A Randomized Pragmatic Trial comparing Anti-Thymocyte Globulin (ATG) with ATG plus Post Transplant Cyclophosphamide (PTCy) for Prophylaxis against Acute and Chronic Graft Versus Host Disease (GVHD) in Matched Donor Hematopoietic Cell Transplants (HCT).

Sponsor

University of Manitoba

Study Co-Chairs:

Dr Kristjan Paulson
Dr. Irwin Walker

Study Number: CTTC XXXX

Summary of Protocol Versions

Version No.	Date	Comments
1.0	April 15, 2025	Draft #1

Contents

1. Protocol Signature Page

I have read the protocol, "A Randomized Pragmatic Trial comparing Anti-Thymocyte Globulin (ATG) to ATG plus Post Transplant Cyclophosphamide (PTCy) for Prophylaxis against Acute and Chronic Graft Versus Host Disease (GVHD) in Matched Donor Hematopoietic Cell Transplants (HCT)" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

2. Project Committees

2.1.Steering Committee

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2.2.Quality of Life Studies

TBD

2.3.Clinical Trials Management Company

TBD

2.4.Economic Studies

TBD

2.5.Data Safety and Monitoring Board

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3. Hypothesis and End-Points

3.1. Hypothesis

The combination of ATG and PTCy will result in superior chronic graft versus host disease, relapse free survival, when compared to current standard of care (either ATG or PTCy alone).

3.2.Primary End-Point

The primary endpoint is chronic graft versus host disease, relapse free survival (CGRFS)

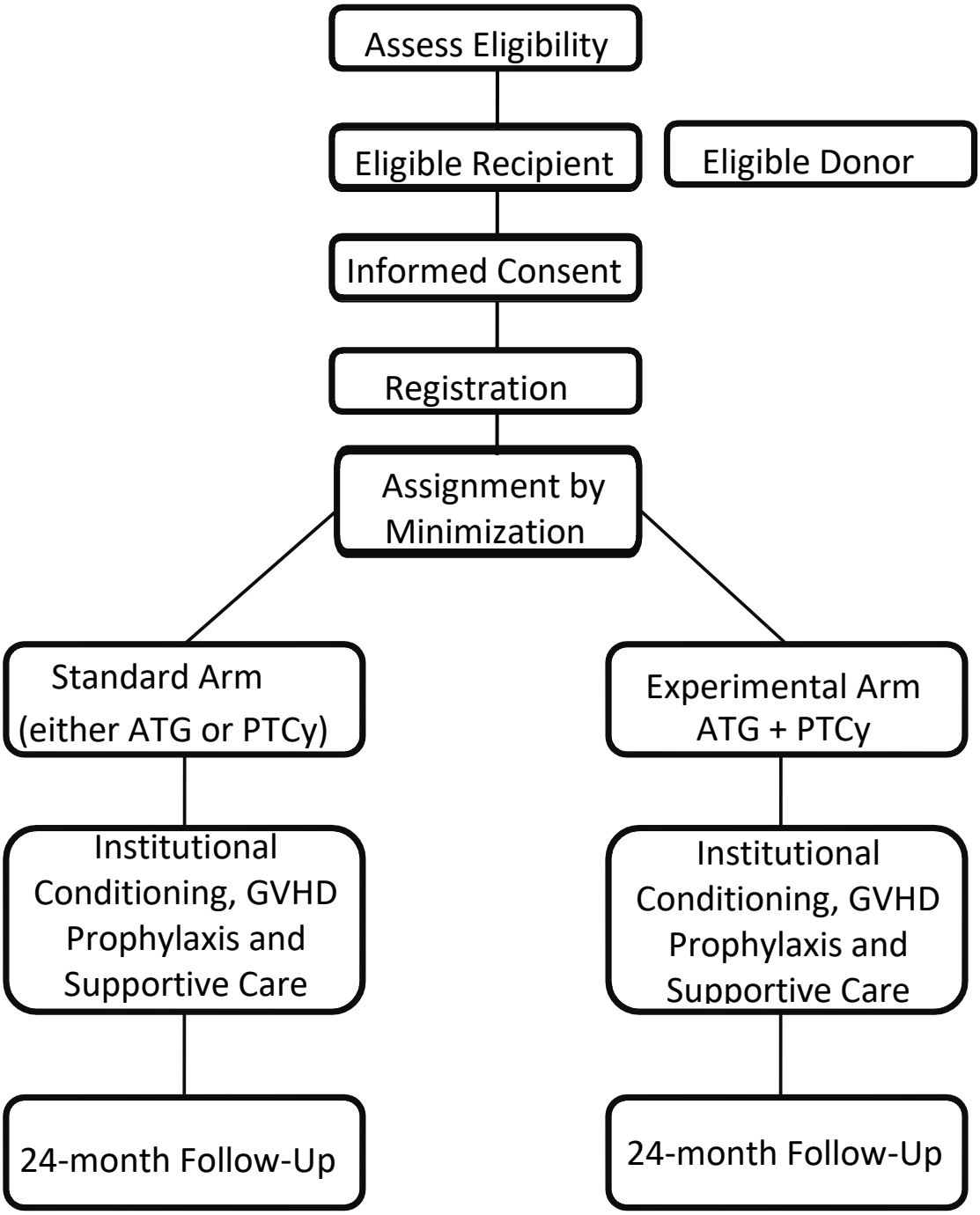
3.3. Secondary [Beneficial] End-Points

- Incidence of chronic graft versus host disease (cGVHD) according to NIH Consensus Guidelines[1]
- Graft versus host disease-, and relapse-, free survival (GRFS)
- Time to engraftment
- Incidence of acute GVHD
- Time to non-relapse mortality
- Time to all-cause mortality
- Time to relapse of hematologic malignancy
- Incidence of graft rejection or failure
- Incidence of serious infection
- Incidence of CMV activation
- Incidence of EBV activation and Post-Transplant Lymphoproliferative Disorder
- Incidence of specific organ grades (NIH) of chronic graft versus host disease[1]
- Number of months on immunosuppression at 12 months
- Doses of immunosuppressive therapy at 12 months
- Presence or absence of immunosuppressive therapy (IST) at 12 -months (Yes/No)
- Specific immunosuppressive medications and doses at 12 months
- The association between the augmented comorbidity/age index and the development and severity of aGVHD[2]
- The association between the augmented comorbidity/age index and the development and severity of cGVHD and post cGVHD diagnosis mortality[3]
- The relationship between distance from the specialized treatment center and different outcomes (postal codes are required).
- The association between baseline socio-demographic variables and overall survival (OS), transplant related mortality (TRM) and different patient reported outcomes
- PK characteristics of ATG
- Quality of Life
- Economic analysis
- Biomarker correlative GVHD studies

4. Project Summary

Title	A Randomized Trial comparing Anti-Thymocyte Globulin (ATG) or Post Transplant Cyclophosphamide (PTCy) with ATG plus PTCy Prophylaxis against Acute and Chronic Graft Versus Host Disease (aGVHD, cGVHD) in Matched Donor Hematopoietic Cell Transplants (HCT).
Hypothesis	The combination of ATG and PTCy will result in superior CGRFS compared to current standard of care (ATG or PTCy alone)
Design	Multicenter, Non-Blinded, Randomized Pragmatic Trial
Sponsor	University of Manitoba
Administrative Support	Cell Therapy and Transplantation Canada (CTTC)
Funding	TBD
Sample size	TBD
Primary endpoint	The primary endpoint is chronic graft versus host disease, relapse free survival (CGRFS)
Inclusion Criteria	Ages 16-70, transplant being performed for a malignant disease, blood progenitor cell grafts from MHC matched (8/8) family or unrelated donors (8/8 or 7/8), and either myeloablative or reduced intensity conditioning.
Exclusion Criteria	Poor condition (centre determined), active infection, HIV infection, T-cell antibody prophylaxis (anti-CD52), use of cord blood grafts or T-cell depleted grafts
Preparative Regimens	Myeloablative or Reduced Intensity protocol (to be declared at outset)
Supportive measures	Institutional practices. Quantitative EBV testing is strongly recommended.
Anti-Thymocyte Globulin	Thymoglobulin® 2 mg/kg to 4.5 mg/kg total dose
Cyclophosphamide PTCy	Cyclophosphamide 50 mg/kg IV on days +3 and +4, for those randomized.
Biomarker Correlative cGVHD Studies	TBD
PK Samples	TBD

5. Overview of Study Design



6. Background

Chronic graft versus host disease (cGVHD) is the most common and the most important long-term complication of bone marrow transplantation, affecting 40-50% of those receiving sibling grafts and 60-80% of those receiving unrelated donor grafts.[4,5] Chronic graft versus host disease is a multi-system disorder[6] that seriously compromises recipients' health[5,7], sometimes negating the disease-curing benefit of transplantation and predisposing patients to secondary cancer[8–10]. Ill-health due to cGVHD is often aggravated by the side effects of the immune suppressive treatments used in its treatment. In this proposal, we outline a study to test a promising intervention that we hypothesize will prevent in some patients, and ameliorate in others, the suffering caused by cGVHD.

ATG has been proposed as a standard of care[11] and all transplant centres in Canada use anti-thymocyte globulin (ATG) to prevent or to minimize the extent of cGVHD. It is used in all transplants with unrelated donors and myeloablative conditioning, and variably in other combinations of donor types and conditioning intensities (data available). Nevertheless, despite widespread use of ATG, cGVHD remains a problem, one fifth of patients still suffering from physical complications and decreased quality of life[5], consequences both of the disease and its treatments. cGVHD remains the most serious and frequent long-term complication of transplantation. An additional concern is the data suggesting that cGVHD is increasing in frequency[12]. Further improvements in the prevention of cGVHD are therefore needed.

Post-transplant cyclophosphamide (PTCy) has emerged as an effective graft-versus-host disease (GVHD) prophylaxis strategy in both haploidentical and matched donor hematopoietic cell transplantation (HCT). In the setting of matched related or unrelated donor transplantation, PTCy offers a simplified, cost-effective, and highly immunosuppressive platform that reduces the incidence of both acute and chronic GVHD without compromising relapse-free or overall survival. The BMT CTN 1703 study evaluated PTCy as a GVHD prophylaxis strategy compared to conventional calcineurin based GVHD prophylaxis, and found reduced rates of severe acute and chronic GVHD, without a difference in overall survival, treatment related mortality, or relapse rates.

There are two current ongoing studies comparing PTCy to ATG. The results of these studies are not yet available, but may become available over the duration of this study. At the current time, either agent would be considered a reasonable strategy.

6.1. Previous Studies

6.1.1. Anti-Thymocyte Globulin

As stated above, ATG is a standard preventive therapy of cGVHD. The Canadian Blood and Marrow Transplant Group demonstrated, in a randomized trial, a decrease in symptomatic NIH-defined chronic graft versus host disease by the addition of ATG to preparative regimens[13]. There were significant improvements in patient-centered endpoints, these being a decreased need for steroids and decreased symptoms attributed to cGVHD. There have now been five randomized controlled trials of anti-lymphocyte serums (ALS), either ATG or ATLG (anti-T cell

globulin Grafalon), all demonstrating absolute decreases in cGVHD by at least 20%. In four studies there were no adverse effects on non-relapse mortality, relapse and survival[13–18] while in the fifth study[19] the decrease in incidence of cGVHD was accompanied by an increase in both relapse and non-relapse mortality (NRM) and decreased survival. The increase in relapse rate and NRM has been postulated by the authors to have been due to an imbalance in ATG dose versus target recipient lymphocyte count resulting in overdosing with resultant inhibition of the graft versus leukemia effect.

Addressing the question of ALS dosing through published clinical data is sparse, inconclusive and conflicting. In a registry study from the European Society for Blood and Marrow Transplant (EBMT) of patients undergoing reduced intensity transplantation from matched sibling donors, Devillier et al found a statistically significantly improved graft versus host disease free and relapse free survival (GRFS) for those patients receiving less than 6 mg/kg of ATG compared to those receiving higher doses[20]. By contrast, Chang et al[21], in a randomized controlled trial in patients undergoing haplo-matched transplants using a non-PTCy containing preparative regimen, found that patients randomized to a dose of 10 mg/kg had a statistically significantly better likelihood of GRFS at five years than patients randomized to 6 mg/kg (multivariate analysis, HR 0.64, p=0.008). Bashir et al compared ATG doses of 4.5 mg/kg (the standard Canadian dose) with 7.5 mg/kg in a short-term Bayesian adaptably randomized trial of patients receiving reduced intensity conditioning and unrelated donor grafts. At 100 days there was no difference in a number of outcomes[22]. There is an overall need for further research on dose and scheduling of ALS to ensure that these agents are delivering their full potential. Use of ALS might then be extended from transplants involving myeloablative regimens and matched unrelated donors to other situations where present acceptance is less uniform.

The occurrence of an increased rate of leukemic relapse in the study of Soiffer et al[19] has highlighted leukemic relapse as a potential ill effect of ALS and together, with other evidence cited above, points to the need for the development of individual dosing protocols. This is not however an objective of our trial, and we will use a product (Thymoglobulin®) and dose not associated with relapse[13,16].

