the default values for EITHER BER_0 or ST_0 below, the calculator will automatically update the other parameter accordingly.

BER_0 =	0.055	*Baseline Event Rate (events/unit time) for Group 0*
ST_0 =	12.603	*Median survival time in Group 0*
CR =	0.000	*Censoring rate - censored/unit time (assumed equal for both groups)*
FU =	1.000	*Planned average length of follow-up, in time units*

Calculate group sizes

	N	Events	Cumulative Event Rate
Group 1	75	18	0.240
Group 0	19	1	0.054
Total	94	19	0.203

Reference: Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39:499-503.

STATISTICAL ANALYSIS PLAN

A Phase II Trial of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplant

Investigational Product:	CD24Fc
Protocol Number:	CD24Fc-002
Development Phase:	2
Sponsor:	OncoImmune, Inc. 12111 Parklawn Dr., Suite 107 Rockville, MD 20852 Tel: PPD Fax: PPD
Protocol Version Number:	Amendment 3.2
Protocol Date:	02 August 2017
SAP Version:	v1.0
SAP Date:	19 February 2018

Protocol: A Phase II Trial of CD24Fc for Prevention of Acute Graft-versus-Host Disease Following Myeloablative Allogeneic Hematopoietic Stem Cell Transplant

Protocol Number:	CD24Fc-002
Protocol Date:	02 August 2017
SAP Version:	v1.0, 19 February 2018

This Statistical Analysis Plan has been reviewed and approved by:

PPD

02/20/2018
Date

Medpace Inc.

PPD

02/27/2018
Date

Medpace Inc.

PPD

02/20/2018
Date

University of Michigan

PPD

02/20/2018
Date

OncoImmune, Inc.

VERSION HISTORY

Version	Date	Description
1.0	19 February 2018	Create Version 1.0 of the SAP

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ADA	Anti-drug antibody
AE	Adverse event
aGVHD	Acute graft-versus-host disease
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
AST	Aspartate Transaminase
ATC	Anatomic therapeutic class
AUC	Area under the plasma concentration versus time curve
BMI	Body mass index
CA 19-9	Cancer antigen 19-9
CBC	Complete Blood Count
cGVHD	Chronic graft-versus-host disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic Myelogenous Leukemia
CMML	Chronic Myelomonocytic Leukemia
CMV	Cytomegalovirus
CK	Creatine kinase
CRFs	Case report forms
DAMPs	Damage-associated molecular patterns
DC	Dendritic cell
DFS	Disease free survival
DLT	Dose limiting toxicities
ECG	Electrocardiogram
eCRF	Electronic case report form
GFS	GVHD free survival
GVHD	Graft-versus-host disease
HCT	Hematopoietic stem cell transplantation
HDL	High-density lipoprotein
HLA	Human leukocyte antigens
hs-CRP	High-sensitivity C-reactive protein
ITT	Intent-to-Treat
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
NMDP	National marrow donor program
NQ	Non-quantifiable
NRM	Non-relapse mortality
OS	Overall Survival
PBSC	Peripheral blood stem cell
PD	Pharmacodynamics
PK	Pharmacokinetics
RBC	Red blood cell
GRFS	GVHD-free and Relapse-free Survival
RP2D	Recommended Phase IIb dose
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TRM	Transplant-related mortality
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical methodology to be implemented for data analysis of the study described in OncoImmune Inc., Protocol CD24Fc-002 (Version 3.2; 2 August 2017). If circumstances arise during the study such that more appropriate analytic procedures become available, the SAP may be revised. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objectives of this Phase II clinical study are to establish the safety, tolerability and efficacy of CD24Fc in combination with standard prophylaxis for preventing acute Graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HCT). The primary objective in each phase of the study is as follows:

- **Phase IIa**: The primary objective of Phase IIa is to evaluate the safety and tolerability of CD24Fc in patients undergoing myeloablative allogeneic HCT, and to define the recommended Phase IIb dose (RP2D) or maximum tolerated dose (MTD) for the addition of CD24Fc to standard GVHD prophylaxis.
- **Phase IIb**: The primary objective of Phase IIb is to determine if the addition of CD24Fc to standard GVHD prophylaxis reduces the incidence of Grade II-IV acute GVHD (aGVHD) after HCT.

2.2 Secondary Objectives

- To estimate Grade II-IV acute GVHD free survival (GFS) at day 180 following HCT.
- To describe incidence of chronic GVHD at one year following HCT
- To describe incidence of relapse at one year following HCT
- To describe incidence of transplant-related mortality (TRM) at one year following HCT
- To describe rates of infection at day 100 following HCT
- To evaluate overall survival (OS) and absence of grade III-IV GVHD and relapse-free survival at one year following HCT

2.3 Correlative and Biologic Studies

- To assess the pharmacokinetic (PK) profile of single CD24Fc and anti-drug antibodies (ADAs) in the target patient population.
- To examine functional responses of antigen presenting cells and T cells with or without administration of CD24Fc.

- To perform phenotyping of T cells, B cells, natural killer (NK) cells and other cellular immune subsets with or without administration of CD24Fc.
- To assess plasma concentrations of pro-inflammatory cytokines, damage-associated molecular patterns (DAMPs), Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides, Total cholesterol and GVHD biomarkers before and after administration of CD24Fc.
- To assess genetic polymorphism of CD24 and Siglec10 genes, and microRNAs such as mir29, in both donor and recipients.

3 STUDY OVERVIEW

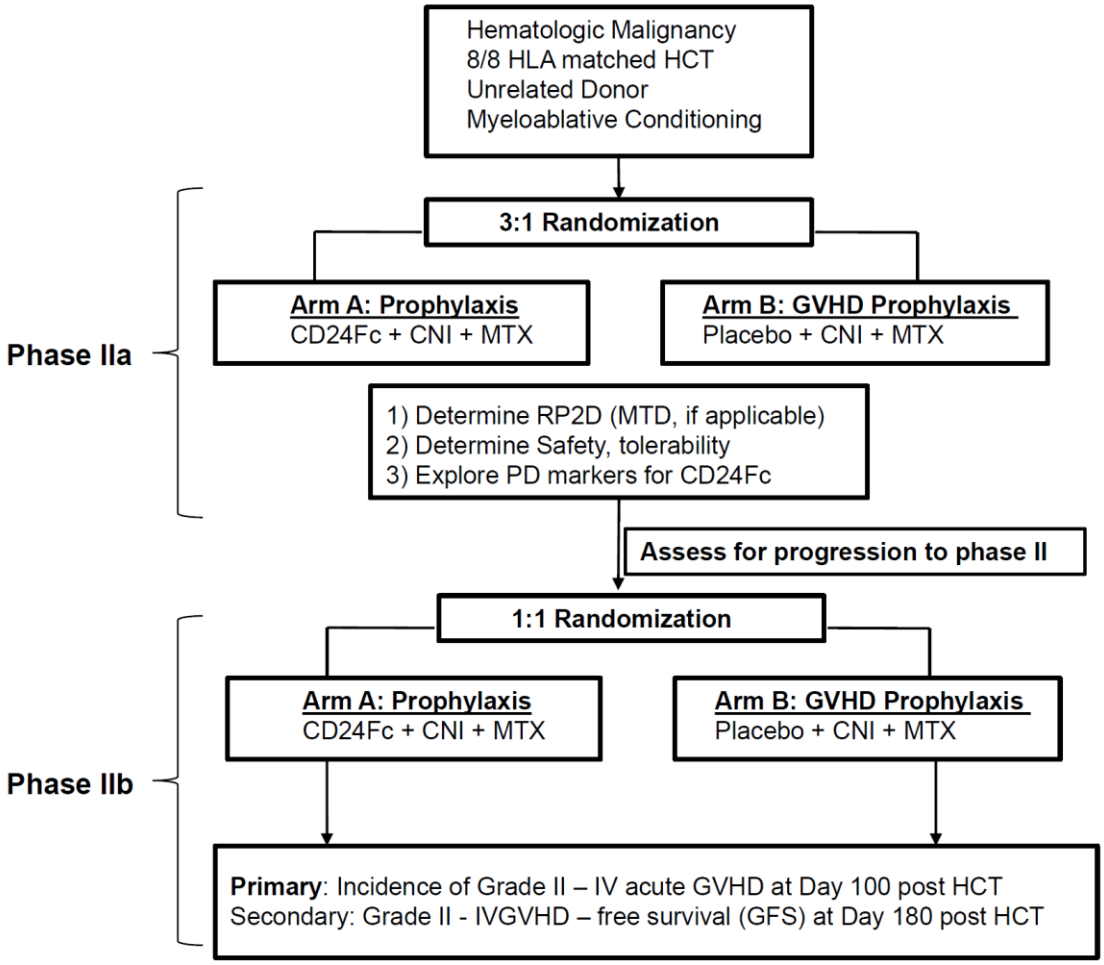
3.1 Overall Study Design and Plan

This is a multi-center Phase II study of aGVHD prevention in patients with hematological malignancies receiving allogeneic HCT. The primary objectives are a) to evaluate the safety and tolerance of single dose and 3 biweekly infusions of CD24Fc with establishment of an RP2D or MTD (Phase IIa) and b) to determine the efficacy of CD24Fc when combined with a standard prophylactic treatment for aGVHD (Phase IIb).

Phase IIa is a randomized double-blind trial comprised of: i) 3 single ascending dose cohorts of 8 patients (3:1 treatment:placebo); and ii) a multi-dosing cohort consisting of 8 patients (3:1 treatment:placebo) that will receive 3 consecutive biweekly administrations of CD24Fc. If CD24Fc demonstrates safety and tolerability in phase IIa, the trial will proceed to an expanded randomized, double-blind, phase IIb component at the RP2D powered to evaluate the efficacy for adding CD24Fc to standard prophylaxis for the prevention of acute GVHD.

