Serial Response and Biomarker-Guided Steroid Taper for Children With GVHD
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ABBREVIATIONS

AA	Ann Arbor
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMT	Bone Marrow Transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIBMTR	Center for International Blood and Marrow Transplant Research
CMP	Comprehensive Metabolic Panel
CMV	Cytomegalovirus
CNS	Central Nervous System
Co-I	Co-Investigator
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCC	Data Coordinating Center
DDI	Drug-Drug Interaction
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
EBMT	European Blood and Marrow Transplant Group
EBV	Epstein-Barr Virus
ELISA	Enzyme-Linked Immunosorbent Assay
ERAP	Electronic Research Application Portal
FDA	Food and Drug Administration
GI	Gastrointestinal
GVHD	Graft-Versus-Host Disease
GVL	Graft-Versus-Leukemia
HCT	Hematopoietic Stem Cell Transplantation
HHV6	Human Herpes Virus 6
HLA	Human Leukocyte Antigen
HRQOL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
IND	Investigational New Drug
IL2Rα	Interleukin-2 receptor-alpha
IRB	Institutional Review Board

IV (or iv)	Intravenously
JC	John Cunningham (virus)
MAGIC	Mount Sinai Acute GVHD International Consortium
MAP	MAGIC Algorithm Probability
MS	Multiple Sclerosis
NCI	National Cancer Institute
NOS	Not Otherwise Specified
NR	No Response
NRM	Non-Relapse Mortality
ORR	Overall Response Rate
OS	Overall Survival
PE	Physical Exam
PI	Principal Investigator
PCP	*Pneumocystis Carinii* Pneumonia
PCR	Polymerase Chain Reaction
PJP	*Pneumocystis Jiroveci* Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PTLD	Post-Transplant Lymphoproliferative Disorder
QOL	Quality of Life
REG3α	Regenerating islet-derived 3 alpha
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
ST2	Suppressor of tumorigenicity-2
TCI	The Tisch Cancer Institute at Mount Sinai
TNFR1	Tumor necrosis factor receptor-1
UGI	Upper Gastrointestinal
VGPR	Very Good Partial Response
VZV	Varicella-Zoster Virus

1.0 STUDY SYNOPSIS

Title	Serial Response and Biomarker-Guided Steroid Taper for Children with GVHD
Phase	II
Methodology	Open label
Study Duration	3 years
Study Center(s)	Mount Sinai, Emory University/Children's Healthcare of Atlanta, Children's Hospital of Los Angeles, Children's Hospital of Philadelphia, Hospital for Sick Children, Memorial Sloan-Kettering Cancer Center, Vanderbilt University, Children's National Medical Center, Texas Children's Hospital/Baylor College of Medicine, Children's Wisconsin/Medical College of Wisconsin, Dana-Farber Cancer Institute/Boston Children's Hospital
Study Rationale	The majority of GVHD that develops in pediatric patients is steroid responsive, but clinical severity alone predicts outcomes too poorly to guide treatment. As a result, patients are treated with prolonged courses of high dose steroids, resulting in serious morbidities including infections, decreased physical functioning, mood disturbances, and reduced quality of life. The Mount Sinai Acute GVHD International Consortium (MAGIC) has developed a novel monitoring system that uses clinical and biomarker criteria at onset and an additional two assessments during the first two weeks of treatment to identify a large subset of patients, (40% of all GVHD) with an exceptional response rate (96%). These patients, who are over treated with current practice, are candidates for the first trial aimed at rapidly tapering steroid dosing based on serial risk assessments to decrease the toxicity of GVHD treatment. The trial will also generate data regarding the illness experience in children treated for acute GVHD, an area with a current large knowledge gap.
Objectives	**Primary Objectives:** To improve the proportion of pediatric patients whose low-risk GVHD is successfully treated with low cumulative doses of steroids from 14% to 42%. **Secondary Objectives:**