6.1.2. Post -Transplant Cyclophosphamide

Post-transplant cyclophosphamide (PTCy) has transformed GVHD prophylaxis paradigms in allogeneic hematopoietic cell transplantation (HCT). Initially developed for use in haploidentical transplantation, PTCy has more recently been applied to matched related and unrelated donor HCT, where it has demonstrated the ability to reduce both acute and chronic GVHD while maintaining disease control. Prospective studies have increasingly validated its efficacy in these settings. The BMT CTN 1703 trial—a multicenter, randomized phase III study—compared PTCy-based prophylaxis (cyclophosphamide, tacrolimus, and mycophenolate mofetil) to conventional tacrolimus/methotrexate in patients undergoing reduced-intensity conditioning with HLA-matched donors. The PTCy arm showed a significant reduction in moderate-to-severe chronic GVHD (4% vs. 35% at 1 year, p<0.001), while overall survival and relapse rates remained similar between groups (Kanakry et al., ASH 2023). Likewise, the Alliance A131811 trial, a phase II study using RIC and PTCy in patients receiving matched donor grafts, demonstrated low incidences of grade III-IV acute GVHD (7%) and chronic GVHD (12%) with a 1-year OS of 76% and progression-

free survival (PFS) of 71% (DeFilipp et al., JCO 2022). These findings underscore the potential of PTCy to provide effective GVHD control without compromising disease outcomes.

Beyond clinical efficacy, PTCy introduces meaningful advantages in terms of transplant logistics, toxicity reduction, and long-term survivorship. Its use simplifies GVHD prophylaxis by reducing reliance on prolonged calcineurin inhibitor therapy, thereby minimizing associated nephrotoxicity, hypertension, and opportunistic infections. Importantly, the lower incidence of chronic GVHD reduces the need for extended immunosuppression, improving patients' quality of life and functional independence post-transplant. Moreover, PTCy-based platforms align with evolving trends toward ambulatory or hybrid inpatient-outpatient transplant models, as they are associated with lower rates of severe complications requiring rehospitalization. Given these benefits and the accumulating body of prospective data supporting its use, there is strong rationale to further study and implement PTCy-based GVHD prophylaxis strategies in the matched donor setting—particularly in reduced-intensity conditioning regimens where balancing immune tolerance and disease control is critical.

6.1.3. Combination PTCy and ATG

The combination of antithymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) is an emerging strategy aimed at optimizing GVHD prophylaxis by leveraging the complementary mechanisms of in vivo T-cell depletion and post-transplant immune modulation. This dual approach seeks to further reduce the incidence of both acute and chronic GVHD while preserving graft-versus-leukemia effects and immune reconstitution. Preliminary data from prospective studies and institutional experiences suggest that ATG+PTCy is associated with low rates of severe GVHD and acceptable non-relapse mortality in both haploidentical and matched donor transplantation. For example, a prospective phase II trial by Salas et al. (BMT 2020) demonstrated that the combination of ATG (4.5 mg/kg) and PTCy in matched unrelated donor transplants resulted in grade III-IV acute GVHD rates of only 6%, chronic GVHD of 12%, and 1-year overall survival of 81%. Similarly, a French study by Blaise et al. (Haematologica 2021) reported favorable outcomes with ATG+PTCy in older AML patients undergoing RIC allo-HCT, noting particularly low chronic GVHD and promising survival. These studies support the hypothesis that combining ATG and PTCy may offer additive or synergistic GVHD protection without excessive immunosuppression. However, larger randomized trials are needed to clarify the optimal dosing, timing, and patient populations most likely to benefit from this approachh.

<<insert data from our pilot study – all I have right now is the ASH abstract data – but hopefully will have data from the 1 year f/u soon?>>

6.2. Conclusions

We believe that acceptance of a trial comparing ATG to ATG plus PTCy would be high, and accrual assured. It is, in our opinion, the next step from ongoing trials comparing ATG with PTCy, and one that is novel among studies involving these agents. If this trial results in superior chronic GVHD, relapse free survival, it would change practice internationally. The CTTC has experience

in conducting randomized trials, three national trials with international collaboration having been published.

7. Proposal

7.1.Overall Objectives and Strategy

We wish to demonstrate in a phase III pragmatic randomized controlled trial a decrease in the incidence of chronic graft versus host disease (cGVHD), from that achieved with ATG or PTCy alone, by the addition of cyclophosphamide following graft infusion (Post-Transplant Cyclophosphamide, PTCy).

A pragmatic trial design in which treating physicians first select their preferred standard GVHD prophylaxis—either ATG or PTCy—and patients are then randomized to receive either the physician-selected standard or the combination of ATG plus PTCy offers a highly feasible and clinically relevant approach to evaluating the additive benefit of dual prophylaxis. This design mirrors real-world practice by allowing physician discretion based on patient-, disease-, and center-specific factors, enhancing external validity and clinician engagement. Randomizing within the context of standard-of-care choices ensures clinical equipoise while enabling the trial to test whether the addition of the alternate agent (ATG to PTCy, or PTCy to ATG) improves GVHD prevention without excess toxicity. By using a pragmatic framework, the trial accommodates variation in transplant platforms and patient populations, increasing generalizability and potential for uptake. Furthermore, this design aligns with evolving clinical uncertainty and practice heterogeneity regarding the optimal prophylaxis strategy, making it both scientifically sound and operationally appealing in a multicenter setting.

A pragmatic trial design offers a powerful and appropriate approach for evaluating the clinical utility of combining antithymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) in allogeneic hematopoietic cell transplantation. In this study, treating physicians first select their preferred standard GVHD prophylaxis—either ATG or PTCy—based on institutional norms and patient-specific considerations. Patients are then randomized to receive either the physician-selected standard alone or the combination of ATG and PTCy. This approach mirrors real-world clinical practice and acknowledges the existing heterogeneity in prophylaxis strategies across transplant centers, thereby enhancing the external validity and applicability of study findings.

Compared to a traditional randomized controlled trial, this pragmatic design provides several key advantages. By embedding the trial within standard care pathways and allowing physician discretion in the selection of initial prophylaxis, the design increases feasibility, accelerates recruitment, and encourages center engagement. It also preserves clinical equipoise while focusing on a clinically relevant question: whether adding the alternate immunosuppressive agent improves outcomes without compromising safety. Importantly, this design accommodates variation in transplant platform (e.g., myeloablative vs. reduced-intensity conditioning), donor type, and institutional practices, thereby ensuring broad generalizability. In an era where both ATG and PTCy are considered acceptable standards for GVHD prevention, this trial structure allows for a nuanced evaluation of their combined use, while remaining closely aligned with how transplant decisions are made in practice.

We have completed a pilot trial of 80 patients, and these patients will be included in the final analysis, along with the pragmatic expansion cohort proposed here.

In accordance with our overall strategy, we propose the performance of a multicenter randomized pragmatic study comparing ATG with ATG plus PTCy. The basic elements are as follows:

- Patients would be randomized to receive either ATG or PTCy alone or ATG plus PTCy.
- The dose of ATG should range between 2 mg/kg to 4.5 mg/kg
- Patients would be undergoing a transplant for any malignant indication
- We would use peripheral blood stem cell grafts (HPC, Apheresis), the commonest method in general use, rather than bone marrow grafts. This would allow a higher acceptance, and closer relevance to current transplant practices. About 90% of sibling and unrelated donor transplants are performed using blood stem cells[40] despite evidence that a lower incidence of cGVHD is achieved with bone marrow grafts[41,42].
- Donors would be HLA-matched (no more than 1 HLA mismatch, using high resolution typing)
- Donors would be either related or unrelated.
- Preparative regimens can be either myeloablative or reduced intensity. The addition of cyclophosphamide can result in unacceptable toxicity to some myeloablative regimens[42] but is safe when combined with myeloablative regimens consisting of fludarabine and busulfan.[30,43]

7.2. The Principal Research Question

Is the combination of ATG and PTCy superior to current standard of care (either agent alone), in terms of the primary endpoint of chronic GVHD, relapse free survival?

8. Safety Considerations

The main risks to participants are those of the transplant procedure itself. The additional risks of participating in the study are those related to the intervention, the administration of Thymoglobulin®, an antiserum prepared in rabbits, and cyclophosphamide. Thymoglobulin® (ATG), though it is used by all bone marrow transplant centres in Canada, is indicated only for renal transplant acute rejection. Therefore, it is described in detail. Cyclophosphamide is a long- established drug that has been used widely by hematologists both for cancer treatment and preparation for transplantation.

8.1. Thymoglobulin® (ATG)

Most patients experience some symptoms during the first infusion, which are in almost all cases easily controlled by brief administrations of steroids, acetaminophen and diphenhydramine. Only rarely will patients have severe reactions resulting in discontinuation. Thymoglobulin® (ATG) is an immunosuppressive agent, so a risk of serious infection needs to be stated. A high risk of

infection appears to be related to doses higher than will be used in this study. In randomized studies by Bacigalupo the serious infections experienced with high doses were not replicated with the use of low doses, being no higher than controls[43]. In our study the dose of ATG will be even lower. Other studies support the conclusion that the risk of serious infection is low with currently used doses, possibly even lower than controls because of a decrease in GVHD and hence a decrease in immune deficiency[24–26]. An increased rate of relapse of leukemia has been reported in related donor transplants[24,25] but without an increase in overall mortality; there was no increased risk of relapse in two randomized trials using unrelated donors[22,27]. Post-transplant lymphoproliferative disorder (PTLD) has been an occasional complication of ATG, a phenomenon related to reactivation of EBV infection, itself a common occurrence following transplantation. Risk factors for the development of PTLD after transplantation include EBV seropositivity, T-cell depletion, administration of ATG, and post-transplant EBV activation[44,45]. Among randomized trials, PTLD occurrence was not reported in the trial of Bacigalupo[16,43] while in the trial of Finke there were six cases, five in the ATG arm, two of whom died, and one in the control arm[17,18]. Prevention of PTLD involves monitoring for activation by QPCR and pre-emptive administration of rituximab at the first sign of significant reactivation[46]. Risks of infection, leukemic relapse and PTLD all need to be stated in the consent form but the level of risk for each appears to be low.

8.1.1. Thymoglobulin® - Product Monograph

Thymoglobulin (Anti-thymocyte Globulin [Rabbit]) is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression and for induction in adult renal transplant recipients. It is not indicated by Health Canada for the treatment in patients receiving hematopoietic cell transplantation. The following text has been extracted selectively from the latest Thymoglobulin® Product Monograph dated 7th March, 2016. Refer to the current Product Monograph for full details.

Background

Thymoglobulin® (Anti-thymocyte globulin [rabbit]) is a purified, pasteurized, gamma immune globulin obtained by immunization of rabbits with human thymocytes. Thymoglobulin® contains a mixture primarily of antibodies to T cell antigens, but it is largely unknown which specificities mediate the alteration in immunoregulation.

Pharmacokinetics

The initial half-life has been found to be approximately 10 days and the terminal half-life approximately 30 days. Active Thymoglobulin® (that fraction which can bind to lymphocytes) has a similar initial half-life but has a much shorter terminal half-life than total or inactive Thymoglobulin®

Regulatory status

In Canada, Thymoglobulin® is labeled as indicated for use in patients having renal transplantation. Thymoglobulin® is not labeled for use in patients undergoing blood and marrow transplantation, but Health Canada has given approval for its use for patients in some research protocols. In some countries it is approved for use in various indications including prevention and treatment of rejection in solid organ transplants, prevention and treatment of graft-versus-host disease (GVHD) in HPCT, and treatment of aplastic anemia (AA).

Mode of action

The in vitro mechanism of action by which polyclonal anti-lymphocyte preparations suppress immune responses is not fully understood. Thymoglobulin® (Anti-thymocyte Globulin [Rabbit]) includes antibodies against T cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD 44, CD45, HLA-DR, HLA Class I heavy chains, and ß2 microglobulin. In vitro Thymoglobulin® (concentrations > 0.1 mg/mL) mediates T cell suppressive effects via inhibition of proliferative responses to several mitogens. In patients, T cell depletion is usually observed within a day from initiating Thymoglobulin® therapy. Thymoglobulin® has not been shown to be effective for treating antibody (humoral) mediated rejections.

The in vivo mechanism of action of Thymoglobulin®, is also not fully understood. The possible mechanisms by which Thymoglobulin® may induce immunosuppression in vivo include T cell clearance from the circulation, modulation of T cell activation, homing and cytotoxic activities, and T cell depletion. The latter may occur through a number of mechanisms including complement-dependent lysis in the intravascular space or the opsonization and subsequent phagocytosis by macrophages. Monitoring Thymoglobulin® therapy reveals that T cell depletion in peripheral blood persists for several days to several weeks following cessation of Thymoglobulin® therapy.