The study design diagrams are provided below in Figure 1:

Figure 1: Overview of Sequential Phase IIa / IIb Study Design for CD24Fc for GVHD Prevention



3.1.1 Phase IIa: Dose Escalation

The primary objectives of Phase IIa study will be to establish an RP2D or MTD, while assessing initial safety and tolerability in the HCT setting. The starting dose will be 240 mg which was found to be safe in healthy patients. The Phase IIa dose-escalation will evaluate up to three single dose levels of CD24Fc and one multi-dosing cohort receiving a dosage of CD24Fc equivalent to the highest single dose. The dose escalation plan is outlined in Table 1.

Table 1 Dose Escalation Plan for CD24Fc

Level	*Dose*	*Schedule*	*CD24Fc (No.)*	*Placebo (No.)*
-1	*120 mg*	*day -1*	*6*	*2*
0	***240 mg***	*day -1*	***6***	***2***

1	***480 mg***	*day -1*	***6***	***2***
2	***960 mg (multi-dose)***	***480 mg (day -1)**** ***240 mg (day 14)*** ***240 mg (day 28)***	***6***	***2***
3	***960 mg (single-dose)***	***Day -1***	***6***	***2***

* If a DLT is encountered in the 480 mg single dosing, the initial dosing will be changed into 240 mg.

In Phase IIa, patients will be enrolled into dose escalating cohorts of 8 patients using a randomized 3:1 ratio (6 dosing patients and 2 placebo) design continuing until the highest predetermined dose level of CD24Fc or until an MTD is reached. Prior to the highest single dose cohort being enrolled, a multi-dosing cohort will be enrolled. If there is sufficient evidence for safety in Phase IIa, then the drug will be considered safe for Phase IIb testing and the study will transition into an approximately 180 patient Phase II placebo-controlled study at 1:1 ratio to assess efficacy of the clinical regimen.

3.1.1.1 Dose Limiting Toxicities

After administration of CD24Fc on day -1, patients will be monitored through day +30 (or +60 in dose level 2) after transplant to assess for dose limiting toxicities (DLTs). The following events will be considered DLTs:

- A DLT will be any Grade III or higher non-hematologic toxicity not clearly related to the underlying malignancy, intercurrent infection, or the HCT conditioning regimen. Hypersensitivity reactions and other infusion-related reactions will not be considered a DLT. Any patient who discontinues the study due to an infusion-related reaction will be replaced in the study.
- Any death not related to relapse or intercurrent infection.
- Engraftment will be defined as absolute neutrophil count (ANC) >500/mm^3 for 3 consecutive days or >2000/mm^3 for 1 day. Failure to engraft by Day +30 will be considered a DLT.

In addition, stopping rules for the occurrence of severe GVHD (Grade III-IV) are in place as in Protocol CD24FC-002 Section 17.5 (Version 3.2; 2 August 2017) and thus the occurrence of Grade IV colitis and/or Grade IV erythroderma (by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 criteria) directly attributable to GVHD would not be considered in the DLT assessment, but would be considered in the stopping rules outlined in that section. Only DLTs encountered during the treatment period will be counted for safety evaluation unless the event reflects an ongoing toxicity that was initiated during the treatment period. The treatment period is defined as the first day of treatment with CD24Fc until 30 days after HCT for the single-dosing cohorts or 60 days after HCT for the multi-dosing cohort. To clarify, the observation of colitis and erythroderma (Grade III-IV) directly attributable to GVHD will not constitute a DLT in the Phase IIa portion of the

study. This is because (a) aGVHD is an expected event after HCT and (b) is the specific disease state for which we are evaluating dose escalation of CD24Fc. In the Phase IIb portion, where efficacy at the RP2D will be evaluated, the study will be monitored for excessive acute GVHD.

3.1.1.2 Maximum Tolerated Dose

Each cohort will initially enroll 8 patients comprised of six patients treated with CD24Fc and 2 patients receiving placebo. Treatment will be assigned randomly.

After all 8 patients in a particular cohort have been evaluated for toxicity from day -1 to day +30 (or day +60 in dose level 2) after HCT, then if no more than 1 of 6 patients receiving CD24Fc encountered DLT, escalation will continue to the next higher dose level. To facilitate this process, the study statistician will necessarily have to unblind the assignments of the patients in order to know whether DLTs occurred in CD24Fc treated versus placebo treated patients. If ≥ 2 patients receiving CD24Fc encounter a DLT, further accrual at that dose level or higher will cease with additional patients treated at an intermediate dose level until the highest dose level is reached for which 0 or 1 of 6 patients encounters DLT which will be declared the MTD. In the event that unacceptable toxicity occurs even at dose level 0, with 2 patients encountering DLTs, then a subsequent cohort of 6 patients will be treated at the -1 dose level, and if ≥ 2 patients encounter DLT at this reduced dose level, then the trial will be suspended until an amendment can be submitted.

3.1.1.3 Determination of Recommended Phase 2 Dose

When the last patient dosed in the Phase IIa study reaches 100 days after HCT, key outcome data will be locked and the study will then be unblinded. At this point, an interim report will be generated in order to define the RP2D. The R2PD will be defined at a dosage of CD24Fc equal to or lower than the MTD and the assessment of Pharmacodynamics (PD) and PK data based on the studies outlined in Section 2.3 will be used to evaluate biological activity of the drug and to assist in deciding RP2D. As a result, the Phase 2 dose will be the lowest dose with maximal effect to the extent that this can be determined from the proposed correlative studies. For example, in the absence of an MTD, if we observe similar biological activity of the drug at two different dose levels, the lower dose will be used as the RP2D.

However, no formal rules for selecting RP2D based on PD will be defined in this protocol and the proposed correlative studies are exploratory. If an MTD has been established, it is possible investigators and sponsor will determine that the RP2D is lower than the MTD based on other safety concerns or the overall tolerability of CD24Fc. This assessment will be based on all available safety and tolerability data, including but not limited to DLT events and comparison to placebo controls.

3.2 Phase IIb

After determination of the RP2D in Phase IIa, the Phase IIb study will involve a randomized, double blind, component where patients will receive either standard GVHD prophylaxis with CD24Fc at the RP2D determined in Phase IIa (Arm A) versus standard GVHD prophylaxis with placebo (Arm B). A total of approximately 90 patients will be enrolled in each treatment arm.

This portion of the study will evaluate whether combining CD24Fc at the RP2D with standard prophylaxis provides evidence of clinical efficacy in the prevention of acute GVHD. Since the potential efficacy of CD24Fc in GVHD prevention is not established, this agent will be combined with a standard of care regimen of tacrolimus and methotrexate in a randomized placebo controlled trial.

3.3 Study Populations

The study population will comprise male and non-pregnant, non-lactating female patients over 18 years old, who are prospective patients for allogeneic HCT for Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Myelodysplastic syndrome (MDS), Chronic Myelomonocytic Leukemia (CMML) and other hematological malignancies. A matched unrelated donor and the recipient must have a Human leukocyte antigens (HLA)-8/8 allelic match at the HLA-A, -B, -C, and -DRB1 loci. Patients must have generally normal or near normal organ function as defined by their treating institutions bone marrow transplant program.

Additional inclusion and exclusion criteria are listed in Protocol CD24FC-002 (Version 3.2; 2 August 2017).

3.4 Randomization and Blinding

3.4.1 Randomization and Blinding for Phase IIa

A total of 32 patients will be randomized in 4 cohorts of 8 patients. The starting dose will be 240 mg which was found to be safe in healthy patients. The dose escalation plan is outlined in Table 1.

Each cohort will initially enroll 8 patients comprised of 6 patients receiving CD24Fc and 2 patients receiving placebo. Treatment will be assigned randomly. Patients will be randomized in blocks of size 4, with 3 patients receiving CD24Fc and 1 patient receiving placebo.

A patient may be designated for replacement per the criteria specified in the protocol. If a patient is designated for replacement, the system will assign the next patient to the same treatment group as the original patient, selecting the lowest matching row in the "Replacement Blocks" section of the schedule.

3.4.2 Randomization and Blinding for Phase IIb

Following confirmation of eligibility and registration, patients will be randomly assigned in an up-front fashion to receive one of the following GVHD prophylaxis regimens in a 1:1 allocation ratio.

Arm A: CD24Fc + Tacrolimus + Methotrexate (n=90)

Arm B: Placebo + Tacrolimus + Methotrexate (n=90)

Randomization will be stratified by study site and source of donor cells (peripheral blood versus bone marrow). The study statistician will create randomization lists for both sites prior to study initiation, and individual copies will be held by the study biostatistician, the primary pharmacists (at sites where the patients are being enrolled) and unblinded study monitors who is independent from the study.

3.4.3 Unblinding of Study Assignment

Both Phase IIa and Phase IIb are randomized double-blinded studies. In situations where the treating physician believes that knowledge of the treatment assignment will clearly enhance patient care, the treating physician will contact either the principal investigator or one of study chairs, who will direct the local study pharmacist to unblind the treating physician. All other members of the study team (except study monitors) will remain blinded to assignment. In the randomized Phase IIa portion unblinding will be necessary if DLTs occur in order to determine dose escalation and for safety monitoring and reporting. When the last patient of the Phase IIa study reached 100 days, the data for aGVHD incidence, DLTs, engraftment, relapse and infection will be locked and the study will be unblinded.

In Phase IIa, unblinding will be necessary if DLTs occur in order to determine dose escalation and for safety monitoring and reporting.

3.5 Study Calendar

Tables 2A and 2B present the visit schedule and procedures to be conducted at each visit for single dose cohorts and the multi-dose cohort, respectively.