	1. To determine the overall response rate at day 28 of treatment 2. To calculate the duration of response 3. To calculate the incidence of serious infections (overall, viral, bacterial, fungal, parasitic) by day 90 of treatment 4. To determine the cumulative steroid exposure through days 28 and 90 of treatment 5. To determine the cumulative incidence of 1-year NRM, relapse, chronic GVHD and overall survival 6. To determine the cumulative incidence of steroid-refractory GVHD in patients by day 90 of treatment **Exploratory Objectives:** 1. To measure quality of life (physical functioning and neuropsychiatric well-being) through day 180 2. To calculate growth velocity in study patients over one year **3.** To calculate the MAGIC algorithm probability at day 28 of treatment
Number of Subjects	50
Inclusion Criteria	1. Newly diagnosed GVHD that meets criteria for Minnesota standard risk (see section 9.0) except isolated skin rash <25% body surface area without other manifestations 2. Ann Arbor 1 GVHD by biomarkers 3. GVHD not previously treated systemically (topical therapies and non-absorbed steroids are allowed) 4. Any donor type, HLA-match, conditioning regimen is acceptable 5. Age 0-21 years at the time of screening 6. Signed and dated written informed consent obtained from patient or legal representative and assent from pediatric patients capable of providing assent
Exclusion Criteria	1. Patients treated for GVHD with >0.5 mg/kg/day prednisone or any steroid treatment for GVHD for more than 2 days prior to screening* 2. Patients receiving corticosteroids >0.1 mg/kg prednisone (or other steroid equivalent) for any indication within 7 days before the onset of acute GVHD except for adrenal insufficiency,

	premedication for transfusions/IV medications, or intermittent use for symptom control such as nausea/vomiting 3. Relapsed, progressing, or persistent malignancy or other condition (e.g., known declining donor chimerism) requiring withdrawal of systemic immune suppression or donor leukocyte infusion (DLI) 4. Patients with uncontrolled infection (i.e., progressive symptoms related to infection despite treatment, persistently positive microbiological cultures despite treatment, viral reactivations unresponsive to treatment, or any other evidence of severe infection) 5. Patient requiring mechanical ventilation or cardiac pressor support 6. A clinical presentation resembling de novo chronic GVHD or overlap syndrome developing before or present at the time of enrollment 7. Patients who are pregnant *Patients on ≤0.5 mg/kg/day prednisone for ≤2 days for new onset GVHD can be eligible as delineated in section 6.0
Study Product(s), Dose, Route, Regimen	Prednisone (or equivalent) at a starting dose of 0.5 mg/kg/day orally or IV and dose adjusted according to clinical and biomarker responses
Duration of Administration	28 days
Statistical Methodology	The primary study measure is the proportion of low-risk GVHD patients who achieve clinical response (CR, VGPR, or PR) on day 28 after being exposed to low cumulative dose of prednisone (≤13.5 mg/kg) or other steroid equivalent during the first 4 weeks of therapy. The expected proportion of patients with low risk (Minnesota standard risk/Ann Arbor 1) GVHD whose steroid exposure is ≤13.5 mg/kg is 14%. Patients with low risk GVHD who have favorable clinical and biomarker responses during the first two weeks of treatment have excellent outcomes, represent 65% of low risk GVHD, and will undergo structured steroid tapers designed to reduce cumulative steroid exposure by 50% or greater. A three-fold increase in the proportion of patients (from 14% to 42%) whose cumulative steroid exposure is ≤13.5 mg/kg would be clinically significant. A sample size of 50 patients provides 90% power with an alpha of 0.001 to detect a difference of 0.28 (0.14 to 0.42) in the proportion treated successfully with reduced steroid exposure.

2.0 LAY SUMMARY

Acute graft-vs-host disease (GVHD) occurs when donor immune cells attack the healthy tissue of a bone marrow or stem cell transplant patient. The most common symptoms are a skin rash, nausea, vomiting, diarrhea, and/or jaundice. The standard treatment for GVHD is to suppress the activity of the donor immune cells using steroid medications such as prednisone. Although most GVHD, especially in children, responds well to treatment, sometimes (around 1/3 of the time) there is either no response to steroids or the response does not last. In those cases, the GVHD can become dangerous and even life-threatening. Unfortunately, doctors cannot predict who will have a good response to treatment based on symptom severity or initial response to steroids. As a result, nearly all children who develop GVHD are treated with long courses of high dose steroids even though that means many patients receive more treatment than they probably need. Steroid treatment can cause short-term complications like infections, high blood sugar, high blood pressure, muscle weakness, depression, anxiety, and problems sleeping and long-term complications like bone damage, cataracts in the eyes, and decreased growth. The risk of these complications increases with higher doses of steroids and longer treatment. It is important to find ways to decrease the steroid treatment in patients who do not need long courses.