Contraindications

Thymoglobulin® is contraindicated in patients with hypersensitivity to rabbit proteins or to any product excipients, or in those with active acute or chronic infections, which would contraindicate any additional immunosuppression. In this protocol, “active infection” is included under Exclusion Criteria.

Serious warnings and precautions

Thymoglobulin® (Anti-thymocyte Globulin [Rabbit]) should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients.

Premedication with antipyretics, corticosteroids, and/or antihistamines may decrease both the incidence and severity of these (acute infusion-associated reactions, IARs) adverse reactions.

In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobulin® and consist of anaphylaxis or severe cytokine release syndrome (CRS). Very rarely, fatal anaphylaxis has been reported.

Emergency measures to treat anaphylaxis should be immediately available.

Thymoglobulin® should be used under strict medical supervision in a hospital setting, and patients should be carefully monitored during the infusions.
Rapid infusion rates have been associated with case reports consistent with CRS. In rare instances, severe CRS can be fatal.
Skin testing is not advised prior to Thymoglobulin® administration.

Adverse Reactions
The most frequent reported adverse events (more than 25% of patients) include: fever, chills, leukopenia, pain, headache, abdominal pain, diarrhea, hypertension, nausea, thrombocytopenia, peripheral edema, dyspnea, asthenia, hyperkalemia, tachycardia, and infection.
Infections (bacterial, fungal, viral, and protozoal), reactivation of infection (particularly cytomegalovirus [CMV]), and sepsis have been reported after Thymoglobulin® administration.
Use of immunosuppressive agents, including Thymoglobulin®, may increase the incidence of malignancies, including lymphoma or post-transplant lymphoproliferative disease (PTLD).

8.2.Cyclophosphamide

Cyclophosphamide is not labeled for use as a preparative agent in bone marrow transplantation, but it is included in standard regimens.

8.2.1. Cyclophosphamide (FDA Information at Drugs.com)

Description
Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is bio-transformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5% to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of Cyclophosphamide.

Indications
Cyclophosphamide is indicated for the treatment of a number (specified) of malignancies and for biopsy proven “minimal change” nephrotic syndrome in children.

Warnings
These include carcinogenesis, mutagenesis, Impairment of Fertility, hemorrhagic cystitis, cardiac dysfunction, susceptibility to infection and, rarely, anaphylaxis.

Adverse effects
In addition to those listed under **Warnings** they include nausea, vomiting, hemorrhagic colitis, mucosal ulceration, alopecia, and interstitial pneumonitis.

9. Eligibility and Study Entry

Only recipients are screened. Donors are not screened for the purposes of this study; they are screened to meet the requirements of medical care, institutional guidelines and applicable government regulations. There are no study interventions that impact donors. The choice of the donor also is outside the procedures of this study other than to satisfy recipient eligibility criteria. Donor age and sex will be collected at this time for the recipient minimization/randomization procedure. Donor cytomegalovirus serostatus will also be collected at screening. Recipients will be screened for study eligibility prior to the start of conditioning. Inclusion and Exclusion criteria must be met as outlined in Sections 9.1 and 9.2 before the recipient can be randomized.

9.1. Inclusion Criteria

1. The participant is aged between 16 and 70
2. The participant has a malignant disease that is the primary indication for transplant
3. The participant will receive a blood progenitor cell graft ("HPC, Apheresis")
4. The participant has a related or unrelated donor, who is either fully MHC matched with the recipient at HLA-A, B, C and DRB1 or is 1-antigen or 1–allele mismatched at these loci.
5. The participant meets the transplant centre's criteria for transplantation, using either myeloablative or non-myeloablative or reduced intensity conditioning[1].
6. The participant has good performance status (Karnofsky ≥60%)
7. The participant is able to understand and sign the informed consent form
8. Ability and willingness to comply with study procedures and schedule, in the Investigator's opinion.

[1] Centres must provide their standard criteria for transplantation and their standard operating procedures (SOP) regarding the decision-making process. This documentation must be submitted to Ozmosis Research and filed in the site trial files. A copy of this source documentation must be accessible for monitoring and auditing purposes. Applicable source documentation must be available at the site for monitor verification.

9.2. Exclusion Criteria

1. The participant is HIV antibody positive
2. The participant has a hypersensitivity to rabbit proteins or Thymoglobulin® pharmaceutical excipients, glycine or mannitol
3. The participant has active or chronic infection (i.e. infection requiring oral or IV therapy)
4. The participant (if female and of childbearing potential) is pregnant or breast-feeding at the time of enrollment
5. The participant (if female and of childbearing potential) does not agree to use an adequate contraceptive method from the time of enrollment until a minimum of one year following transplant[2]
6. The participant (if male and fertile) does not agree to use an adequate contraceptive method from the time of enrollment until a minimum of one year following transplant[2]

9.3. Donor Selection

The donor must be either fully MHC matched at HLA-A, B, C, and DRB1 loci or 1-antigen or 1–allele mismatched at either HLA-A, B, C or DRB1 loci (i.e. either a 7/8 or 8/8 match, considering only HLA-A, -B, -C and DRB1).

Donors will be evaluated according to one or both of FACT Standard and Health Canada regulations, or other national regulations. Donor choice is according to these regulations and standard institutional practice.

Donors should be chosen for likelihoods of best survival and lowest risk of GVHD, these being complete HLA mismatch, non-multiparous females, and young donor age.

9.4. Informed Consent

The participant and/or the participant's legally authorized guardian must acknowledge in writing that consent to become a study participant has been obtained.

Participants 16-18 Years of Age

Sites should follow the requirements of their local REB with respect to the consent process for participants aged 16-18.

Delayed Transplant

If a transplant is delayed more than 1 month, consent must be obtained again in writing (using the current REB approved consent form).

[2] Adequate methods of birth control include: Abstinence, previous tubal ligation, vasectomy, oral injectable or implantable contraceptives, condoms, foam, or IUD.

9.5. Registration and Randomization

All patients will be screened by one of the principal investigators or sub-investigators prior to entry into this study. An explanation of the study and discussion of the expected side effects and full disclosure of the "informed consent" document will take place. Eligible and consented patients will be registered into the study.

Registration will be done through Ozmosis Research Inc. Sites will assign each patient with a patient ID number which should be used on all documentation and correspondence.

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. Access to the eCRFs will only be granted once this has been received. All sites should call Ozmosis Research Inc. Clinical Trials Manager/Specialist (CTM/CTS) at the number listed on the front page to verify study availability.

No patient can receive protocol treatment until eligibility has been confirmed and the Patient Enrollment Fax has been submitted to Ozmosis Research Inc. All eligibility criteria must be met at the time of enrollment. There will be no exceptions. Any questions should be addressed with Ozmosis Research Inc. prior to enrollment.

The Patient Enrollment Fax must be completed and signed by the investigator prior to enrollment. There are 3 sections to the Patient Enrollment Fax:

- SCREENING (top section): This section is completed by the site and should be faxed to 416-598-4382, or e-mailed to ozmclinical@ozmosisresearch.ca at the time of screening.

- ENROLLMENT/RANDOMIZATION (middle section): This section is completed by the site at the time of enrollment. The site will fax the signed and completed Patient Enrollment Fax to Ozmosis Research Inc. at 416-598-4382, or e-mail to ozmclinical@ozmosisresearch.ca.

- CONFIRMATION OF ENROLLMENT (bottom section): Ozmosis will return the form with the Confirmation of Enrollment section completed along with the study arm to which the patient has been randomized. Only after this has been received by the site can the patient receive study drug(s).

All eligible patients registered into the study will be entered into a patient registration log at Ozmosis Research Inc. The following information will be required at the time of registration:

- Trial code
- Treatment centre and investigator
- Patient's initials and/or date of birth

Note: It is the responsibility of the investigator in charge to satisfy him or herself that the patient is indeed eligible before requesting registration.

Randomization must be done no earlier than 14 calendar days before the planned date of transplant and no later than 1 day prior to the start of conditioning. The Study Chair may allow

randomization to be done prior to 14 calendar days before the planned date of transplant, but the site must submit a written request to Ozmosis Research, and the early randomization must be approved in writing by a Study Chair.

9.5.1. Participants Who Become Ineligible after Randomization

It may occur that a participant's status changes unexpectedly following randomization, such that they are no longer deemed fit to continue with transplant. In most cases this would be due to relapse of leukemia or active infection. When this occurs, the course of action is at the clinical discretion of the site transplant team. The site may choose to: (1) Delay transplant until patient is deemed fit to continue; (2) Cancel the transplant altogether (see Section 9.5.3); or (3) Proceed with the transplant even though the patient's status has changed, if deemed safe to continue by the treating investigator; in case (3) the patient will be off study but will be followed (See Section 9.5.4). **Sites should always keep in mind that it is best to randomize a participant as close to the start of the preparative regimen as possible so that this situation can be avoided.**

As the study progresses, the study steering committee and DSMC will carefully monitor the percentage of participants who are randomized, but then become ineligible. (Participants who become ineligible will not be replaced.)

9.5.2. Delayed Transplant

If a scheduled transplant is postponed following randomization, the participant can remain on study as long as the inclusion and exclusion criteria are met within 21 calendar days before the rescheduled transplant date. A revised Patient Enrollment Fax should be submitted prior to the start of the preparative regimen and no sooner than 21 days before the rescheduled transplant date. Please see section 9.4 for requirements regarding participant consent in this situation.

9.5.3. Cancelled Transplant

In this case, the participant is no longer eligible; however, because the study design is "intention to treat", the participant's survival status will be followed for up to two years from the date of randomization.

9.5.4. Transplant Proceeds (Inclusion/Exclusion Criteria Not Met)

In this case, participants randomized to receive PTCy should NOT receive the study drug (PTCy). A change in eligibility status may mean there is greater risk involved with receiving PTCy. An experimental drug or procedure should not be administered unless all eligibility criteria are met.

Regardless of what arm the participant has been assigned to, all study related laboratory procedures should still be followed as per protocol. All study data should be collected as per protocol. All questionnaires should be administered according to the schedule specified in the protocol. All assessments for GVHD should be completed according to the protocol.

10. Treatment Plan

10.1. Study Arms

The recipient will be randomized (minimized) to one of two study arms; see section 10.2 for overview.

- **Arm A (Standard):** Participants will receive a designated preparative regimen (either myeloablative or RIC) as outlined in Section 10.3 with ATG (Thymoglobulin®) or PTCy alone

- **Arm B (Experimental):** Participants will receive a designated preparative regimen (either myeloablative or RIC) as outlined in 10.3 with ATG (Thymoglobulin ®) plus PTCy.

This is not a blinded study. Participants randomized to Arm A (standard arm) will NOT receive a placebo.

10.2. Overview

<table>
<tr><th></th><th>Day
–2</th><th>Day
–1</th><th>Day
0</th><th>Day
1</th><th>Day
2</th><th>Day
3</th><th>Day
4</th></tr>
<tr><td>Standard Arm</td><td>0.5</td><td>2</td><td rowspan="3">Graft Infusion</td><td>2</td><td></td><td></td><td></td></tr>
<tr><td>ATG only</td><td>ATG mg/kg</td><td>ATG mg/kg</td><td>ATG mg/kg</td><td></td><td></td><td></td></tr>
<tr><td>Experimental Arm</td><td>0.5</td><td>2</td><td>2</td><td></td><td>50</td><td>50</td></tr>
<tr><td>ATG plus PTCy</td><td>ATG mg/kg</td><td>ATG mg/kg</td><td>ATG mg/kg</td><td></td><td>PTCy mg/kg</td><td>PTCy mg/kg</td></tr>
</table>

10.3. Preparative Regimens

The addition of PTCy may increase the toxicity of standard regimens. Validated regimens should be chosen for patients randomized to receive both ATG and PTCy. Validated regimens containing PTCy have not included methotrexate or mycophenolate, and these agents may not be necessary. The following regimens that include PTCy have been published and are recommended for this trial. Other regimens must be discussed with the Study Chair. Centres must declare and undertake to use one myeloablative and one reduced intensity regimen throughout the trial. The recommended regimens are outlined below.

Note: Myeloablative regimens are those with busulfan >8 mg/kg; melphalan >140 mg/m^2; TBI >500cGy single dose or >800cGy fractionated. A suggested definition of non-myeloablative (or RIC) is busulfan ≤8 mg/kg; melphalan ≤140 mg/m^2; TBI ≤500cGy single dose or ≤800cGy fractionated[47].

10.3.1. Myeloablative Regimen:

Busulfan and Fludarabine[30]

Notes:

i. The inclusion of methotrexate in a myeloablative regimen may not be safe if combined with PTCy. However, a myeloablative regimen of FluBu4 plus PTCy without methotrexate has been shown to be both safe and effective, and the steering committee recommends its use[30].
ii. Methotrexate or other agent can be used when randomization is to ATG alone (Arm A).
iii. There is no experience with the use of PTCy with the myeloablative cyclophosphamide/total body radiation (CyTBI) regimen.