Table 2A. Study Calendar for Single Dose Cohorts

	PRE-HCT								
Observations	Day -28 to -7 (enrollment)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 3)	Weekly from + 0 to + 29 (± 3)	+ 30 (± 5)
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			x	x	x	x	x
Laboratory testing[2]	x	x			x	x	x	x	x
ECG monitoring[3]		x		x					
CD24Fc (Study Agent) [4]			x						
Hematopoietic Stem Cell Transplant (HCT)					x				
Vital Sign monitoring[5]		x	x	x					
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
Toxicity Assessment (NCI Criteria)			x		x	x	x	x	x
Assess Engraftment									x
Bone marrow aspirate & biopsy	x								
Chimerism									x
Anti-drug-antibody/PK samples		x		x		x	x		x
hs-CRP		x					x		x
Fasting Lipid Panel including LDL		x					x		x
Research samples (Patient)[7]	x	x					x		x
Research sample (Donors)[8]					x				

Table 2A. Study Calendar Cont.

				FOLLOW-UP PERIOD			
Observations	Weekly from +30 to +100 (± 5)	Every other week from +30 to +100 (± 5)	+ 42 (± 5)	+ 100 (± 7)	Quarterly: Day +180 and Day +270 (± 14)	+ 365 (± 14)	GVHD Onset (± 3)
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	x			x	x	x	x
Laboratory testing[2]		x		x			
ECG monitoring[3]			x				
CD24Fc (Study Agent)[4]							
Vital Sign monitoring[5]							
Acute GVHD assessment[6]	x			x	x		x
Chronic GVHD assessment				x	x	x	
Concomitant Medications	x			x	x	x	x
Toxicity Assessment (NCI Criteria)	x			x			
Assess Engraftment							
Bone marrow aspirate & biopsy				x			
Chimerism				x			
Anti-drug-antibody/PK samples			x	x			x
hs-CRP				x			x
Fasting Lipid Panel including LDL				x			x
Research samples (Patient)[7]				x			x
Research sample (Donors)[8]							

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 30, ± 5 days for observations from day 31 until day 100, and ± 7 to 14 days for observations from day 100 to day 365. Collection windows do not apply to early PK studies which should be collected around the time of CD24Fc infusion.**

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 Pulmonary Function Test may be assessed up to 6 weeks prior to enrollment.
2) Laboratory tests include Complete Blood Count (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 at a minimum of three times (e.g. every 48-72 hours) for the first week post CD24fc infusion (day 0 to day 7) and then per institution clinical practice guidelines. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin then performed weekly through day 29 and performed every other week through day 100 post HCT. Laboratory testing may be more frequent per standard HCT practice.
3) 12 lead ECG monitoring will be performed at 3 time points to assess cardiac safety signals. On Day -1, the ECG should be measured within four hours of start of study drug infusion and 2 hours (± 15 minutes) post drug (i.e. 2 hours after the start of infusion). ECG should be measured 3 hours (± 15 min) post drug in the 960mg dosing cohort due to prolonged infusion time (i.e. 3 hours after the start of infusion).
4) Per protocol, CD24Fc will be administered on day -1. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Frequent vital sign monitoring is required following CD24Fc infusion. Vital signs will be recorded prior to infusion and at approximately 15, 30, 60, and 120 minutes from the start of the CD24Fc infusion.
6) Assessment for aGVHD will occur weekly through day 100. Following day 100 acute and chronic GVHD assessments will occur approximately at a quarterly schedule (day 180 and day 270 ± 14 days). Consensus aGVHD grading will be used to report disease severity (APPENDIX C)
7) Research samples include PBSC and serum from patients at indicated time points to be cyropreserved for correlative immunologic studies.
8) In the pre-HCT period, a research sample from the donor HCT product will also be cryopreserved prior to infusion.

Table 2B. Study Calendar for Multi-Dose Cohort

	PRE-HCT	**POST-HCT**							
Observations	Day -28 to -7 (enrollment)	- 1 PRE Drug	-1	- 1 2 hr POST Drug	0	+7 (± 2)	+14 (± 4)	+ 28 (± 4)	Weekly from + 0 to +60 (± 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			x	x	x	x	x
Laboratory testing[2]	x	x			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	x	
Acute GVHD assessment[6]						x	x	x	x
Chronic GVHD assessment									
Concomitant Medications	x	x			x	x	x	x	x
Toxicity Assessment (NCI Criteria)			x		x	x	x	x	x
Assess Engraftment								x	
Bone marrow aspirate & biopsy	x								
Chimerism								x	
Anti-drug-antibody/PK samples[7]		x		x		x	X (see note 7)	X (see note 7)	(see note 7)
hs-CRP		x					x	x	
Fasting Lipid Panel including LDL		x					x	x	
Research samples (Patient)[8]	x	x					x	x	
Research sample (Donors)[9]					x				

Table 2B. Study Calendar Cont.

					FOLLOW-UP PERIOD			
Observations	Weekly from +60 to +100 (± 5)	Every other week from +60 to +100 (± 5)	+ 42 (± 5)	+60 (±5)	+ 100 (± 7)	Quarterly: Day +180 and Day +270 (± 14)	+ 365 (± 14)	GVHD Onset (± 3)
Informed Consent								
Medical History and Examination	x		x	x	x	x	x	x
Pre-HCT organ function and infectious disease testing[1]								
Pregnancy test (if applicable)								
Karnofsky Performance Status	x		x	x	x	x	x	x
Laboratory testing[2]		x	x	x	x			
ECG monitoring[3]			x	x				
CD24Fc (Study Agent)[4]								
Vital Sign monitoring[5]								
Acute GVHD assessment[6]	x				x	x		x
Chronic GVHD assessment					x	x	x	
Concomitant Medications	x				x	x	x	x
Toxicity Assessment (NCI Criteria)	x				x			
Assess Engraftment								
Bone marrow aspirate & biopsy					x			
Chimerism					x			
Anti-drug-antibody/PK samples[7]			x	x (see note 7)	x			x
hs-CRP					x			x
Fasting Lipid Panel including LDL			x	x	x			x
Research samples (Patient)[8]			x	x (see note 8)	x			x
Research sample (Donors)[9]								

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. Collection windows do not apply to early PK studies which should be collected around the time of CD24Fc infusion.**

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 Pulmonary Function Test may be collected up to 6 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. CBC with differential, serum electrolytes with creatinine, AST, ALT, and total bilirubin then performed weekly through day 59 and performed every other week through day 100 post HCT. Laboratory testing may be more frequent per standard HCT practice.
3) 12 lead ECG monitoring will be performed at 3 time points to assess cardiac safety signals. On Day -1, Day 14 and Day 28, the ECG should be measured within four hours of start of study drug infusion and 2 hours (± 15 minutes) post drug (i.e. 2 hours after the start of infusion).
4) Per protocol, CD24Fc will be administered on day -1, day 14 and day 28. See protocol section 7.1 for instructions on identifying and managing infusion reactions.
5) Frequent vital sign monitoring is required following CD24Fc infusion. Vital signs will be recorded prior to infusion and at approximately 15, 30, 60, and 120 minutes from the start of the CD24Fc infusion.
6) Assessment for aGVHD will occur weekly through day 100. Following day 100 acute and chronic GVHD assessments will occur approximately at a quarterly schedule (day 180 and day 270 ± 14 days). Consensus aGVHD grading will be used to report disease severity (APPENDIX C).
7) Anti-drug-antibody / PK samples: Blood samples should be taken before infusion and 2 hours after completing the CD24Fc infusion (on day -1, day 14, and day 28). Additional ADA/PK samples to be drawn on day 7, day 21, day 35, day 42, day 56, day 70, and day 100.
8) Research samples include PBSC and serum from patients. Research samples should be taken at the following time points to be cyropreserved for correlative immunologic studies: Baseline (Day -7, prior to initiating conditioning), prior to infusion on Day -1, Day 14, and Day 28, Day 42, Day 56 and Day 100.
9) In the pre-HCT period, a research sample from the donor HCT product will also be cryopreserved prior to infusion.

4 STUDY VARIABLES

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable in Phase IIa

Not applicable for Phase IIa.

Efficacy analyses are considered as secondary for Phase IIa.

4.1.2 Primary Efficacy Variable in Phase IIb

The incidence of Grade II-IV aGVHD following HCT will be the primary efficacy endpoint in the Phase IIb portion of the study.

4.1.2.1 Cumulative Incidence of Grade II-IV Acute GVHD

The primary efficacy variable of the Phase IIb portion is the cumulative incidence of Grade II-IV aGVHD at day +100 following matched unrelated donor myeloablative HCT. This reflects the most established GVHD endpoint in the HCT field based on prior GVHD prevention studies. Acute GVHD will be monitored through aGVHD assessments beginning on day 0 (date of HCT) and continuing approximately weekly through day +100. Following day +100, aGVHD assessments will occur approximately quarterly through day +270.

Consensus aGVHD grading will be used to report disease severity. Acute GVHD severity will be determined by the Investigator and graded from 0-IV for the skin, liver, and gut and this will be used to determine the overall clinical severity. The overall clinical grade from 0-IV will be determined based on Protocol CD24FC-002 Appendix C (Version 3.2; 2 August 2017).

The cumulative incidence of acute Grade II-IV GVHD will be calculated starting on the date of transplantation until the earlier of the documented Grade II-IV aGVHD or death (as a competing risk). Patients that are alive with no occurrence of Grade II-IV acute GVHD through day +100 will be censored at their last assessment for aGVHD on or prior to day +100.

4.1.3 Key Secondary Efficacy Variable

The key secondary efficacy variable in Phase IIb will be acute Grade II-IV GVHD free survival through day +180 following HCT.

4.1.3.1 Acute GVHD Free Survival

In Phase IIb, Grade II-IV acute GFS is also a key secondary endpoint at day +180. Grade II-IV acute GFS is defined as the time from the date of HCT to the earlier of the dates of the first documented Grade II-IV aGVHD (as assessed by the Investigator) or death due to any cause.