10.3.2. Reduced Intensity Regimen:

Busulfan and Fludarabine ("FluBu2") with or without low dose TBI[33,48–50]

Note: Even with reduced intensity regimens the addition of methotrexate or mycophenolate to PTCy may not be safe, and is likely not necessary as evidenced by experience with PTCy for haplo-identical donor transplants.

Alemtuzumab is not permitted.

10.4. Source of Progenitor Cells

For all patients this will be blood stem cells (HPC, Apheresis). Neither T-cell depletion of the graft nor the use of cord blood is permitted.

10.5. Administration of Thymoglobulin® (ATG)

As a pragmatic RCT, ranges of acceptable doses of ATG will be considered eligible. The pilot study, and previous Canadian RCT used a dose of 4.5 mg/kg over three days, and will be considered the maximum dose. At the discretion of the centre, doses as low as 2 mg/kg will be considered. Investigators should try to be consistent in their internal practices from patient to patient.

Details of administration (pre-medications, infusion rate, etc.) can be according to local centre practice. Appendix 3 has a set of suggested orders.

Important:

- Although Thymoglobulin® and progenitor cells are compatible, they should not be infused at the same time, for reasons of determining the cause of reactions.

- Progenitor cells should be infused as soon as possible after arrival from the donor centre as delays can affect the outcome, particularly with respect to progenitor cells obtained from the marrow.

10.6. Administration of PTCy

Patients randomized to Arm B will receive 50 mg/kg/day IV (ideal body weight) cyclophosphamide on days 3 and 4, with the first dose starting 62 to 72 hours after the start of allograft infusion. Cyclophosphamide is dosed by ideal body weight according to Baltimore practice (Fuchs, E, unpublished study, personal communication). Mesna is administered in four doses each on days 3 and 4 at a total daily dose of 80% of the cyclophosphamide dose.

10.7. Calcineurin Inhibitors

Blood stem cell grafts will be used in this study and a calcineurin inhibitor added on the day following PTCy as in the cited studies. A study of PTCy without the addition of a calcineurin inhibitor has been published but this utilized bone marrow grafts.[27]

10.8. Graft versus Host Disease Prophylaxis

Cyclosporine or tacrolimus will be used in conjunction with both myeloablative or non-myeloablative regimens, in both study arms. **Methotrexate and Mycophenolate are NOT used for those patients randomized to ATG plus PTCy (Arm B)**. See section 10.3.

Cyclosporine or tacrolimus will be administered orally or intravenously according to standard practice at the site. The starting dose will be according to institutional practice. After initiation of cyclosporine or tacrolimus, the dose will be adjusted to maintain adequate trough levels according to standard institutional practice.

Tapering of cyclosporine (or tacrolimus) in the absence of significant acute GHVD will be according to institutional practice. **In each institution it is essential that the same tapering schedule be followed for patients on both arms of the study.** If a participant develops acute graft versus host disease prior to or during the tapering of cyclosporine or tacrolimus, further adjustments of the dose and decisions about the initiation and speed of tapering will be according to institutional practice.

10.9. Graft versus Host Disease Diagnosis

Acute Graft versus host disease will be diagnosed and graded according to Harris et al[51] (Appendix 5). Chronic Graft Versus Host Disease will be diagnosed and staged according to NIH Consensus criteria[1] (one “diagnostic” manifestation or one “typical” manifestation plus other supportive evidence).

10.10. Acute Graft versus Host Disease Treatment

Grades 2-4 acute GVHD, which requires treatment, will be treated with corticosteroids, either intravenous methylprednisolone or oral prednisone according to institutional practice.

If the acute GVHD does not respond or progresses during the initial treatment with corticosteroids, the dose of corticosteroids may be increased and/or additional agents may be used according to local institutional practice. All treatments for acute GVHD will be recorded.

10.11. Chronic Graft versus Host Disease Treatment

Chronic GVHD which requires systemic treatment, will initially be treated according to institutional practice. Biopsy of involved organs or tissues is strongly recommended but not required.

If the chronic GVHD does not improve with initial therapy consisting of prednisone with or without cyclosporine or tacrolimus, the dose of corticosteroids may be increased, or additional agents may be used according to local institutional practice.

NOTE:

If the onset of cGVHD requires the initiation or continuation of immune-suppression beyond routine institutional practice, it is strongly recommended that attempts be made to taper immunosuppressive therapy between days 180 and 365 and the reason for failure be recorded.

All therapies and dosages for chronic GVHD will need to be recorded at 12 months as an important secondary end-point is the dosage of immunosuppressive drugs at 12 months.

10.12. Supportive Care

In general, supportive care measures are administered according to standard practices at each institution.

10.12.1. Veno-occlusive Disease Prophylaxis

The use of agents for veno-occlusive disease prophylaxis will be according to local institutional practice.

10.12.2. Antibacterial Prophylaxis During the Neutropenic Period

Prophylactic antibiotics, if used, will be administered according to local institutional practice.
Herpes Simplex Virus (HSV) Prophylaxis will be according to local institutional practice.

10.12.3. Antifungal Prophylaxis

Antifungal prophylaxis will be according to local institutional practice. Antifungal prophylaxis (e.g. fluconazole 400 mg po/IV qd) is recommended when corticosteroids (equivalent of prednisone 1 mg/kg/day or greater) are used to treat graft versus host disease. Posaconazole should be instituted at the onset of GVHD, either acute or chronic.

10.12.4. Management of Cytomegalovirus (CMV)

Neither ganciclovir nor foscarnet will be used for primary prophylaxis. Letermovir, if approved and incorporated into institutional protocol, may be used for prophylaxis. The general approach to the prevention of CMV disease will be based on monitoring followed by pre-emptive treatment of CMV infection (viremia). The frequency and duration of CMV monitoring will be according to local institutional practice, weekly from day 0 to day 120, thereafter when clinically indicated. Treatment of CMV infection or CMV disease will be initiated according to local institutional practice.

10.12.5. Management of Epstein Barr Virus (EBV)

There has been a lack of randomized trials to guide management. The most recent and authoritative guide is that from the Sixth European Conference on Infections in Leukemia[46] (ECIL-6).

Activation of latent EBV is common after allogeneic transplantation[52–54], occurring in one-third of those receiving T-replete grafts and two-thirds of T-cell depleted grafts, but rarely results in clinical consequences. Occasionally, activation of EBV leads to the development of the serious complication of Post-Transplant Lymphoproliferative Disorder (PTLD, LPD). In the study by Finke[17] there were five cases of PTLD among 103 participants randomized to ATLG and one case among 98 controls. Anti-lymphocyte globulin was thus shown to be an important risk factor. However, in the randomized studies of Kroger[14] and of Soiffer[19] PTLD was not seen.

A**uthorities are recommending screening of at-risk populations.**

Screening

All enrolled patients are to be routinely screened for EBV activation by PCR or, preferably, by QPCR, according to local resources, weekly from day 0 to day 120, then thereafter only in selected cases depending on the degree of immunosuppression, the severity of graft versus host disease, and existing low level activation[46]. If sites have already established a standard approach to EBV monitoring that is different from this recommended approach, the site will be permitted to continue to follow their standard approach; however, a copy of the standard approach must be submitted to Ozmosis Research for the Study Chair to review. A copy will be kept in the study files and site files.

Indications for Treatment

As there are no laboratory or standards published, and because methodologies, reported units (eg G Equ/mL vs copies/mL) and probably sensitivities, vary, threshold levels at which treatment should be initiated cannot be stated. Physicians are advised to take into account knowledge about local methodology. (The local laboratory director and solid organ transplant physicians should be consulted.) The reported level, rising titres, and/or clinical features all need to be

taken into account; there should be a low threshold for imaging, and biopsy of enlarged lymph node should be considered where feasible when making a decision regarding treatment. It is strongly recommended that plasma or serum based assays utilized should allow for the reporting of 1,000 copies/mL at a minimum.

Treatment

Treatment of activation will be either pre-emptive or therapeutic depending on the clinical situation. The recommended treatment is rituximab 375 mg/m^2, to be repeated weekly as necessary till resolution, clinically and by PCR. In the event of resistance, infusion of EBV-specific T-cells are recommended. These are not generally available; inquiries regarding current availability can be directed to Atara Biotherapeutics Inc (www.atarabio.com; Willis Navarro wnavarro@atarabio.com)

Reporting

Cases of both significant EBV reactivation (i.e. requiring treatment) and PTLD are to be reported.

10.12.6. Pneumocystis Jirovecii Prophylaxis

All participants are to receive pneumocystis jirovecii prophylaxis. This will be according to institutional practice.

10.12.7. Blood Product Support

Irradiated red blood cell and platelet transfusions will be used. Transfusion thresholds will be according to local institutional practice.

10.12.8. Administration of Growth Factors Following Graft Infusion

Neutrophil recovery is a secondary study endpoint and growth factors such as filgrastim should not be routinely used following the infusion of bone marrow or peripheral blood. However, if a participant develops primary engraftment failure (absolute neutrophil count of less than 0.5 x 10^9/L on Day +28), filgrastim may be administered and an additional infusion of donor cells with or without additional conditioning. Filgrastim may be used at any time in a participant's course if considered necessary by the attending physician. This is to be recorded in the eCRF.

10.12.9. Prophylactic Intravenous Gammaglobulin

It is recommended that prophylactic intravenous gammaglobulin not be routinely administered post-transplantation. As immunoglobulin levels are to be recorded in the follow-up period, administration of gammaglobulin needs to be reported in the eCRF.

11. Evaluation of Outcomes

11.1. Primary Endpoint

The primary endpoint is feasibility, a compound endpoint requiring recruitment of 80 patients, within budget, and without a 10% decrease in overall survival in the experimental arm compared to the standard arm at day 100 for all patients.

11.2. Secondary Endpoints

11.2.1. Time to Engraftment (Hematological Recovery)

Time to neutrophil and platelet engraftment will be analyzed for ALL participants (myeloablative and RIC) and separately for patients receiving myeloablative HPCT.

- Time to Neutrophil Recovery/Engraftment: This is defined as the time from transplant (Day 0) to the first day of achieving an absolute neutrophil count of 0.5 x 10^9/L or greater for 3 consecutive measurements on different days.
- Time to Platelet Recovery/Engraftment: This is defined as the time from transplant (Day 0) to the first day of achieving a platelet count of greater than 20x10^9/L for 3 consecutive measurements on different days without requiring platelet transfusions in the previous 7 days.
- Primary Graft Failure: This is defined as the absence of neutrophil recovery (absolute neutrophil count less than 0.5 x 10^9/L) in patients surviving until at least Day +28 post-transplant

11.2.2. The Incidence of Acute GVHD

The incidence of acute GVHD up to Day 100 will be compared. The incidence of acute GVHD at Day +100 and Months 6, 12 and 24 will also be compared. Acute GVHD will be graded according to the Harris Criteria (Appendix 5).

11.2.3. The Incidence of Chronic GVHD (Regardless of Need for Treatment) According to NIH Consensus Guidelines[1]

This is based on the presence or absence of cGVHD of all grades and also specifically "mild", "moderate" and "severe" at Day +100, and at 6, 12 and 24-months post-transplant, according to the NIH diagnostic criteria[10] (Appendix 6).

11.2.4. Time to Non-relapse Mortality

This is the time to death in the absence of disease relapse. In cases of death where there has been disease relapse death is classed as relapse mortality even when the immediate cause of death may be from infection or organ failure.

11.2.5. Time to All-cause Mortality

This is the time to death from any cause.

11.2.6. Time to Relapse of Hematologic Malignancy

This is the time from transplant to relapse of disease. It is the persistence or recurrence of the original malignancy based on standard pathology testing for myeloid malignancies and progression or recurrence of the original malignancy based on standard pathology or radiology testing for lymphoid malignancies. The day of relapse is the day of the first diagnostic test

demonstrating relapse. Evidence of minimal residual disease by molecular testing in the absence of other data will not be considered relapse.

11.2.7. Graft Rejection or Failure (Yes vs. No)

This is a loss of previous hematological recovery (see above) as indicated by a neutrophil count $<0.5 \times 10^9$/L and/or platelet count $<20 \times 10^9$/L of unknown cause (e.g. excluding medications, sepsis, leukemic relapse etc.) and in the presence of marrow hypoplasia involving the affected cell line(s).

11.2.8. Serious Infection

ATG is a risk factor for infection. All infections regardless of grade will be recorded in the eCRFs (and reported as SAEs according to sections 14.1.2. and 14.1.8). In addition, the following information will also be recorded in the eCRF: Type of organism (bacterial, viral, fungal or protozoal) (suspected or documented); Activation of CMV requiring treatment (section 10.12.4); Activation of EBV either with symptoms or requiring treatment (section 10.12.5); Primary organ involved.

11.2.9. CMV and/or EBV Activation

This is the presence of a positive test (CMV antigen, PCR or QPCR) for CMV and/or EBV viremia. A positive test is one that represents an indication for treatment, the threshold being defined by each institution. Positive tests at levels below treatment indications are not to be reported as "activation". CMV and EBV screening will be according to local institutional practice. (See Sections 10.12.4 and 10.12.5)

11.2.10. Organ Specific and Global Severity Ratings of cGVHD (NIH)

These are individual organ system and global ratings according to NIH Consensus Guidelines as assessed at Day + 100, and at 6, 12, and 24 months.