For the purposes of GFS, events will be considered as either death or the occurrence of Grade II-IV aGVHD (as assessed by the Investigator) following HCT. Thus GFS will be calculated in days as:

- Grade II-IV GFS = date of death/Grade II-IV aGVHD – date of HCT + 1

Patients that are alive and have no documented occurrence of Grade II-IV aGVHD at the data cutoff date will be censored at the last date of aGVHD assessment on or prior to day +180.

Furthermore, Grade III-IV acute GFS through Day +180 following HCT is defined as the time from the date of HCT to the earlier of the dates of the first documented Grades III-IV aGVHD (as assessed by the Investigator) or death due to any cause. For the purposes of this endpoint, events will be considered as either death or the occurrence of Grade III-IV acute GFS (as assessed by the Investigator) following HCT. Grade III-IV acute GFS will be calculated in days as:

- Grade III-IV GFS = date of death/grade III-IV aGVHD – date of HCT + 1

Patients that are alive and have no documented occurrence of Grade III-IV aGVHD at the data cutoff date will be censored at the last date of aGVHD assessment on or prior to day +180.

4.1.4 Other Secondary Efficacy Variables

The following secondary efficacy variables will be considered.

- Cumulative incidence of chronic GVHD (cGVHD) at one year following HCT
- Incidence of relapse at one year following HCT
- Non-Relapse Mortality (NRM) at one year following HCT
- Disease Free Survival (DFS) at one year following HCT
- Incidence of infection at day +100 following HCT
- OS at one year following HCT
- GvHD-Free and Relapse-Free Survival (GRFS) at one year following HCT

4.1.4.1 Cumulative Incidence of Chronic GVHD

Chronic GVHD assessments will occur approximately quarterly beginning on day +100 after HCT until one year after HCT.

Chronic GVHD assessments will be performed for the following areas: skin, gastrointestinal, eyes, lung, liver, mouth, joints/fascia, genitals, and other organs. Chronic GVHD severity will be Graded as I (mild), II (moderate), or III (severe) for each area where chronic GVHD is present. A global severity will also be assessed by the investigator.

The cumulative incidence of cGVHD at one year will be calculated starting on the date of HCT until the earlier of the documented cGVHD or death (as a competing risk).

Patients that are alive and do not experience cGVHD at the end of the follow-up period (day +365) will be censored at the last date of evaluation.

4.1.4.2 Incidence of Relapse

Patients that undergo HCT will be evaluated for the relapse of disease until the end of the 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 31 or day 61) until one year post HCT. If applicable, the date of relapse and type will be recorded in on the eCRF.

The cumulative incidence of relapse at one year will be calculated starting on the date of HCT until the earlier of the documented relapse or death (as a competing risk).

Patients that are alive and do not experience relapse at the end of the follow-up period (day +365) will be censored at the last date of evaluation.

4.1.4.3 Cumulative Incidence of Non-Relapse Mortality

Patients that undergo HCT will be assessed for mortality related to the HCT procedure (TRM) through the end of the follow-up period.

TRM will be evaluated through the cumulative incidence of NRM at one year and will be calculated starting on the date of HCT until death without relapse or relapse (as a competing risk).

Patients that are alive at the end of the follow-up period (day +365) without relapse will be censored at the last date they were known to be alive.

4.1.4.4 Disease Free Survival

In Phase IIa and Phase IIb, patients that undergo HCT will be evaluated for the relapse of disease until the end of the follow-up period. If applicable, the date of relapse and type will be recorded in on the electronic case report form (eCRF). DFS will be defined as the length of time after HCT to the earlier of death or disease relapse.

For patients that undergo HCT, DFS will be calculated as:

- DFS = date of death/relapse – date of HCT + 1

Patients that are alive and do not experience disease relapse at the end of the follow-up period will be censored at the last date of evaluation.

4.1.4.5 Overall Survival

Patients that undergo HCT will be followed for OS through the end of the follow-up period lasting approximately 365 days after the date of HCT.

OS will be calculated in days as:

- OS = date of death – date of HCT + 1

Patients that are alive at the end of the follow-up period will be censored at the last date that they were known to be alive.

4.1.4.6 GVHD-Free and Relapse-Free Survival

GRFS is a composite endpoint in which events include Grade III-IV aGVHD, cGVHD requiring systemic immunosuppressive therapy, relapse, or death from any cause. GRFS is defined as the time from the date of HCT to the earlier of the dates of the first documented Grade III-IV GVHD, first documented disease relapse, or death from any cause.

GRFS will be calculated in days as:

- GRFS = date of grade III-IV GVHD/relapse/death – date of HCT + 1

Patients that are alive and have no documented occurrence of Grade III-IV aGVHD, cGVHD requiring systemic immunosuppressive therapy, or relapse at the data cutoff date will be censored at the last assessment date.

4.2 Safety Variables

Safety parameters will include assessments for DLTs, adverse events (AEs), Treatment-emergent adverse events (TEAEs), prior and concomitant medications, dosing and extent of exposure, Karnofsky Performance Status (KPS), vital sign measurements, clinical laboratory parameters, Electrocardiogram (ECG) parameters, ADAs, and bone marrow aspirate.

4.2.1 Dose Limiting Toxicities

The incidence of DLTs is the primary endpoint for the Phase IIa portion of the study. For the definition of DLTs, please refer to Section 3.1.1.1.

The incidence of DLTs occurring during the DLT evaluation period (day +30 after HCT for single dose cohorts or day +60 for multi-dose) will determine if further dose escalation will occur.

4.2.2 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product regardless of causality assessment. An AE 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 patients have been started on the investigational drug and recorded on the appropriate eCRF.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs.

The relationship of each AE to study drug will be recorded as:

- *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

AEs will be collected from the time of the infusion of the investigational drug, continuously through the Treatment Period. The exact days may vary depending on the last day of administration of study drug without constituting a deviation. Thus, the assessment and reporting period for AEs including DLT potentially related to the study drug (CD24Fc) will extend through day 30 post HCT for the single-dosing cohorts or day 60 post HCT for the multi-dosing cohort. All SAEs that the investigator considers related to study drug occurring after 30 days post HCT for the single-dosing cohorts or 60 days post HCT for the multi-dosing cohort must be reported to the Principal Investigator and Coordinating Center.

The grading scales found in the revised NCI CTCAE v4.03 will be utilized for all events with an assigned CTCAE grading. If a CTCAE grade is not given it will not be imputed. AEs will be coded and classified by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA, v19.0).

For each episode of an AE, all changes to the CTCAE grade attained, as well as the highest attained CTCAE (Version 4.0) grade, should be recorded. The assessment by the Investigator regarding the relationship between study drug and the AE will also be recorded.

4.2.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version 2016E B2). Prior medications are medications used and stopped before the first dose of study drug. Concomitant medications are medications that were taken on or after the first dose of study drug.

4.2.4 Comorbidity Index

Additional medical history information related to potential cardiac, psychiatric, hepatic, renal, pulmonary, and other comorbidities will be collected during screening. The risk value for each area will be assessed and in addition a total score and total risk category (Low, Intermediate, and High) will be recorded.

4.2.5 Dosing and Extent of Exposure

Study drug (CD24Fc or placebo) will be administered on day -1 as an IV solution prior to patients undergoing HCT for single-dose cohorts. For the multi-dose cohort, study drug will be administered on day -1 as well as day 14 and day 28 post HCT.

The treatment date(s) and actual dose(s) administered will be recorded.

4.2.6 Karnofsky Performance Status

In Phase IIa and Phase IIb, the KPS will be evaluated at the times indicated in the Study Calendar (Table 2A and Table 2B) and recorded on the eCRF by the Investigator.

4.2.7 Vital Signs

Vital signs will be measured at the times indicated in the Study Calendar (Table 2A and Table 2B), including frequent monitoring after administration of study drug. Vital sign measurements will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

4.2.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the time points specified in the Study Calendar (Table 2A and Table 2B). The following tests will be performed in both the Phase IIa and Phase IIb portions of the study. The clinical laboratory evaluation will include:

- **Hematology**: white blood cells (WBCs), hemoglobin, hematocrit, platelets, red blood cells (RBCs), mean corpuscular volume (MCV), mean corpuscular hemoglobin (absolute and concentration), red blood cell width, mean platelet volume, neutrophils, lymphocytes, monocytes, eosinophils, basophils
- **Serum chemistry**: sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, calcium, protein, albumin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), phosphorous, amylase, lipase, uric acid, cancer antigen 19-9 (CA 19-9), C-reactive protein

Abnormal laboratory values will be recorded on the eCRF and graded according to the scales found in NCI CTCAE v4.03.

4.2.9 Engraftment, Graft Failure and Chimerism

4.2.9.1 Engraftment and Engraftment Failure

Patients undergoing HCT will be monitored for transplant engraftment after the procedure is completed. Engraftment will be evaluated through the collection of hematology laboratory samples at the times indicated in the Study Calendar (Table 2A and Table 2B).

Engraftment for neutrophils will be defined as the first of three consecutive days in which the ANC is >500/uL. Engraftment for platelets will be defined as the first of three consecutive days in which the platelet count is >20,000/uL, without transfusion support within the preceding 7 days.

Primary engraftment failure will be defined as ongoing ANC < 500/uL by day 28 post HCT. Failure to attain platelet count ≥ 20,000/uL will not be considered engraftment failure. In addition, patients who engraft prior to day 28 and later have ANC < 500/uL or platelet transfusion requirement will not be considered to have engraftment failure.

4.2.9.2 Chimerism

Patients undergoing HCT will undergo donor chimerism monitoring at the times indicated in the Study Calendar (Table 2A and Table 2B). The percentage of CD3, CD33, and overall donor cells will be recorded.

4.2.10 Electrocardiograms

12-lead ECG monitoring will be performed at the time points in the Study Calendar (Table 2A and Table 2B) in order to assess cardiac safety signals both before and after infusion. The ECG will be assessed by the Investigator for overall clinical significance. In addition, the heart rate (bpm), PR (msec), RR (msec), QRS duration (msec), QT (msec), QTc interval (msec), and QTcF (msec) will be recorded.