11.2.11. Quality of Life and Socio-demographics

Quality of Life (QOL) will be assessed using 7 validated questionnaires. The socio-demographic questionnaire will be completed once at time of enrollment in the study. Time estimated to complete the questionnaires is 20-30 minutes.

The ProMIS tool: PROMIS is a validated set of instruments, commonly used to measure quality of life, and has been accepted as the standard tool for measuring quality of life in patients after transplant.[55,56] A variety of ProMIS instruments are available, of varying length and with focus on different subsets of physical and mental health. We will use the ProMIS 29 (a series of 29 specific questions on physical, mental, and social well being), and the ProMIS Global tool to generate a summary score.

EQ-5D: The EQ-5D measures five items, mobility, self-care, usual activities, pain/discomfort and anxiety/depression with three response levels per item. The EQ-5D has been specifically designed to complement other quality of life measurements. This instrument is also useful with respect to economic evaluation.[57]

The Social Activity Log (SAL): This is a measure of the social activities outside of routine daily responsibilities. The SAL is intended to capture activities of patients with people other than those with whom the patient lives.[58]

ENRICHD Social Support Instrument (ESSI): the ESSI is a 7 item scale which measures how the patients perceive the social support, both physical and emotional they receive from caregivers which makes it different from the SAL which measures objective participation in social activities. This scale was originally developed for use with patients with cardiac disease.[59,59]

Patient Health Questionnaire-9 (PHQ-9): PHQ-9 is a measure of depression comprising the nine diagnostic symptom criteria of the DSM-IV for Major Depressive Disorder (MDD). Patients will rate the frequency of the 9 symptoms over the past 2 weeks on a 4-point Likert scale (0 = not at all, 1 several days, 2 = more than half of the days, and 3 = nearly every day). The total score of the PHQ-9 ranged from 0 to 27, with higher scores indicating greater severity of depressive symptoms. Unlike other depression screening tools, the PHQ-9 is relatively a short tool which makes it easily applicable.[60]

Cancer and Treatment Distress Scale (CTXD): The CTXD was created and validated specifically among recipients of HCT. It comprises a 25-item inventory of distress developing secondary to cancer management. Groups of items include uncertainty, family, finances, health burden, appearance and sexuality, and managing the medical system. Items are rated for severity of distress/worry they have caused in the past week.[61]

Chronic GVHD Symptom Scale: The 30 item cGVHD symptom scale measures degree of bother of cGVHD manifestations in skin, energy, lung, nutrition, psychological, eye and mouth. Responses are captured on a five-point Likert scale (“no symptoms, or not bothered at all”, “slightly bothered,” “moderately bothered,” “bothered quite a bit,” or “extremely bothered”). Scores for each domain are converted to a 0-100 scale where higher scores indicating more bother. In a previous study, although the SF-36 and FACT-BMT were sensitive to changes in overall health, only the chronic GVHD symptom scale was sensitive to changes in patient-perceived chronic GVHD severity.[62]

Socio-Demographic Questionnaire: This questionnaire will be completed only at the time of enrollment. It will take 5 minutes to complete. It will collect data on race, gross income, highest level of education, marital and current work status. Recent studies have demonstrated an association between these variables with patient reported outcomes and survival outcomes of HCT recipients. Hamilton el at showed that among 421 HCT recipients diagnosed with cGVHD, higher income ($P = .004$), ability to work ($P < .001$), and having a partner ($P = .021$) were

associated with better mean Lee chronic GVHD symptom scores. Higher income (P = .048), educational level (P = .044), and ability to work (P < .001) also were significantly associated with better QOL and improved activity.[63] In a similar analysis of outcomes of 6207 unrelated-donor myeloablative HCT recipients transplanted between 1995–2004 for acute or chronic leukemia or myelodysplastic syndrome, lower income level was significantly associated with worse OS and higher TRM.[64]

Administration of QOL and Socio-demographic Questionnaires:

Questionnaires will be completed during the study visit or by a telephone interview. A variety of options for questionnaire completion are being allowed in order to maximize the questionnaire completion rate. Although patients are followed closely after progenitor cell transplant at the transplant centers for the first 100 days post-transplant, many are from out-of-town and eventually return to their home community. The option to conduct the questionnaires by telephone interview is expected to increase the rate of questionnaire completion.

With respect to the "Health Care Questionnaire-9 (PHQ-9)", source documents and clinic databases may be used to obtain the data if the patient is too ill to participate (or cannot recall all the required details). This is the only questionnaire in which sources other than the participant can be used to obtain the answers to the questions.

Questionnaire administrator: This is the person who explains to the participant how to complete the questionnaire and/or who conducts the questionnaire interview. A study coordinator, research nurse, clinic nurse and/or administrative staff member with the transplant centers can act as a questionnaire administrator. The physician caring for the participant should not act as the questionnaire administrator. The questionnaire administrator should conduct a brief check of the completed questionnaires in order to ensure questions have not been missed accidentally or answered incorrectly. (The participant should not be questioned in detail regarding answers or missing answers, but instructions can be repeated.) The questionnaire administrator should indicate the method of questionnaire completion that was utilized at the bottom of the form.

Participants will complete their initial QOL and sociodemographic questionnaires prior to beginning their conditioning regimen. It is anticipated that missing data will be minimal due to the variety of questionnaire completion methods that will be allowed.

Assessments will be conducted +/- 30 days for the post-transplant assessments. Relapsed patients are eligible for ongoing QOL assessments (as appropriate depending on their situation). Participants can be enrolled in the study even if they are not able to complete all study questionnaires due to language issues. Study participants will be asked to complete all questionnaires for which there is a validated version in the applicable language.

11.3. Economic Analysis

A cost-effectiveness analysis will be conducted alongside this pilot randomized trial to determine the incremental cost and outcome of ATG compared with ATG plus post-transplant cyclophosphamide in patients with hematopoietic cell transplants. A cost utility analysis framework will be used, and will be conducted adhering to recommended Canadian practices in economic evaluation[65]. Outcomes include cost, quality adjusted life years (QALYs), and cost per QALY gained. The perspective will be the Canadian healthcare payer, and the time horizon will be over a lifetime to account for all relevant clinical costs and consequences of treatment. A discount rate of 5% will be applied to both costs and effects. All costs will be reported in Canadian dollars inflated to 2020 costs using the consumer price index for healthcare goods in Canada - https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000601.

As not all outcomes required for the economic analysis will be fully captured within this pilot randomized trial, a cost-effectiveness model will be created, informed by the pilot randomized controlled trial, literature sources, and expert opinion as required. A decision model will be created using Data Pro (TreeAge software). A Markov model will be used to account for health states that are relevant to this disease and its treatment, based on the clinical outcomes used in the trial. Proposed health states include presence or absence of chronic graft-versus-host disease, relapse free survival, as well as the occurrence of complications related treatment including opportunistic infections. The model will be constructed with input from the clinical team, and face validity, technical accuracy, and internal validity of the model will be assessed[66,67].

Effectiveness of the two treatment strategies will be modelled by modifying transition probabilities to various health states, again informed by the pilot randomized controlled trial as well as anticipated outcomes that may be seen in the definitive study in sensitivity analysis. While quality of life is being captured within the pilot study, quality-of-life for specific health states may not be available from the trial given small number of events. As such a literature review will be done to determine utility-based quality of life in patients with chronic graft versus host disease[68], those with relapsed disease, as well as those with opportunistic infections.

Resource utilization for each of the health states will be informed by literature review and expert opinion. This will include healthcare resource utilization associated with the health states of interest including chronic graft-versus-host disease, relapse free survival, as well as opportunistic infections. The modelling exercise to estimate resource utilization in this pilot project will assist in informing a micro-costing study in the definitive trial that may allow trial-based estimates of resource utilization and costs that occur in each comparator arm.[69]

Uncertainty in parameter estimates that are used in the model will be fully interrogated by conducting one way into a sensitivity analysis on all variables in the model over a plausible range

informed by the pilot study, data sources used to inform the model, as well as expert opinion. Probabilistic sensitivity analysis and cost-effectiveness acceptability curves will also be created[65].

11.4. Biomarker Correlative cGvHD studies

TBD

12. Criteria for Removal from Protocol Therapy and Off Study Criteria

All participants will be followed from registration until death or at least 24 months from the day of transplant. Participants will be considered off study if their transplant is delayed for any reason and it is not possible to proceed to transplant; the participant withdraws consent from the study; the participant is unable to tolerate the study treatment; the participant is unable to complete all required study procedures; the sponsor decides to stop the study; a regulatory authority withdraws permission for the study to continue.

13. Statistical Considerations

13.1. Sample Size

<< Insert section from Tony>>

13.2. Stratification/Minimization

We will seek to achieve a balanced allocation of treatments over prognostic factors for cGVHD. Known *a priori* prognostic factors are participant age (16-30, 31-50, > 50); female donor for male recipient[76]; degree of tissue type matching (full match; one antigen/allele mismatch); choice of donor (related vs. unrelated); donor age (< 30, 31-50, >50); disease type (acute myeloblastic leukemia, myelodysplastic syndrome) [75–77]. In addition to balancing for the above variables that are risk factors for cGVHD it will also be necessary to balance those variables that will influence relapse and mortality: Disease Risk Index, and type of preparative regimen (myeloablative vs. non-myeloablative)[78] and co-morbidity by augmented HCT-CI[79,80]. Finally, it will be necessary to balance by centre to allow for differences in clinical practice.

Given the moderate size of the trial and the numerous strata that would result from our stated aim of achieving balance upfront for the above-mentioned factors it would be impractical to use stratified randomization; furthermore, potentially large overall imbalances in treatment allocation could occur, defeating the purpose of stratified randomization. Instead patients will be allocated to the treatment groups based on a method of dynamic allocation referred to as minimization[81]. As the name implies the method attempts to minimize the differences between treatment groups

in terms of these factors. Unlike stratified randomization, where each strata represents a combination of each of the factors identified, minimization tries to achieve overall balance by trying to achieve balance within each individual factor, not every combination of factors. This alternative approach to balancing factors between treatment groups allows the possibility of balancing over more factors. As demonstrated in a simulation study minimization can incorporate 10 to 20 factors without difficulty.

Using minimization in our study the first patient will have their treatment randomly allocated (akin to flipping a fair coin). For each subsequent patient we will determine which treatment would lead to better balance between the groups with respect to the baseline prognostic variables identified a priori. Each patient is then randomized using a weighting in favour of the treatment that would minimize the imbalance. A weighting of 4 to 1 will be used in this study. That is, there will be a probability of 0.8 of receiving the treatment that minimizes the imbalance. Thus, the study statistician (T. Panzarella) will prepare two randomization lists using a computer random number generator before the study begins: 1) a simple randomization list where both treatments occur equally often; this list will only be used when the two treatments have equal sums for the levels of the baseline prognostic factors; and 2) a list in which the treatment with the smaller total of patient levels occurs with probability 0.8 while the other treatment occurs with probability 0.2. Allocation will occur centrally by Ozmosis Research (see Section 9.5). This approach ensures that the process of treatment allocation will be concealed from staff at the participant's centre.

13.3. Analysis

Feasibility measures that comprise the primary endpoint will be summarized using descriptive statistics; for categorical data using frequencies, percentages and proportions, and for continuous data using either the mean and standard deviation or the median and inter-quartile range, as appropriate.

Secondary endpoints that are defined as the time to an event (e.g. CRFS) will be described over time by either the Kaplan-Meier estimate, if no competing events are applicable, or the cumulative incidence method, if competing events are present. Comparisons of time to failure endpoints will be conducted using either the log rank test or Cox's proportional hazards model if the endpoint is free of competing risks, or Gray's test and the Fine and Gray model in the context of competing risks. Endpoints describing an incidence will be compared between treatment groups using Fisher's exact test. Dose comparisons of immunosuppressive agents will be performed using either the Student's t- test or its non-parametric equivalent, Mann-Whitney test, if assumptions of the t-test do not hold.

As these comparisons are not based on a priori considerations of statistical power the p-values and confidence intervals generated will be considered exploratory. Effect sizes will be considered more for their clinical importance than their statistical significance.

PK parameters for ATG will be computed by standard methods of analysis. The primary PK parameter that will be determined is AUC, however, other parameters may also be evaluated.

13.4. Handling of Missing Data

Missing values represent a potential source of bias in a clinical trial. As stated in the ICH[3] guideline "STATISTICAL PRINCIPLES FOR CLINICAL TRIALS" (guideline E9), "Unfortunately, no universally applicable methods of handling missing values can be recommended". Multiple imputation is a strategy for handling missing data that attempts to incorporate missing data uncertainty, and so will be utilized in this study.

13.5. Loss to Follow-up

In similar multicenter randomized studies[13,82], the CBMTG centres have been able to demonstrate a high level of compliance. Based on that study, we anticipate 100% compliance both with the preparative regimen and with administration of the GVHD prophylaxis. These are the primary areas in which compliance problems might be expected. Since BMT is a medically intensive intervention and requires follow-up by the BMT center frequently within the first 1-2 years post-BMT, the possibility of loss to follow-up is very low. This was not an issue in the above mentioned CBMTG studies, in which only 1 of 228 patients was lost to follow-up. In this study, we anticipate that we will lose ≤5% of patients to follow-up.

14. Adverse Events – Definitions and Reporting

14.1. Definitions, Attribution and Documentation

14.1.1. Definition of an Adverse Event

The ICH[4] definition of an adverse event is: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

For the purposes of this study, ATG + PTCy (group B) is the "experimental" treatment on this trial.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur

[3] International Conference on Harmonization, www.ich.org.

[4] International Conference on Harmonization, www.ich.org.

after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator should be reported as an adverse event.

14.1.2. Definition of a Serious Adverse Event (SAE)

The ICH definition of a Serious Adverse Event is any untoward medical occurrence that either:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (or admission to ICU)
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly/birth defect.

- Is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours.

  OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study or for prophylactic insertion of a gastric feeding tube).

  OR

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgement. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 28 days after the final administration of the study drug, and any death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported.

All serious adverse events (SAE) must be recorded on eCRFs. In addition, all serious adverse events are subject to reporting using the SAE form and must be submitted to Ozmosis Research Inc. (refer to section 14.1.8)

Pregnancies occurring in study subjects/sexual partner(s) will be treated procedurally as SAEs. Pregnancies occurring in study subjects or their sexual partner(s) after study drug treatment should be reported separately on Pregnancy Report Form and the subject has to discontinue the trial medication.

Symptomatic and/or treated EBV/CMV reactivation will be considered an SAE (as this is a potentially life-threatening adverse event).

Asymptomatic CMV and EBV reactivations that require treatment are classed as SAEs for this trial. Laboratory determined reactivations that do not require treatment are not SAEs for this trial.

14.1.3. Definition of an Unexpected Adverse Reaction

According to the ICH Guidelines: An unexpected adverse reaction is one in which the nature or severity is not consistent with the applicable product information (e.g. Investigator's Brochure).

For the purposes of this study, an unexpected adverse reaction is one that would not be expected during or following the administration of ATG.

14.1.4. Attribution of Causality and Definitions

For all AEs, relationship to study drug will be reported on the appropriate AE eCRF page. The PI must judge whether the study drug(s) (ATG and/or PTCy) caused or contributed to the AE in which case it is considered to be an ADR, and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and study drug administration;
- There is a plausible biological mechanism through which study drug may have caused or contributed to the AE;

Not related (unlikely related or unrelated): It is highly unlikely or impossible that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

- another cause of the AE is evident and most plausible;
- the temporal sequence is inconsistent between the onset of the AE and study drug administration; a causal relationship is considered biologically implausible;

14.1.5. Adverse Event Monitoring and Source Documentation

All participants are to be assessed for adverse events according to local institutional practice following standard HPCT except where additional assessment is required per protocol. Source documentation of adverse events should be according to institutional practice, except in cases where additional information is required to be documented by the protocol.

Donors are individuals who are remote from this study, donating at distant sites, mostly from beyond Canada. In providing a progenitor cell product they will be undergoing procedures that will not differ from those that they would have undergone had the participant not been enrolled in this research study. Donor safety is protected by adherence to the regulations or standards of their country of origin (e.g. FACT, Health Canada, Federal Drug Authority, JACIE etc). Transplant centres involved in this study are responsible for monitoring safety of recipients, and of family donors only.

14.1.6. Adverse Event Reporting

Adverse Events will be reported in the eCRFs on both study arms. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

Adverse event reporting should begin on the day the preparative regimen commences and all adverse events must be recorded up until Day 30 post-transplant. After Day 30, only SAEs thought to be related to protocol treatment will be recorded.

14.1.7. Grading of Adverse Events

The NCI Common Toxicity Criteria (CTCAE) Version 5.0 will be used to grade adverse events that participants experience. A copy of version 5.0 of the CTCAE can be downloaded from the CTEP home page [http://ctep.info.nih.gov]. Additionally, if assistance is needed the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

14.1.8. Reporting Serious Adverse Events (SAEs)

All serious adverse events (SAE) defined as per ICH guidelines and other adverse events must be recorded on case report forms. In addition, all serious adverse events must be reported by using the

SAE form and must be submitted to Ozmosis Research Inc. SAEs should be reported within 24 hours of becoming aware of the event.

Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by fax or e-mail to:

Ozmosis Research Inc.
Phone: 416-634-8300
Fax: 416-598-4382
E-mail: ozmsafety@ozmosisresearch.ca

The initial information should always contain:
- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

The time period for reporting of SAEs is from the start of the preparative regimen to 30 days post-transplant. Additionally, any SAEs that occur subsequent to the SAE reporting period (30 days after transplant) that the Investigator assesses as at least possibly related to the protocol treatment (i.e., the relationship cannot be ruled out) should also be reported. The exception is participants who relapse prior to the end of the study follow-up period. Please see next paragraph for instructions regarding participants who relapse.

Participants who relapse:

Once a participant has relapsed, it is not necessary to report SAEs to Ozmosis Research, except in the case of death. If a participant with disease relapse dies prior to the end of the study follow-up period, then an SAE report must be submitted to Ozmosis Research.

Important Note Regarding EBV:

14.1.9. Reporting of Participant Deaths

All participant deaths must be reported to Ozmosis Research within 24 hours of the site's knowledge of the death using the SAE report form. This requirement is applicable from the start of the preparative regimen up to end of study follow-up (24 months or death, whichever occurs first).

Death is considered a separate SAE from the SAE that precedes the death (i.e. the SAE leading to the death). A separate SAE form must be completed.

14.1.10. Reporting of Secondary Malignancies

If a participant develops a secondary malignancy at any time during study follow-up, this must be reported on the SAE Form and transmitted to Ozmosis Research within 24 hours from the time the transplant centre becomes aware (for review by the Study Chair). Post-Transplant Lymphoproliferative Disorder is included as a second malignancy.

14.1.11. Pregnancies (Sites)

Pregnancies occurring during study follow-up (24 months) must be reported by the investigational staff within 1 working day of their knowledge of the event using the Pregnancy Notification Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Pregnancies in partners of male participants included in the study must also be reported.

14.2. Reporting of Serious Adverse Events to Health Canada

Ozmosis Research Inc. will provide expedited reports of SAEs to Health Canada according to applicable guidelines and regulations (including the 7-day notification for death and life-threatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

14.3. Reporting of SAEs to Research Ethics Boards (REBs)

Ozmosis Research Inc. will forward reports of all SAEs to the study chairs. Ozmosis Research Inc. will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to Sanofi-Genzyme. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to REBs must be kept on file at Ozmosis Research Inc.

Documentation can be any of the following:

- letter from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a centre should also be reported to local REBs

14.4. Reporting of SAEs to Sanofi-Genzyme

Ozmosis Research Inc. will forward to Sanofi-Genzyme copies of all documentation sent to regulatory authorities.

[Sanofi Group Entity Pharmacovigilance Contacts: Reports by email will be sent to: CL-CPV-Receipt@sanofi.com; Fax: 33 (1) 60 49 70 70 (for backup only)]

Ozmosis Research will be responsible for communicating with Genzyme regarding follow-up information related to SAEs. If Genzyme requires further information regarding an SAE they will notify the Ozmosis who will follow up with sites. Genzyme will not contact sites directly.

14.5. Review of SAEs by the Medical Monitor and Statistician

The Study Chair (or delegate as agreed upon by the Steering Committee) will act as the Medical Monitor for the study. The role of the medical monitor is to:

- Review all individual SAEs that are reported
- Visit sites as necessary to review data related to the safety of the participants enrolled
- Communicate with the DSMC regarding any SAEs which may necessitate a change to the protocol and/or consent form
- Communicate with site personnel, regulatory agencies, REB's, etc as necessary

The Medical Monitor will not review summarized SAE data (unless asked to do so by the DSMC). The statistician will review summarized SAE data every 6 months (or more frequently if necessary).

15. Data Safety Monitoring Committee

During the course of the study, an independent Data Safety Monitoring Committee (DSMC) will review efficacy and safety data. The DSMC will convene every 6 months. Additional meetings/conferences calls will be conducted as necessary. The DSMC will use their experience in reviewing the data submitted to them which will be done every 6 months. Specific concerns of the investigators will be addressed, these being overall mortality, frequency of hospitalization and incidences of post-transplant lymphoproliferative disorder in the experimental arm (PTCy) which are sufficiently adverse compared to those in the control arm.

All SAEs received by Ozmosis Research will be submitted to the DSMB as follows: Unexpected SAE's and/or SAEs felt to be significant with respect to participant safety will be submitted, via email, to the DSMB within 48 hours of receipt by Ozmosis Research. All other SAE's will be submitted to the DSMB as part of the routine 6-month review process.

16. Records and Reporting

16.1. Documentation of Subject's Participation

A statement acknowledging the participation of a subject in this clinical trial must be documented in the subject's medical records along with the signed ICF.

16.2. Regulatory Requirements

The following documents are required:

<u>For participating Canadian centres:</u>

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to Ozmosis Research Inc. prior to any drug shipment.
- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research Inc. to the sites.
- Ozmosis Research Inc. will submit via fax or e-mail to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

16.3. Data Management

The data will be collected in eCRFs using a Medidata database.

Please see the study specific eCRF Completion Guidelines which have been provided to your site by Ozmosis Research Inc. The timelines and details for completion of eCRFs are included in these guidelines.

16.4. Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her initials. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, tests will be made available to Ozmosis Research Inc., McMaster University, the study sponsor, the Canadian HPFB/TPD, the REB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

16.5. Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the REB. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

16.6. Registration of the Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

16.7. Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research Inc. or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all source documents and detailed records of treatment disposition. The Investigator should retain these records for 25 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

17. Regulatory Ethics Compliance

17.1. Investigator Responsibilities

The investigator at each site is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH Guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

18. Quality Assurance and Quality Control

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

18.1. On Site Monitoring and Auditing

Ozmosis Research Inc. will organize on-site monitoring of this study to be conducted as per the monitoring plan.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate. Other audits may be conducted by the study sponsor, Ozmosis Research Inc., or Genzyme.

19. Administrative Procedures

19.1. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor. All protocol amendments will be approved by the REB prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

19.2. Protocol Deviations and Violations

All violations or deviations are to be reported to the site's REB (as per REB guidelines). All REB correspondence is to be forwarded to Ozmosis Research. The site must notify Ozmosis Research and/or sponsor immediately of any protocol violations.

Ozmosis Research Inc. is responsible for reporting of critical deviations to Sanofi-Genzyme, defined as a deviation from applicable regulations in the conduct of studies, the nature, significance or persistence of which may adversely affect the rights, safety, well-being of subjects

or patients, the quality or integrity of data. Examples include: serious deviations from obligations of the Institution or investigators under its responsibility; non-adherence to principles governing the rights of subjects (such as adequate ethical review and informed consent or respect of data protection principles); allegation or confirmation of fraudulent practices involving intentional hidden, fabricated or falsely altered information (scientific misconduct).

19.3. Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

20. Legal Aspects

20.1. Publication Policies and Disclosure of Data

For publications, the first author will be the Principal Investigator of the study. Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the Principal Investigator.

Appendix 1 – Karnofsky Functional Scale

Karnofsky Functional Scale

- 100% - normal, no complaints, no signs of disease
- 90% - capable of normal activity, few symptoms or signs of disease
- 80% - normal activity with some difficulty, some symptoms or signs
- 70% - caring for self, not capable of normal activity or work
- 60% - requiring some help, can take care of most personal requirements
- 50% - requires help often, requires frequent medical care
- 40% - disabled, requires special care and help
- 30% - severely disabled, hospital admission indicated but no risk of death
- 20% - very ill, urgently requiring admission, requires supportive measures or treatment
- 10% - moribund, rapidly progressive fatal disease processes
- 0% - death

Appendix 2 – Schedules of Events

Schedule of Events (Day -37 to Engraftment)

Study Procedures	Day -37 to start of prep regimen	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 3	Day 4	Day 6	Day 7	Day 11+[22]
		+/- 5 calendar day window for procedures													
Consent[1]	X														
Randomization[2]	X														
History and Physical	X														
Height, Weight and BMI	X														
Karnofsky[3]	X														
CBC, diff	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Augmented HCT-CI[4]	X														
Disease Risk Index[5]	X														
Chemistry[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Group	X														
Antibody Screen	X														
Infectious Disease Markers[7]	X														
EBV by PCR or QPCR[8]	X								X	Weekly until Day 120					
CMV by PCR or QPCR[9]	X								X	Weekly until Day 120					
Beta-HCG (females)[10]	X														
MUGA/Echocardiogram[11]	X														
Pulmonary Evaluation[12]	X														
Renal Evaluation[13]	X														
BM Biopsy[14]	X														
Preparative Regimen		According to regimen													
HCT[15]									X						
ATG - all patients							X	X		X					
Cyclophosphamide (PTCy) – Arm B only[16]											X	X			
Assessment of Acute GVHD[23]															
Bearman Scale (Mucositis)[17]										X	X	X	X		X
Adverse Events			Collected from the start of preparative regimen until 30 days post-transplant[21]												
Concomitant Medications	X		Continuous until 30 days post-transplant												
Hospitalizations		Record number and durations of all hospitalizations													
Biomarker samples[18]	X														
PK samples[19]							X	X	X	X	X			X	X[19]
Questionnaires[20]	X														
Donor CMV serostatus	X														

Laboratory testing and clinical assessment continue daily until engraftment then according to centre practice and clinical indications.