4.2.11 Echocardiogram/MUGA

Echocardiogram/ Multiple Gated Acquisition (MUGA) assessments will be performed at the time points in the Study Calendar (Table 2A and Table 2B). The presence of any clinical abnormalities identified by the Investigator and left ventricular ejection fraction will be recorded.

4.2.12 Anti-drug Antibodies

For ADA analysis in the single dose cohorts, blood samples will be collected prior to study drug infusion and 2 hours (±30 minutes) after completing the CD24Fc infusion on day -1 and on days +7 (±2), +14 (±3), +30 (±5), +42 (±5), and +100 (±7). For the multi-dose cohort, ADA

samples will be collected prior to study drug infusion and 2 hours after completing study drug infusion on day -1, day +14 and day +28.

Blood samples will be tested for the presence of antibodies against CD24Fc.

4.2.13 Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy will be collected during Screening and on day 100 (±7) post HCT as indicated in the Study Calendar. The adequacy of the obtained sample for analysis, percent cellularity (if applicable), and blasts percentage will be recorded.

4.3 Pharmacokinetic Variables

For PK analysis in the single dose cohorts, blood samples will be collected prior to study drug infusion and 2 hours (±30 minutes) after completing the CD24Fc infusion on day -1, and on days +7 (±2), +14 (±3), +30 (±5), +42 (±5), and +100 (±7).

For the multi-dose cohort, PK samples will be collected prior to study drug infusion and 2 hours after completing study drug infusion on day -1, day +14 and day +28 (Note: these days should be adjusted to the precise day of infusion if the CD24Fc is delayed). Samples will also be collected days +7 (±2), +21 (±3), +35 (±5), +42 (±5), +56 (±5), +70 (±5) and +100 (±7) after HCT.

4.3.1 Plasma Concentration

The individual time-concentration profile of CD24Fc will be measured for each patient based on the PK samples collected at the time points listed above.

4.3.2 Pharmacokinetic Parameters

Plasma PK parameters of CD24Fc will be calculated from the individual time-concentration profiles using standard noncompartmental methods for all patients in the Pharmacokinetic Population. The following PK parameters will be calculated for each patient with sufficient plasma concentration data available for analysis. PK parameters will be calculated using actual collection times.

The following PK parameters of CD24Fc will be calculated for the single-dose cohorts and Day -1 for multi-dose cohort after coadministration with methotrexate and tacrolimus:

Parameters	**Units**	**Description**
C_{max}	ng/mL	Maximum observed plasma concentration. If not unique, then the first maximum is used.
t_{max}	h	The time of maximum observed plasma concentration
$AUC_{0\text{-}42d}$	ng·h/mL	The area under the plasma concentration versus time curve (AUC), from time 0 to day 42, as calculated by the log-linear trapezoidal method
$AUC_{0\text{-}last}$	ng·h/mL	The area under the plasma concentration versus time curve, from time 0 to t_{last}, where t_{last} is the time of the last measurable plasma drug concentration
AUC_{extrap}	%	Percentage of $AUC_{0\text{-}inf}$ that is due to extrapolation from t_{last} to infinity, calculated as: $100 \times [1 - (AUC_{0\text{-}last}/AUC_{0\text{-}inf})]$, where t_{last} is the time of the last measurable plasma drug concentration
$AUC_{0\text{-}inf}$	ng·h/mL	The area under the plasma concentration versus time curve, from time 0 extrapolated to infinity, calculated as: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last}/\lambda_z$, where C_{last} was the last measurable plasma drug concentration
Lambda z (λ_z)	h^{-1}	Apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
$t_{½}$	h	Apparent terminal elimination half-life, calculated as: $ln(2)/\lambda_z$
CL	L/h	Total body clearance after intravenous administration, calculated as: $Dose/AUC_{0\text{-}inf}$
V_Z	L	Volume of distribution based on the terminal elimination phase, calculated as: $Dose/(AUC_{0\text{-}inf} \times \lambda_z)$

The following PK parameters of CD24Fc will be calculated for Day 28 of the multi-dose cohort, if applicable:

Parameters	Units	Description
C_{max}	ng/mL	Maximum concentration between dose time and dose time + Tau. If not unique, then the first maximum is used.
t_{max}	h	The time of maximum observed plasma concentration during a dosing interval
C_{min}	ng/mL	Minimum concentration between dose time and dose time + Tau (at Tmin)
T_{min}	h	Time of minimum concentration sampled during a dosing interval
AUC_{0-14d}	ng·d/mL	The area under the plasma concentration versus time curve, from time 0 to tau, as calculated by the log-linear trapezoidal method
C_{avg}	ng/mL	Calculated as AUC_{0-14d} divided by Tau
Cl_{ss}	L/h	calculated as: Dose/AUC_{0-14d}

The following PK parameters of CD24Fc will be will be calculated using all the PK concentration data collected, if applicable:

Parameters	Units	Description
AUC_{0-last}	ng·d/mL	The area under the plasma concentration versus time curve, from time 0 on Day 1 to the last measurable concentration after the last dose on Day 28, as calculated by the log-linear trapezoidal method
AUC_{0-100d}	ng·d/mL	The area under the plasma concentration versus time curve, from time 0 on Day 1 to Day 100, as calculated by the log-linear trapezoidal method; when computed using actual sample collection time, the actual time for subject's 100 day sample is used in place of the nominal 100 days

The PK parameters λ_z and $t_{½}$ will not be presented for patients who do not exhibit a terminal elimination phase in their concentration-time profiles. To estimate the first-order terminal elimination constant, linear regression of concentration (on the logarithmic scale) vs time will be performed using at least 3 time points with measurable plasma concentrations. Uniform weighting will be selected to perform the regression analysis to estimate PK parameters.

The constant λ_z will not be assigned if the terminal elimination phase is not apparently linear (as it appears on a semi-logarithmic scale), if t_{max} is one of the last 3 data points, if the regression coefficient is less than 0.8, if the extrapolated is greater than 40%, or if the estimated elimination rate indicates a positive slope. In cases where λ_z is not assigned, the values of associated parameters such as $t_{½}$ and AUC_{0-inf} will not be calculated.

The Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin® Professional) will be used in the computation of AUCs.

4.4 Biological Outcomes and Pharmacodynamic Variables

Blood samples for correlative and biological studies at the time points specified in the Schedule of Assessments. The variables to be measured as part of these exploratory studies in this trial include, but are not limited to, the following:

- **PD studies**: will evaluate Siglec-10 (human homolog of Siglec-G) expression, intracellular phosphorylation status of SHP-1, and activation status of Nuclear Factor kappa B (NF-kB) components within immune subsets, namely APCs and T cells.
- **Cellular immunology correlatives**: will examine a) Ex vivo T cell responses (cytokine release, proliferation) to dendritic cells (DCs) from patients treated with and without CD24Fc; b) T cell phenotyping, to assess expression of CD44, CD62L, CD25, PD-1, PDL-1, CD127 and intracellular staining of Foxp3, IFN-γ, and IL-17 to identify CD4+CD25+FoxP3+ Tregs, naïve (CD45RA+), memory (CD45RO+) T cells and additional T cell subsets; c) NK cell subsets; d) B-cell subsets; e) Treg and conventional T cell functional responses to nominal and specific antigens and f) ADA levels.
- **Inflammatory mediators and biomarkers of GVHD**: will include a) pro-inflammatory cytokines (TNFα, IL-1, IL-6, IL-8); b) previously established plasma GVHD biomarkers47 and c) DAMPs (HMGB1, uric acid, ATP, etc.).
- **Lipids**: Lipid panel, LDL, HDL, Triglycerides, and Total cholesterol.

5 SAMPLE SIZE DETERMINATION

A maximum total of 212 patients are expected to complete the Phase IIa and Phase IIb components of this trial. This estimate assumes a maximum of 32 patients recruited to the Phase IIa dose escalation component and a maximum of 180 patients enrolled in Phase IIb.

With 180 patients (90 per arm), and assuming a Type I (alpha) error rate of 5%, there will be 80% power to detect a reduction in the primary endpoint of GVHD incidence at day 100 from 50% to 30% in Phase IIb of the trial. The total sample size will be lower if DLTs are encountered in Phase IIa or a stopping rule is met in Phase IIb.

6 ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all randomized patients in the Phase IIa or Phase IIb part of the study. The ITT Population will be used for demographic and baseline summaries.

6.2 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population in each phase will include all randomized patients study who received any amount of study drug (CD24Fc or placebo) and underwent HCT. The mITT Population will be used for efficacy analyses.

6.3 Dose Limiting Toxicity Evaluable Population

The DLT Evaluable Population will include all patients in Phase IIa who received any amount of CD24Fc and who completed the DLT evaluation period without DLT or had a DLT during the DLT evaluation period. The DLT evaluation period will begin after administration of CD24Fc on day -1 and continue through day +30 (or +60 in dose level 2) after transplant to assess for DLTs. The DLT Evaluable Population will be used for analysis of the incidence of DLTs in Phase IIa.

6.4 Safety Population

The Safety Population in each phase will consist of all patients in either Phase IIa or Phase IIb who received CD24Fc or placebo. The Safety Population will be used for safety analyses and will be analyzed according to the actual treatment received.

6.5 Pharmacokinetics Population

The PK Population will include all patients in the ITT Population in Phase IIa or Phase IIb who received CD24Fc and for whom at least 1 evaluable post-baseline PK sample was obtained. The PK Population will be used for PK analysis.

6.6 Pharmacodynamics Population

The PD Population will include all patients in the ITT Population in Phase IIa or Phase IIb who received any amount of CD24Fc or placebo, had a baseline PD assessment, and where applicable at least 1 post-baseline PD assessment. The PD Population will be used for PD analysis.

7 GENERAL STATISTICAL CONSIDERATIONS

The primary objective of the Phase IIa portion of this study is to evaluate the safety and tolerability of single dose and 3 biweekly infusions of CD24Fc in order to establish an RP2D or MTD. If such a dose is established, the study will proceed to Phase IIb in order to determine the efficacy of CD24Fc when combined with a standard prophylactic treatment for acute GVHD.

Unless otherwise stated, descriptive statistics including the number of observations (n), mean, standard deviation, median, minimum, and maximum will be presented for continuous

variables. Frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of non-missing values in a dose group.

Summary tables will be presented separately for Phase IIa and Phase IIb and by treatment arm. For Phase IIa, summary tables will present results by cohort for each dose and placebo, where the placebo patients will be combined across dose cohorts. For Phase IIb, summary tables will present results by treatment group.

7.1 Adjustment for Covariates

In Phase IIb, the primary and key secondary efficacy analyses will be stratified by transplant source (peripheral blood stem cell [PBSC] or bone marrow).

7.2 Baseline Definition

Where applicable, baseline measurements will be defined as the last observation before the first administration of the study drug (CD24Fc or placebo).

7.3 Multicenter Studies

The center effect will not be considered for this study.

7.4 Multiple Comparisons

Not applicable for Phase IIa.

For Phase IIb, formal statistical tests are planned for the primary and key secondary efficacy endpoints. To control the family-wise type 1 error rate at 5%, a sequential testing procedure will be utilized to test the primary and key secondary efficacy endpoints, with each being tested at $\alpha = 0.05$. If the primary endpoint is statistically significant at $\alpha = 0.05$, testing may continue to the key secondary efficacy endpoint.

No adjustment to the type I error rate will be made for the interim futility analysis.

There is no plan to control for the overall alpha for other secondary efficacy analyses.

7.5 Missing Data

In general, missing data values will be recorded as missing and will not be imputed for the statistical analysis unless specified otherwise. Only recorded data values will be used for the reporting of descriptive statistics, unless specified otherwise.

Missing Dates: In cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will

be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

7.5.1 Missing Pharmacokinetics Data

For missing predose concentration values in single dose data, the missing component(s) will be assumed as zero. For steady-state, the minimum observed during dose interval will be used as predose concentration values.

Non-quantifiable (NQ) data will be handled based on the current knowledge of drug PK measures. If one or more NQ values occur in a profile before the first measurable concentration or after the last measurable concentration, they will be assigned a value of zero concentration. For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value.

7.6 Examination of Subgroups

No subgroup analyses are planned for the study. The efficacy analysis will include adjustment for the source of donor cells (peripheral blood versus bone marrow) in order to reduce the potential for bias.

8 STATISTICAL ANALYSIS

The statistical analyses will be performed by Medpace Inc.

8.1 Patient Population Data

8.1.1 Patient Disposition

Patient disposition will be summarized for all screened subjects. The following patient disposition categories will be included in the summary for the Phase IIa portion:

- Patients who were screened;
- Patients who were randomized;
- Patients who received study drug (CD24Fc or Placebo);
- Patients who underwent HCT;
- Patients who completed treatment;
- Patients who did not complete treatment
- Patients who completed the study through Days +28, +100, +180, +270, +365;
- Patients who completed the study; and
- Patients who discontinued early from the study.

The patient disposition summary in the Phase IIb portion will include the same categories as above.

For patients who were randomized but discontinued from treatment or discontinued early from the study, a summary will be provided by the primary reason for discontinuation.

The number of patients in each defined analysis population will be tabulated by treatment arm and in total in both Phase IIa and Phase IIb.

All patient disposition data will be listed.

8.1.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment group and in total for the ITT, mITT Population and the Safety Population. Gender, age group, race, and ethnicity will be summarized with contingency tables. Age at informed consent, height, baseline body weight and body mass index (BMI) will be described with summary statistics (n, mean, standard deviation, median, minimum, and maximum).

Baseline disease characteristics will also be summarized by treatment group and in total using descriptive statistics. The comorbidity index total score will be summarized using descriptive statistics. Primary disease diagnosis, prior radiation therapy, baseline KPS, comorbidity index total score risk category (low, intermediate, and high) will be summarized using contingency tables.

All demographic data and baseline characteristics data will be listed by patient in Phase IIa and Phase IIb.

8.1.3 Transplantation Information

In Phase IIa and Phase IIb, HCT transplantation related information will be summarized descriptively by treatment group for the ITT, mITT Population and the Safety Population

Response status prior to HCT, GVHD prophylaxis regimen, conditioning regimen, donor-recipient gender disparity, donor-recipient CMV status, donor-recipient blood type, and transplant source will be tabulated by treatment group and summarized in tables.

Donor-recipient HLA typing including HLA-A, HLA-B, HLA-C, and HLA-DRB1 will be listed by patient. All HCT transplantation data will be listed by patient.

8.1.4 Medical and Surgery History

Medical and Surgery history will be collected at the screening visit. The reported medical history terms will be coded using the MedDRA (v19.0).

All reported medical history conditions and surgeries will be listed by patient for the ITT Population in Phase IIa and Phase IIb.

8.2 Efficacy Analyses

The primary efficacy analysis and secondary efficacy analyses in Phase IIb will be performed based on the mITT Population. Efficacy analyses for Phase IIa will be based on the mITT Population and will be descriptive, that is, no formal hypothesis test will be performed on the Phase IIa data. Efficacy data from the Phase IIa part of the study and Phase IIb part of the study will be summarized separately.

Summary tables and analyses will present results by treatment group in Phase IIa and Phase IIb. For Phase IIa, placebo patients will be combined across dose cohorts.

8.2.1 Primary Efficacy Analysis

The primary efficacy endpoint for Phase IIb is the cumulative incidence of Grade II-IV aGVHD at day +100 following HCT for the mITT Popualtion. The cumulative incidence for Grade II-IV aGVHD between the two treatment groups will be compared using competing risks regression on treatment arm via the semiparametric method of Fine and Gray [1], stratified by the donor stem cell source, to account for the competing risk of death without Grade II-IV aGVHD. The hypothesis test will compare the resulting cumulative incidence estimates and determine the statistical significance of the difference in the cumulative incidence functions by day +100 between the two treatment arms (CD24Fc or placebo) in Phase IIb.

The hypothesis test for the primary efficacy variable in Phase IIb will be carried out with a type I (alpha) error rate of 5% (two-sided). The primary efficacy analysis will compare whether subjects treated with the combination of CD24Fc plus standard prophylaxis have a cumulative incidence of Grade II-IV aGVHD equal to that of subjects receiving standard GVHD prophylaxis with placebo, stratifying for the source of donor stem cells. The point estimate of the hazard ratio and the accompanying 95% confidence interval will also be presented.

The primary analysis will be performed using intention to treat principle; hence all randomized patients in the mITT Population in Phase IIb will be included for the primary analysis based on the randomized treatment group, regardless of the actual treatment received.

The estimate of the cumulative incidence of Grade II-IV aGVHD by day +100 as well as the 2-sided 95% confidence intervals will be obtained from the cumulative incidence function and presented by treatment arm. Plots of the cumulative incidence curves will be presented by treatment arm.

In Phase IIa, the estimate of the cumulative incidence of acute Grade II-IV GVHD will be presented by treatment arm for the mITT Population (with subjects receiving placebo pooled across enrollment cohorts). Plots of the cumulative incidence curves for Grade II-IV aGVHD will be presented by treatment arm.

In addition to the analysis described above, the aGVHD assessments by day +100 will be summarized for each treatment group using the highest stage by organ system and the maximum overall grade post transplant through visit day +100.

All aGVHD assessments will be listed by patient.

8.2.2 Key Secondary Efficacy Analysis

The key secondary efficacy endpoint for Phase IIb is Grade II-IV acute GVHD-free survival at day +180. GFS analysis will be performed based on the mITT Population.

In Phase IIb, the secondary hypothesis will compare for equality of Grade II-IV acute GFS by day +180 between the two treatment groups using the stratified log rank test with donor stem cell source as the stratification factor. The hazard ratio of the treatment effect along with the 95% confidence intervals will be calculated using the Cox proportional hazard model with treatment as an explanatory variable and stratified by the donor stem cell source.

The Kaplan-Meier estimate of the median Grade II-IV acute GFS as well as the 2-sided 95% confidence intervals will be presented by treatment arm. The estimated Grade II-IV acute GFS rate at day +180 will also be presented by treatment arm as well as the 95% confidence intervals. Plots of the Kaplan-Meier curves will be presented by treatment arm.

In addition, in Phase IIb, the Kaplan-Meier estimate of the median Grade III-IV acute GFS through day +180 as well as the 2-sided 95% confidence intervals will be presented by treatment arm. The estimated Grade III-IV GFS rate at day +180 will also be presented as well as the 95% confidence intervals for each treatment arm.

In Phase IIa, the Kaplan-Meier estimate of Grade II-IV acute GFS and Grade III-IV acute GFS through day +180 will be presented by treatment arm for the mITT Population (with subjects receiving placebo pooled across enrollment cohorts). Plots of the Kaplan-Meier curves for GFS will be presented by treatment arm.

8.2.3 Other Secondary Efficacy Analyses

8.2.3.1 Cumulative Incidence of Chronic GVHD at One Year

Analyses for cGVHD will be performed using the cumulative incidence function for the mITT Population in the same manner as the primary efficacy endpoint (Section 8.2.1). The cumulative incidence of chronic GVHD at one year and the 95% confidence intervals will be presented by treatment arm for Phase IIa and Phase IIb.

For Phase IIb, the cumulative incidence functions of cGVHD by one year between the two treatment groups will be compared using Fine and Gray competing risks regression model with treatment as an explanatory variable and stratified by the donor stem cell source. The point estimate of the hazard ratio and the corresponding 95% confidence intervals will be presented.

In addition to the analysis described above, the cGVHD assessments will be summarized for each treatment group using the highest stage by organ system and the maximum overall grade post transplant through one year.