[1] Consent must be signed within 2 months of the start of preparative regimen (day -67) and prior to completion of questionnaires and randomization (minimization); however, the remaining screening evaluations are standard of care. Results dated prior to date of signing of consent can be used for screening purposes, as long as the evaluations are completed within the time period specified in the protocol (Day --37 up to start of preparative regimen unless otherwise specified in the footnotes below)
[2] Randomization to occur no earlier than 14 days prior to planned date of HCT and no later than 1 day prior to start of the preparative regimen. Minimization factors as per section 13.2 of the protocol will be collected at the time of randomization.
[3] See Appendix 1: Karnofsky Functional Score
[4] See Appendix 7: Augmented Co-Morbidity Scale
[5] See Appendix 8: Disease Risk Index.
[6] Chemistry includes: creatinine, total bilirubin, AST, ALT, ALP, albumin and ferritin. Ferritin is estimated once only, during day -37 to start of preparative regimen.
[7] Infectious disease markers: CMV antibody, Hepatitis B surface antigen, total antibody to Hepatitis B core antigen, hepatitis C antibody, HIV-1 and HIV-2 antibodies, HTLV-1 and HTLV-2 antibodies and VDRL or equivalent testing for syphilis; West Nile virus testing (according to local institutional practice); EB virus antibodies (VCA-IgG and Epstein Barr nuclear antigen (EBNA)); testing for HSV antibody is optional. Testing for infectious disease markers must be done within 30 days prior to transplant.
[8] EBV by PCR or QPCR weekly until day 120 then as clinically indicated.
[9] CMV by PCR or QPCR weekly until day 120 then as clinically indicated.
[10] Beta-HCG is to be done in females of child bearing potential within 30 days prior to transplant.
[11] Cardiac evaluation with assessment of ejection fraction by radionucleotide scan or echocardiogram.
[12] Pulmonary evaluation with spirometry (FEV1) and diffusing capacity (DLCO) corrected for anemia.
[13] Renal evaluation with 24-hour urine for measured creatinine clearance OR serum calculated GFR by CKD-epi
[14] BM Biopsy within 30 days of transplant, to include morphology and, if required after diagnostic assessment, cytogenetic and molecular analysis. BM Biopsy is to be collected at suspected relapse of acute myeloblastic leukemia or progression of myelodysplatic syndrome.
[15] The following hematopoietic stem cell product information will be collected: total volume of product, CD34 count and total cell count. The infusion start and end time will also be required.
[16] First dose of cyclophosphamide to be given 62 to 72 hours after the start of allograft infusion
[17] See Appendix 4: Stomatitis, Bearman Scale. The maximum grade on the Mucositis Bearman Scale needs to be completed.
[18] See Section 11.4 Biomarker Correlative GVHD Studies. For subjects who provide consent for the correlative portion of the study.
[19] PK samples to be collected 15 +/- 5 minutes before and after the start/end of each ATG infusion and 15 +/- 10 minutes before and 30 +/- 10 minutes after graft infusions, and on Days 3, 7, 14 and 28. Refer to Section 11.5 for details. For subjects who provide consent for the PK sample portion of the study.
[20] See Section 11.2.12. Socio-demographic Questionnaire; ProMIS 29; ProMIS Global; EQ-5D; Social Activity Log (SAL); ENRICHD Social Support Instrument (ESSI); Patient Health Questionnaire-9 (PHQ-9); Cancer and Treatment Distress Scale (CTXD); Chronic GVHD Symptom Scale. The window for completing questionnaires is +/- 30 calendar days.

[21] Any SAEs that occur subsequent to the SAE reporting period (30 days after transplant) that the Investigator assesses as at least possibly related to the protocol treatment (i.e., the relationship cannot be ruled out) should be reported.
[22] Patients will continue study assessments, as per the discretion of the investigator, until engraftment. Date of neutrophil engraftment and date of platelet engraftment will be recorded in the database (as per definitions in section 11.2.1).
[23] See Schedule of Events (Engraftment to Month 24) footnote 1.

Appendix 2 - Schedule of Events (Engraftment to Month 24)

Study Procedures	Day 20	Day 28	Day 30	Day 50	Day 60	Day 75	Day 100	Mo 6	Mo 12	Mo 18	Mo 24	Onset of cGvHD or aGvHD
	+/- 5 calendar day window for procedures											
CBC and differential			X	X			X					X
Absolute CD4 and CD8							X	X	X	X	X	
IgG, IgA and IgM							X	X	X	X	X	
Assessment of acute GVHD[1]												X
CGVHD Assess Forms[2]							X	X	X	X	X	X
Karnofsky[3]							X	X	X	X	X	
Weight							X	X	X	X	X	
EBV by PCR or QPCR[4]		Weekly until day 120										
CMV by PCR or QPCR[5]		Weekly until day 120										
Report IS Therapy[6]							X	X	X	X	X	
Hospitalizations		Record number and durations of all hospitalizations										
Concomitant Medications		Continuous until 30 days post-transplant										
Adverse Events		Collected from the start of preparative regimen until 30 days post-transplant[12]										
Biomarker samples[7]					X		X	X[9]	X[9]			X[10]
PK sample[13]		X										
Questionnaires												
QOL tools[8]							X	X	X	X	X	
BM Biopsy[11]		See footnote										

Note: At time of Diagnosis of CGVHD complete Diagnosis and Scoring Forms, and take Biomarker Sample

[1] See Appendix 6: aGVHD and cGVHD Assessment and Reporting Form. For aGVHD, participants will be assessed daily while in hospital and then according to local institutional practice for the presence and severity of acute GVHD, but reports need only be submitted as follow: The aGVHD box (only) needs to be completed at time of diagnosis of aGVHD and on days 30, 50, 100, and in the event of "late" aGVHD (after day 100).

[2] See Appendix 6: aGVHD and cGVHD Assessment and Reporting Form. For cGVHD, there are two sections, a Diagnosis form to document clinical manifestations at diagnosis (only), and a Scoring form. The diagnosis form should be filled out only once, at the time of diagnosis of cGVHD. The Scoring form should

be filled in at the time of diagnosis of cGVHD (if applicable), and at 100 days, and at 6, 12, 18 and 24 months post-transplant (even if no cGVHD), or until relapse or death (whichever occurs first).

[3] See Appendix 1: Karnofsky Functional Scale.

[4] EBV PCR or QPCR weekly until day 120 then as clinically indicated.

[5] CMV PCR or QPCR weekly until day 120 then as clinically indicated.

[6] IS = immunosuppressive therapy drugs and doses, including steroids, calcineurin inhibitor, mycophenolate or other, including photopheresis.

[7] See Section 11.4: Biomarker Correlative GVHD Studies. For subjects who provide consent for the correlative portion of the study.

[8] See Section 11.2.12. EQ-5D; Social Activity Log (SAL); ENRICHD Social Support Instrument (ESSI); Patient Health Questionnaire-9 (PHQ-9); Cancer and Treatment Distress Scale (CTXD); ProMIS 29; ProMIS Global; Chronic GVHD Symptom Scale. The window for completing questionnaires is +/- 30 calendar days.

[9] Collect this sample only if no late aGVHD or cGVHD has developed previously.

[10] Collect within 2 weeks of cGVHD onset, if cGVHD occurs, then take no more samples after this time.

[11] BM Biopsy is to be collected at suspected relapse of acute myeloblastic leukemia or progression of myelodysplatic syndrome.

[12] Any SAEs that occur subsequent to the SAE reporting period (30 days after transplant) that the Investigator assesses as at least possibly related to the protocol treatment (i.e., the relationship cannot be ruled out) should be reported.

[13] PK sample to be collected on Day 28. Refer to Section 11.5. For subjects who provide consent for the PK sample portion of the study.

Appendix 3 – Suggested ATG Orders

Suggested Orders for Administration of Thymoglobulin® [5]

1. Rabbit anti-human immunoglobulin, (Thymoglobulin®, ATG) 0.5 mg/kg (actual body weight) =_____mg, IVPB (IV Piggy Back) over 4-6 hours on _____(day -2).
   Provided in 500 mL NS. Pre-medication required, please see below.

2. Rabbit anti-human immunoglobulin, (Thymoglobulin®, ATG) 2.0 mg/kg (actual body weight) =_____mg, IVPB (IV Piggy Back) over 4-6 hours on _____ and _____(days -1 and Day +1[14]).
   Provided in 500 mL NS. Pre-medication required, please see below.

3. Premedications for each infusion of Thymoglobulin®
   a. acetaminophen 1000 mg PO DAILY pre-ATG infusion
   b. diphenhydramine 50 mg IVPB DAILY pre-ATG infusion
   c. methylprednisolone sodium succinate 40 mg IVPB q12h x 6 doses; give first dose pre-ATG infusion

4. Meperidine 25-50 mg IVPB q4h PRN for rigors with ATG-infusion

[5] Courtesy of Dr James Russell, Director, Alberta Blood & Marrow Transplant Program, Tom Baker Cancer Centre.
Please Note: The final dose of Thymoglobulin is given on day 0 at the Tom Baker Cancer Centre; however, in the CBMTG 0801 trial, the final dose will be given on day +1.

Appendix 4 – Stomatitis, Bearman Scale

Regimen Related Toxicity: Bearman Toxicity Scale

Criteria Stomatitis (Mucositis)

	Grade I	Grade II	Grade III
Stomatitis **Toxicity**	● Pain and/or ulceration not requiring a continuous IV narcotic drug	● Pain and/or ulceration requiring a continuous IV narcotic (morphine drip)	● Severe ulceration and/or mucositis requiring preventative intubation ● Severe ulceration – resulting in documented aspiration pneumonia with or without intubation

Appendix 5 – Acute GVHD Staging and Grading

Acute Graft Versus Host Disease Staging and Grading

GVHD Target Organ Staging (Harris et al., Biol Blood Marrow Transplant. 2016 Jan;22(1):4-10. doi: 10.1016/j.bbmt.2015.09.001. Epub 2015 Sep 16.)

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 34 umol/L	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day
1	Maculopapular rash <25% BSA	34 –51 umol/L	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day
2	Maculopapular rash 25 – 50% BSA	52-103 umol/L	-	Adult: 1000–1500 ml/day or 5–7 episodes/day
3	Maculopapular rash > 50% BSA	104–257 umol/L	-	Adult: >1500 ml/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>257 umol/L	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based upon most severe target organ involvement):

- **Grade 0: No stage 1–4 of any organ**
- **Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement**
- **Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI**
- **Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI**
- **Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI**

Appendix 6 - AGVHD and CGVHD Assessment and Reporting Form

Following pages

This Section has forms for Reporting GVHD Status and for Scoring of CGVHD by NIH criteria

Chronic GVHD Diagnosis Form

Participant Code: 099-|__|__|__|-|__|__|__|

Circle Time Point (circle one):

Day 100 Month 6 Month 12 Month 24 Diagnosis of Chronic GVHD

WHEN IN DOUBT REFER TO Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389,401.e1.