All chronic GVHD assessments will be listed by patient.

8.2.3.2 Cumulative Incidence of Relapse at One Year

The cumulative incidence of relapse at one year will be estimated using the cumulative incidence function for the mITT Population in the same manner as the primary efficacy endpoint (Section 8.2.1). The cumulative incidence of relapse at one year and the 95% confidence intervals will be presented by treatment arm for Phase IIa and Phase IIb.

For Phase IIb, the cumulative incidence functions of relapse by one year between the two treatment groups will be compared using Fine and Gray competing risks regression model with treatment as an explanatory variable and stratified by the donor stem cell source. The point estimate of the hazard ratio and the corresponding 95% confidence intervals will be presented.

The number and percentage of subjects with relapse will be tabulated by treatment arm for Phase IIa and Phase IIb for the mITT Population.

All relapse assessments will be listed by patient.

8.2.3.3 Cumulative Incidence of Non-Relapse Mortality at One Year

The cumulative incidence of NRM at one year will be estimated using the cumulative incidence function for the mITT Population in the same manner as the primary efficacy endpoint (Section 8.2.1). The cumulative incidence of NRM at one year and the 95% confidence intervals will be presented by treatment arm for Phase IIa and Phase IIb.

For Phase IIb, the cumulative incidence functions of NRM by one year between the two treatment groups will be compared using Fine and Gray competing risks regression model with treatment as an explanatory variable and stratified by the donor stem cell source. The point estimate of the hazard ratio and the corresponding 95% confidence intervals will be presented.

The number and percentage of patients with NRM will be tabulated by treatment arm for Phase IIa and Phase IIb for the mITT Population.

8.2.3.4 Disease Free Survival at One Year

In Phase IIb, DFS will be analyzed for the mITT Population using the same analysis method as for the key secondary endpoint GFS (Section 8.2.2). The Kaplan-Meier estimate of the median DFS as well as the 2-sided 95% confidence intervals will be presented by treatment arm. DFS rate at One year and the 2-sided 95% confidence intervals will be presented by treatment arm. The estimated hazard ratio of the treatment effect on DFS and the 95% confidence intervals will be presented.

In Phase IIa, the Kaplan-Meier estimate of DFS will be calculated by treatment arm for the mITT Population (with subjects receiving placebo pooled across enrollment cohorts).

8.2.3.5 Rate of Infection

In Phase IIa and Phase IIb, the number and percentage of patients experiencing infections will be tabulated by treatment group for the mITT Population (CD24Fc dose level and regimen or placebo). For Phase IIb, the proportion of patients experiencing infections will be compared using Cochran-Mantel-Haenszel (CMH) test adjusted for donor stem cell source.

The number and percentage of patients experiencing infections will also be tabulated by type of infection and site of infection and treatment group. The summaries will be presented separately for Phase IIa and Phase IIb.

All patient infection data will be listed by patient.

8.2.3.6 Overall Survival at One Year

In Phase IIb, OS will be analyzed for the mITT Population using the same analysis method as for the key secondary endpoint GFS (Section 8.2.2). The Kaplan-Meier estimate of the median OS as well as the 2-sided 95% confidence interval will be presented by treatment arm. The estimated OS rate at one year will be presented along with the 95% confidence intervals for each treatment arm. The estimated hazard ratio of the treatment effect on OS and the 95% confidence intervals will be presented.

In Phase IIa, the Kaplan-Meier estimate of OS will be presented by treatment arm for the mITT Population (with subjects receiving placebo pooled across enrollment cohorts).

8.2.3.7 GVHD-Free and Relapse-Free Survival (GRFS) at One Year

In Phase IIb, GRFS will be analyzed for the mITT Population using the same analysis method as for the key secondary endpoint GFS (Section 8.2.2). The Kaplan-Meier estimate of the median GRFS as well as the 2-sided 95% confidence interval will be presented by treatment arm. The estimated GRFS rate at one year will be presented along with the 95% confidence intervals for each treatment arm. The estimated hazard ratio of the treatment effect on GRFS and the 95% confidence intervals will be presented.

In Phase IIa, the Kaplan-Meier estimate of GRFS will be presented by treatment arm for the mITT Population (with subjects receiving placebo pooled across enrollment cohorts).

8.3 Safety Analyses

Safety will be evaluated by presenting summaries of AEs, clinical laboratory parameters, vital signs, physical examination findings, KPS status, and ECG findings for each treatment group

(CD24Fc dose level and regimen or placebo). In general, separate safety analyses will be presented for Phase IIa and Phase IIb.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. No formal statistical tests will be performed for the safety parameters and analyses will be presented separately for each study phase.

The analysis of DLTs will be based on the DLT Evaluable Population in Phase IIa and all other safety analyses will be based on the Safety Analysis Sets in Phase IIa and Phase IIb.

8.3.1 Dose Limiting Toxicities

In Phase IIa, the incidence of DLTs in the DLT Evaluable Population is the primary safety endpoint for this portion of the study.

For Phase IIa, the number of DLTs identified among the DLT evaluable patients in the DLT Evaluable Population will be listed and summarized for each dose of CD24Fc by SOC and preferred term.

The MTD and/or RP2D of CD24Fc will be determined by the incidence of DLTs in the DLT Evaluable Population in Phase IIa according to the guidelines in Section 3.1.1.3.

8.3.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. A TEAE is defined as an AE that started after first administration of the study drug (CD24Fc or placebo) or worsened in severity after dosing.

AEs will be coded using MedDRA (v19.0). The severity of all AEs will be graded according to the revised NCI CTCAE v4.03. All summaries will be based on the Safety Populations in Phase IIa and Phase IIb and each phase will be analyzed separately.

An overview of TEAEs will be provided which summarizes patient incidence of all TEAEs, treatment-emergent serious adverse events (TESAEs), Grade 3/4/5 TEAEs, TEAEs leading to deaths, TEAEs leading to discontinuation of the study, drug-related TEAEs, drug-related TESAEs, drug-related Grade 3/4/5 TEAEs, and drug-related TEAEs leading to discontinuation of the study.

The number and percentage of patients with TEAEs will be tabulated by MedDRA SOC and preferred term for each treatment group and in total, with patients receiving placebo in Phase IIa pooled across enrollment cohorts. Drug-related TEAEs, TESAEs, Grade 3/4/5 TEAEs, and TEAEs leading to discontinuation will be summarized in the same manner. For these summaries, patients with multiple AEs will be counted only once per SOC and preferred term.

By-patient listings will be provided for deaths, SAEs, Grade 3/4/5 AEs, and AEs leading to discontinuation of study. A by-patient AE listing including, but not limited to, verbatim term, preferred term, SOC, NCI CTCAE grade, and relationship to study drug will be provided.

8.3.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (Version 2016E B2). Prior medications include medications that were taken prior to and stopped before the first dose of the study treatment. Concomitant medications include medications that were taken on or after the first dose date of the study treatment.

The number and percentage of patients taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term by treatment group and in total for the Safety Populations in Phase IIa and Phase IIb. Prior medications will be summarized in the same manner.

All prior and concomitant medications will be listed by patient.

8.3.4 Dosing and Extent of Exposure

Each dose of study drug (CD24Fc or placebo) will be administered by an intravenous infusion over a minimum of 60 minutes.

The number of patients completing the indicated treatment will be tabulated for each cohort and in total Phase IIa and Phase IIb.

For the multi-dose cohort in Phase IIa, the number and percentage of patients completing 1, 2, and 3 doses respectively will be tabulated. The number and percentage of patients with dose held will also be presented.

All study drug administration data will be listed by patient.

8.3.5 Vital Signs

Vital sign assessment includes measurement of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), respiratory rate (bpm), and temperature (°C), will be obtained at the times indicated in the Study Plan. Descriptive statistics (i.e. number of observations (n), mean, standard deviation, median, minimum, and maximum) by treatment group (CD24Fc dose level and regimen or placebo) will be used to summarize vital signs measurements, including change from baseline by scheduled assessment and the minimum and maximum post-treatment values.

Vital sign assessments will be listed by patient.

8.3.6 Clinical Laboratory Assessments

Standard clinical laboratory profiles for safety assessments (serum chemistry and hematology) will be evaluated.

- **Chemistry**: includes sodium, chloride, bicarbonate, potassium, ALT, AST, amylase, ALP, LDH, and creatine kinase, bilirubin (total and direct), total protein, albumin, magnesium, calcium, creatinine, blood urea nitrogen, uric acid, lipase, glucose; CA 19-9, and high-sensitivity C-reactive protein (hs-CRP).
- **Lipid profile**: cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol/HDL ratio.
- **Hematology**: includes hemoglobin, hematocrit, platelets, RBCs, red cell indices (MCV, mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]); and WBCs with differential (neutrophils, lymphocytes, monocytes, basophils, and eosinophils).

Descriptive statistics (i.e. number of observations (n), mean, standard deviation, median, minimum, and maximum) by treatment arm (CD24Fc dose level and regimen or placebo) will be used to summarize clinical laboratory measurements including actual values, change from baseline by scheduled assessment, and the minimum and maximum post-treatment values. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum post-treatment values.

Abnormal laboratory results will be graded according to NCI CTCAE version 4.03, if applicable. Shift tables from baseline to the worst post-baseline value according to the NCI CTCAE grade will be provided for selected chemistry parameters (ALT, AST, total bilirubin, ALP, and creatinine). Both scheduled and unscheduled visits will be considered.

The number and percentageof subjects with the following potentially clinically significant abnormal liver function test will be summarized by treatment group:

- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Potential Hy's Law cases: ALT or AST ≥3 xULN, total bilirubin ≥2xULN, and ALP < 2xULN

Additionally, the number and percentage of subjects with treatment-emergent laboratory abnormalities (any grade and grade ≥ 3) will be presented by treatment arm for selected chemistry laboratory parameters. Treatment-emergent laboratory abnormalities are defined as post baseline laboratory abnormalities with worsening CTCAE grade from baseline. Post-baseline laboratory abnormality with unknown baseline grade will be considered as treatment-emergent.

Line plots will be provided for the mean value over time for hematology parameters including neutrophils and platelet.

All clinical laboratory data will be listed by patient.

8.3.7 Engraftment and Engraftment Failure

The engraftment status of patients in each treatment group (CD24Fc dose level and regimen or placebo) will be summarized separately for the Safety Population in Phase IIa and Phase IIb.

The following categories will be summarized:

- Patients who achieve neutrophil engraftment
- Patients who achieve platelet engraftment

For patients who achieved neutrophil engraftment and platelet engraftment, the time to neutrophil and platelet engraftment will be summarized using descriptive statistics.

In addition, the number and percentage of patients with primary engraftment failure will be presented.

All engraftment data will be listed by patient.

8.3.8 Chimerism

The donor chimerism of patients in the Safety Population in Phase IIa and Phase IIb who underwent HCT will be assessed. The percentage of CD3, CD33, and overall donor cells will be recorded at day +30 and day +100 post HCT.

The percentage of CD3, CD33, and overall donor cells will be summarized at each scheduled time point using descriptive statistics for each treatment arm in each phase (CD24Fc dose level and regimen or placebo). Chimerism results will also be summarized using the following categories: 100%, 90% to <100%, 50% to <90%, and <50%.

All donor chimerism data will be listed by patient.

8.3.9 Electrocardiogram

A 12-lead ECG will be performed pre-dose during the day -1, within four hours pre drug infusion and 2 hours (± 15 minutes) post drug, and at the day +42 Visit.

Descriptive statistics will be provided for ECG interval data (PR, QRS, QT, QTcB, and QTcF) by treatment arm (CD24Fc dose level and regimen or placebo) in Phase IIa and Phase IIb. The corrected QT intervals using Bazett's and Fridericia's formula will be calculated as follows: $QT_cB = QT/(RR)^{1/2}$ and $QT_cF = QT/(RR)^{1/3}$.

Descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group will be used to summarize ECG measurements including actual values, change

from baseline by scheduled assessment, and the minimum and maximum post-treatment values. Both scheduled and unscheduled post-treatment values will be considered for the summaries of the maximum post-treatment values.

The number and percentage of patients with elevated QT (based on QTcB and QTcF) over post baseline period will be presented for the following categories: QTcB or QTcF >450 msec, >480 msec, and >500 msec at post baseline, and increase in QTcB or QTcF from baseline >30 msec and >60 msec.

All ECG data will be listed by patient.

8.3.10 Karnofsky Performance Status

A shift table from baseline to the worst post-baseline value will be provided for the KPS score.

All KPS assessment results will be listed by patient.

8.3.11 Echocardiogram/MUGA

The number of percentage of patients with clinical abnormalities in echocardiogram/MUGA scan at screening will be tabulated. The LV ejection fraction (LVEF) will be summarized by treatment group in Phase IIa and Phase IIb.

All echocardiogram data will be listed by patient.

8.3.12 Anti-Drug Antibodies

The number and percentage of patients with positive ADA results based on confirmation assay will be tabulated at each scheduled time point and overall at post-baseline for subjects who received CD24Fc.

All ADA assessments will be listed by patient.

8.3.13 Bone Marrow Aspirate and Biopsy

Bone marrow aspirates samples will be collected during screening and at day 100 (±7).

The blast percentage and percent cellularity will be summarized with descriptive statistics by treatment group for both actual values and changes from baseline.

All bone marrow aspirate and biopsy assessments will be listed by patient.

8.3.14 Other Safety Variables

All other variables will be listed by patient.

8.4 Pharmacokinetic Analyses

PK Analyses will be based on the PK Population in Phase IIa and Phase IIb.

8.4.1 Concentration Data

Plasma concentrations of CD24Fc will be summarized by dose level and regimen using descriptive statistics (number of observations (n), mean, standard deviation, coefficient of variation percentage, standard error of the mean, median, minimum, and maximum) at each scheduled evaluation time point.

Mean plasma concentrations of CD24Fc versus nominal time points will be plotted by dose level and regimen on both the linear scale and semi-logarithm scale. Median plasma concentrations of CD24Fc versus nominal time points will be provided.

Actual sampling times that differ from the scheduled sampling times and fall outside the allowable window will be listed but excluded from summary statistics and associated graphs.

All individual patient plasma concentrations and actual blood sampling times will be listed.

8.4.2 Pharmacokinetic Parameters

Pharmacokinetic parameters after administration of CD24Fc will be summarized separately by dose level and regimen using descriptive statistics (n, mean, standard deviation, coefficient of variation percentage, standard error of the mean, median, minimum, and maximum). Geometric mean and geometric coefficient of variation percentage will be provided for the summary of C_{max}, C_{min} and AUCs.

The effect of the presence of ADAs on PK parameters of CD24Fc may be explored.

All PK parameters will be listed by patient.

8.5 Pharmacodynamic and Biological Outcome Analysis

Pharmacodynamic analyses and other correlative biological studies will be performed based on the PD Population. All analyses will be descriptive and no formal hypothesis testing will be conducted.

Pharmacodynamic variables (e.g., Siglec-10 expression) at scheduled time points and changes and percent changes from baseline will be summarized using descriptive statistics by treatment arm (CD24Fc dose level and regimen or placebo).

Additional exploratory biological outcome analyses including cellular immune subsets (including but not limited to T cells and dendritic cells), serum inflammatory markers and biomarkers of GVHD, and lipids will also be summarized using descriptive statistics.

PD results and biological outcome assessments over time may also be presented graphically.

All PD and biological outcome assessments will be listed by patient.

8.6 Interim Analysis

When the last patient dosed in Phase IIa reaches 100 days after HCT, key outcome data will be locked and the Phase IIa portion of the study will be unblinded. At this point, an interim report will be generated in order to define the RP2D. The RP2D will be defined at a dosage of CD24Fc equal to or lower than the MTD and will further consider PK and PD data. The Phase IIb dose will be the lowest dose with maximal effect to the extent that this can be determined from the proposed correlative studies.

Further, the Phase IIb portion of the study will contain an interim analysis for futility (lack of evidence of lower GVHD rate in Arm A versus Arm B), as well as for unacceptably greater rates of engraftment failure or mortality in Arm A versus Arm B. The interim analysis for futility will be done after 50% of the enrollment (90 patients) has been reached.

A final analysis comparing the GVHD rates in the two arms will be done after all patients are evaluable. At the interim analysis, the trial will be halted if the numbers of patients with Grade II-IV GVHD in the two arms differs by 2 or less, i.e. 10 patients in one arm and 12 in the other. This corresponds to a chi-squared test for comparing the GVHD rates in the two arms having a p-value of 0.5 or higher. The final analysis will require a p-value of 0.05 or less to define statistical significance and this value will not be adjusted for any interim analyses.

Table 3 contains the minimum number of patients with the indicated events in Phase IIb regardless of treatment assignment that would lead to the study being terminated for excessive graft failure, mortality before day 100, or excessive Grade III-IV acute GVHD. A graft failure rate exceeding 5% will be considered excessive. Similarly, based upon national benchmarks for survival outcomes reported from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry for myeloablative unrelated donor HCT evidence that the true day 100 mortality exceeds 25% would be considered excessive. Based on these assumptions, with 30 evaluable patients, the trial would be terminated if at least 4 patients experienced graft failure or if at least 11 patients died within 100 days of transplant from any cause. Additionally, for patients receiving the RP2D dose of CD24Fc, evidence of greater than a 35% incidence of Grade III-IV aGVHD at day 100 would be considered excessive and the trial would be halted.

Number of Evaluable Patients	Number of Patients with Graft Failure within 28 Days	Number of Patients Deceased within 100 Days	Number of Patients with Grade III-IV aGVHD within 100 Days
30	4	11	13
60	8	22	26
90	12	33	39

Table 3: Stopping Bounds for Engraftment Failure, Mortality, and acute GVHD

The stopping boundaries were determined from cumulative binomial probabilities. With a true graft failure rate of 0.05, the study would terminate early (see at least 4 of 30 patients with graft failure by Day 28, etc.) with a probability of 0.06, while with true graft failure rates of 0.10 and 0.15, the study would terminate early with probabilities of 0.352 and 0.678, respectively. Moreover, stopping early occurs most often after 30 patients, meaning that in settings of excessive graft failure, stopping will occur very quickly. Similarly, with a true Day 100 mortality rate of 25%, the study would terminate early (see at least 11 of 30 patients dying within 100 days of transplant, etc.) with probability 0.105, while with true mortality rates of 0.30 and 0.35, the study would terminate early with probabilities of 0.27 and 0.492, respectively.

With a true Day 100 Grade III-IV aGVHD rate of 35%, the study would terminate early (see at least 13 of 30 patients with Grades III-IV aGVHD within 100 days of transplant, etc.) with probability 0.220, while with true mortality rates of 0.26 and 0.35, the study would terminate early (see at least 11 of 30 patients dying within 100 days of transplant) with probabilities of 0.132 and 0.492, respectively.

9 GENERAL INFORMATION

9.1 Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.3 or higher. The Medpace standard operating procedures (Medpace documents GL-DS-02-S2.2 and GL-DS-03-S1.1) will be followed for the validation of all SAS programs and outputs.

9.2 Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document and will be finalized before database lock for the study.

10 CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

For the primary efficacy endpoint, cumulative incidence of Grade II-IV aGVHD, the protocol states non-relapse mortality (NRM) will be considered as a competing risk. However, all deaths will be considered as compelting risk in the statistical analysis.

11 REFERENCES

[1] Fine, Jason P., and Robert J. Gray. "A proportional hazards model for the subdistribution of a competing risk." Journal of the American statistical association 94.446 (1999): 496-509.