Actual Date of Assessment: |__|__| |__|__|__| |__|__|__|__|
DD MMM YYYY

Tick box for each clinical feature that is present

SKIN

Diagnostic:

- ☐ **Poikiloderma**
- ☐ **Lichen planus-like features**
- ☐ **Deep Sclerotic features**
- ☐ **Morphea-like features**
- ☐ **Restriction of mouth opening from sclerosis**

Distinctive:

- ☐ **Depigmentation**
- ☐ **Papulosquamous lesions**

Other:

- ☐ Ichthyosis
- ☐ Keratosis pilaris
- ☐ Hyperpigmentation
- ☐ Hypopigmentation

Common:

- ☐ Erythema (erythroderma)
- ☐ Pruritis
- ☐Maculopapular rash

MOUTH

Diagnostic:

- ☐ **Lichen-type features**
- ☐ 2014 EXCLUDED Hyperkeratotic plaques - leukoplakia

Distinctive:

- ☐ **Xerostomia**
- ☐ **Mucocele**
- ☐ **Mucosal atrophy**
- ☐ **Pseudomembranes**
- ☐ **Ulcers**

Other: (none)

Common:

- ☐ Gingivitis
- ☐ Mucositis
- ☐ Erythema
- ☐ Pain

NAILS	SCALP AND BODY HAIR
Diagnostic: (none) **Distinctive:** ☐ **Longitudinal ridging, splitting or brittle features** ☐ **Onycholysis** ☐ **Pterygium unguis** ☐ **Nail loss (usually symmetric; affects most nails)** Other: (none) Common**:** (none)	**Diagnostic:** (none) **Distinctive:** ☐ **New onset of scarring or nonscarring scalp alopecia** ☐ **Scaling** Other: ☐ Thinning scalp hair, typically patchy, coarse or dull ☐ Premature gray hair Common: (none)
EYES	**GENITALIA**
Diagnostic: (None) **Distinctive:** ☐ **New onset dry, gritty, or painful eyes** ☐ **Cicatricial conjunctivitis** ☐ **Keratoconjunctivitis sicca** ☐ **Confluent areas of punctuate keratopathy** Other: ☐ Photophobia ☐ Periorbital hyperpigmentation ☐ Blepharitis (erythema of the eyelids with edema) Common: (none)	**Diagnostic:** ☐ **Lichen planus-like features** ☐ **Lichen sclerosis-like features** ☐ **Vaginal scarring or stenosis** ☐ **Clitoral/labial agglutination** ☐ **Phimosis and scarringor stenosis of the urethral or meatus (males).** **Distinctive:** ☐ **Erosions** ☐ **Fissures** ☐ **Ulcers** Other: (none) Common: (none) ☐ **Not examined** ☐ **Not applicable**

GI TRACT	LIVER
Diagnostic: ☐ **Esophageal web** ☐ **Strictures or stenosis in the upper to mid third of the esophagus** **Distinctive: (none)** Other: ☐ Exocrine pancreatic insufficiency Common: ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss	**Diagnostic: (none)** **Distinctive: (none)** Common: ☐ Chronic cholestatic syndrome ☐ Acute hepatitis-like syndrome
LUNGS **Diagnostic:** ☐ **Biopsy-proven bronchiolitis obliterans** ☐ **BOS diagnosed by pulmonary function tests – see criteria opposite** Note: In the presence of a distinctive manifestation of chronic GVHD, the clinical diagnosis of BOS is sufficient to establish the diagnosis of chronic GVHD	1. FEV1/vital capacity<.7 or thefifth percentile of predicted. A. Vital capacity includes forced vital capacity or slow vital capacity, whichever is greater. B. The fifth percentile of predicted is the lower limit of the 90% confidence interval. C. For pediatric or elderly patients, use the lower limits of normal, defined according to National Health and Nutrition Examination Survey III calculations 2. FEV1<75% of predicted with ≥10% decline over less than 2 years. FEV1 should not correct to>75% of predicted with albuterol, and the absolute decline for the corrected values should still remain at ≥10% over 2years. 3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs, computed tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, broncho-alveolar lavage) 4. One of the 2 supporting features of BOS: A. Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT, OR B. Evidence of air trapping by PFTs: residual volume>120% of predicted or residual volume/total lungcapacity elevated outside the 90% confidence interval.

MUSCLE, FASCIA, JOINTS	HEMATOPOIETIC AND IMMUNE
Diagnostic: ☐ Fasciitis, joint stiffness or contractures secondary to sclerosis **Distinctive:** ☐ Myositis or polymyositis **Other:** ☐ Edema ☐ Muscle cramps ☐ Arthralgia or arthritis **Common:** (none)	**Diagnostic:** (none) **Distinctive:** (none) Other: ☐ Thrombocytopenia ☐ Eosinophilia ☐ Lymphopenia ☐ Hypo or Hyper - gammaglobulinemia ☐ Autoantibodies (AIHA and ITP) Common: (none)

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0 – 3) based on its functional impact where applicable (none - 0; mild - 1; moderate - 2; severe - 3)

Esophageal stricture or web ___ **Ascites (serositis) ___** **Myasthenia Gravis ___**

Polymyositis __ **Pericardial Effusion ___** **Nephrotic Syndrome ___**

Cardiomyopathy ___ **Cardiac conduction defects ___** **Pleural Effusion(s) ___**

Peripheral Neuropathy ___ **Coronary artery involvement ___**

OTHERS: Specify:_____

<u>Acute Graft Versus Host Disease</u>:

1. Has there been a diagnosis of acute GVHD between the date of the last assessment and today's date?

Yes No

2. If yes, circle the maximum grade of acute GVHD (according to Harris Criteria):

None Grade I Grade II Grade III Grade IV

3. What is the grade of acute GVHD (according the Harris Criteria) at this time point?

None Grade I Grade II Grade III Grade IV

Participant Code: 099-|__|__|__|-|__|__|__| Actual Date of Assessment: |__|__| |__|__|__| |__|__|__|__|

Karnofsky Performance Status:

- ☐ 100% - normal, no complaints, no signs of disease
- ☐ 90% - capable of normal activity, few symptoms or signs of disease
- ☐ 80% - normal activity with some difficulty, some symptoms or signs
- ☐ 70% - caring for self, not capable of normal activity or work
- ☐ 60% - requiring some help, can take care of most personal requirements
- ☐ 50% - requires help often, requires frequent medical care
- ☐ 40% - disabled, requires special care and help
- ☐ 30% - severely disabled, hospital admission indicated but no risk of death
- ☐ 20% - very ill, urgently requiring admission, requires supportive measures or treatment
- ☐ 10% - moribund, rapidly progressive fatal disease processes
- ☐ 0% - death.

Immunosuppressive Therapy for <u>Treatment</u> of GVHD (list all therapies):

Name of Therapy	Dose	Route	Reason
1.			
2.			
3.			
4.			

THE REMAINING ITEMS ARE COMPLETED AT THE TIME OF DIAGNOSIS OF cGVHD ONLY.

Date of onset of first episode of chronic GVHD: |__|__| |__|__|__| |__|__|__|__| ☐ Not applicable
DD MMM YYYY

List immunosuppressive therapy at the time of diagnosis of chronic GVHD but ***<u>prior</u>*** to start of or increase in immunosuppressive therapy *treat* cGVHD

Name of Therapy	Dose	Route	Reason
1.			
2.			
3.			
4.			

Date of form

Date of form completion: |__|__| |__|__|__| |__|__|__|__|
DD MMM YYYY

Person completing the form (print name): **Signature:**

_____

_____

The data recorded in this form was collected from the following sources:

☐ In-person assessment / interview ☐ Clinic Notes ☐ Telephone interview ☐ Diagnostic Reports

Chronic Graft Versus Host Disease - Organ Scoring Page 1 of 3

USE THIS FORM ONLY IF CGVHD HAS BEEN DIAGNOSED BY NIH CRITERIA.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

Chronic Graft Versus Host Disease - Organ Scoring Page 2 of 3

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Chronic Graft Versus Host Disease - Organ Scoring Page 3 of 3

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

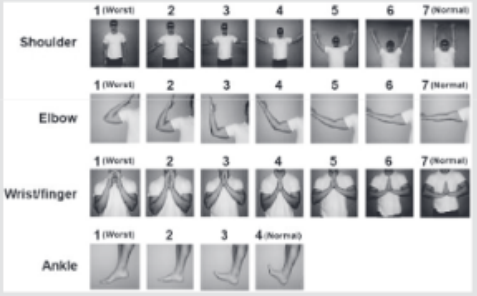
Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Criteria below

Photographic Range of Motion (P-ROM)



Mild chronic GVHD 1 or 2 Organs involved with no more than score 1 plus Lung score 0

Moderate chronic GVHD 3 or More organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1

Severe chronic GVHD At least 1 organ with a score of 3 OR Lung score of 2 or 3 **Key points: In skin:** higher of the 2 scores to be used for calculating global severity. **In lung:** FEV1 is used instead of clinical score for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score)

Appendix 7 – Augmented Co-Morbidity Scale

Definitions and Weighted Scores of Co-Morbidities (augmented comorbidity/age index)

Elsawy et al BBMT 2018:S1083-8791(18)30775-4, Sorror Blood 2013:121:2854-286 , Vaughn et al BBMT 2015:Aug;21(8):1418-24 , Sorror et al Blood 2005:106:2912-2919

NOTE: See P.2 for explanation and formula for corrected DLCO.

Name: _____ Hospital ID #: _____

Definitions of comorbidities included in the augmented comorbidity/age index and their corresponding scores		
Comorbidity	**Definition**	**Score**
HCT-CI		
Arrhythmia	Any type of arrhythmia that has necessitated the delivery of a specific anti-arrhythmia treatment at any time point in the patient's past medical history.	1
Cardiac	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis requiring treatment at any time point in patient's past medical history.	1

Diabetes	Requiring treatment with insulin or oral hypoglycemic agents continuously for 4 weeks before start of conditioning	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Any disorder requiring continuous treatments for 4 weeks before start of conditioning	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT> ULN to 2.5 × ULN; at least two values of each within 2 or 4 weeks before start of conditioning.	1
Obesity	Patients with a body mass index >35 kg/m2 for patients older than 18 years or a BMI-for-age of ≥ 95th percentile for patients of ≤ 18 years of age	1
Infection	Requiring antimicrobial treatment starting from before conditioning and continued beyond day 0	1
Rheumatologic	Requiring specific treatment at any time point in the patient's past medical history	2
Peptic ulcer	Based on prior endoscopic or radiologic diagnosis	2
Moderate/severe renal	Serum creatinine > 2 mg/dl (at least two values of each within 2 or 4 weeks before start of conditioning), on dialysis, or prior renal transplantation	2

Moderate pulmonary	Corrected DLco (via Dinakara equation) and/or FEV1 of 66%-80% or dyspnea on slight activity	2
Prior malignancy	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer	3
Heart valve disease	Of at least moderate severity, prosthetic valve, or symptomatic mitral valve prolapse as detected by echocardiogram	3
Severe pulmonary	Corrected DLco (via Dinakara equation) and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN; at least two values of each within 2 or 4 weeks before start of conditioning	3
Augmented comorbidity/age index: all of the above *plus*		
High ferritin	Values of ≥2500 as measured the closest prior to start of conditioning	1
Mild hypoalbuminemia	Values of <3.5-3.0 as measured the closest prior to start of conditioning	1
Moderate hypoalbuminemia	Values of < 3.0 as measured the closest prior to start of conditioning	2
Thrombocytopenia	Values of <100,000 as measured the closest prior to start of conditioning	1

Age	≥40 years	1

*DLCO may be affected by non-pulmonary factors, particularly smoking (COHb) and anemia. A correction factor for anemia was used in the development of this index as follows:
Corrected DLCO (Dinakara method) = measured DLCO/(Hb x 0.007). Hb is in G/L.

Appendix 7 Page 2: Definitions and Weighted Scores of Co-Morbidities (augmented comorbidity/age index)

Comments regarding patient suitability:

LEGEND and EXPLANATIONS:

EF indicates ejection fraction; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide; and FEV_1, forced expiratory volume in one second.
* One or more vessel-coronary artery stenoses, requiring medical treatment, stent, or bypass graft.

†To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4

Appendix 8 - Disease Risk Index

The Disease Risk Index (DRI) is a validated tool to categorize groups of patients undergoing allogeneic stem cell transplantation (HCT) for hematologic malignancy by disease risk. It is intended for research purposes, to stratify patients in broad disease risk categories for retrospective or prospective studies.

Investigators should use the tool provided by CIBMTR to assign risk status:

https://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/DRI.aspx

Reference: Armand P et al. Validation and refinement of the disease risk Index for allogeneic stem cell transplantation. Blood 123(23):3664-3671, 2014

Appendix 9 – Abbreviations

AA	Aplastic anemia
ALS	Anti-lymphocyte serums
ATG	Anti-Thrombocyte Globulin
ATLG	Anti-T cell Globulin Grafalon
AUC	Area under the curve
aGVHD	Acute graft versus host disease
CBMTG	Canadian Blood and Marrow Transplant Group
cGVHD	Chronic graft versus host disease
CMV	Cytomegalovirus
CRFS	Chronic graft versus host disease and relapse free survival
CTTC	Cell Therapy and Transplantation Canada
CyTBI	Cyclophosphamide/total body radiation
EBMT	European Society for Blood and Marrow Transplant
EBV	Epstein Barr Virus
GRFS	Graft versus host disease-, and relapse-, free survival
GVHD	Graft versus host disease
HCT	Hematopoietic Cell Transplants
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cells
HPTC	Hematopoietic progenitor cell transplantation
HSV	Herpes Simplex Virus
IRB	Institutional Review Board
LPD	Lymphoproliferative Disorder
MHC	Major Histocompatibility Complex
NRM	Non-Relapsed Mortality
OS	Overall Survival
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic
PTCy	Post-Transplant Cyclophosphamide
PTLD	Post transplant lymphoproliferative disorder
QOL	Quality of Life
QPCR	Quantitative Polymerase Chain Reaction
REB	Research Ethics Board
RIC	Reduced Intensity Conditioning
TRM	Transplant Related Mortality

Appendix 10 – References

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