The doctors conducting this research have developed a blood test (GVHD biomarkers) that predicts whether a patient will respond well to steroids. In a study of 85 pediatric patients (age up to 21 years), they found that children who have low GVHD biomarkers at the start of treatment and for the first two weeks of treatment have a very high response rate to steroids (96%) that lasts. In this study, we will monitor GVHD symptoms and biomarkers during treatment and decrease the steroid treatment by 50% in patients who have GVHD that is expected to respond very well to treatment. We will do this by starting treatment at a lower dose and tapering quickly so long as the biomarkers remain low and the symptoms are responding. To avoid undertreating patients who may need higher doses, we will increase the steroid dose if symptoms worsen or biomarkers increase. We will assess how many patients respond well to lower steroid dosing and what steroid complications develop. We will also use surveys to obtain patient's own assessment of their quality of life (down to age 5 years). We hope that the results of this research will help us develop treatments for GVHD that are both effective and safer than currently available.

3.0 BACKGROUND AND RATIONALE

3.1 Acute GVHD

Allogeneic hematopoietic cellular transplantation (HCT) is an important treatment for high-risk hematologic malignancies whose curative potential depends on the graft-versus-leukemia (GVL) effect, which is mediated by alloreactive T cells in the donor graft. GVL effects are closely associated with graft-versus-host disease (GVHD), which is mediated by those same T cells[1]. Graft-versus-host disease (GVHD) targets the skin, liver and gastrointestinal (GI) tract and requires treatment in 35% of pediatric allogeneic transplant recipients[2]. GVHD is the leading cause of non-relapse mortality after HCT[1,3,4]. The six-month cumulative incidence of non-relapse mortality (NRM) in children treated for GVHD (13%) is driven by GVHD of the GI tract. Unfortunately, the severity of symptoms at diagnosis predicts risk for NRM too poorly to guide treatment. For example, the Minnesota classification system uses GVHD symptom severity at diagnosis to stratify patients into high and standard risk groups but cannot identify a "low" risk subgroup who are very likely to respond to treatment and survive long term[5]. Thus, all patients, even those who have good outcomes, are treated with a prolonged course of high dose systemic steroids, which results in **over treatment** for the majority of patients[6,7].

3.2 Current Standard of Care for Pediatric GVHD

The Mount Sinai Acute GVHD International Consortium (MAGIC) is a collaborative effort among 21 academic adult and pediatric hematopoietic cell transplant centers in North America, Europe and Asia to study GVHD. In addition to interventional trials, MAGIC has been conducting a natural history trial since 2014 that has prospectively collected clinical data and research samples on 700 children who received a first allogeneic transplant including 250 who developed GVHD that required treatment. Consensus guidelines for GVHD treatment recommend high starting prednisone doses (1-2 mg/kg/day) and slow tapers every 5-7 days in responding patients resulting in a cumulative prednisone dose of 20-40 mg/kg in the first four weeks of treatment. MAGIC data confirms this calculation in pediatric patients whose mean cumulative prednisone exposure is 27.1 mg/kg (±0.5 mg/kg) in the first four weeks. The clinical response after 4 weeks of steroid treatment often serves as the primary endpoint in acute GVHD clinical trials and is a widely accepted surrogate for NRM and long-term survival[8-10]. However, an early clinical response after one week of systemic treatment does not determine treatment success or result in less steroid exposure. MAGIC data showed that the cumulative steroid dose was the same in patients who responded rapidly within 7 days (26.9±2.1 mg/kg) and those who did not (28.0±0.8 mg/kg).

Our natural history study also shows that physicians only occasionally limit steroid exposure. For example, only 14% of children with low risk GVHD (described below) are treated with <50% of the mean prednisone steroid dose (i.e., ≤13.5 mg/kg), even though their outcomes are as good as those observed in patients treated with greater steroid exposure. These data indicate that GVHD in children is often over-treated.

3.3 Steroid Treatment Toxicities

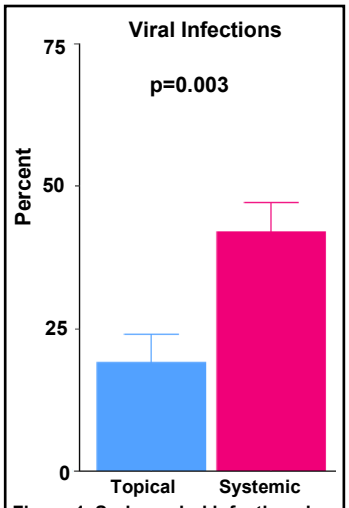

Figure 1. Serious viral infections in patients treated with topical steroids (blue, n=69) or systemic steroids (pink, n=108)

Steroid treatment causes chronic physical complications and reduces QOL[11-14] that correlate with cumulative steroid exposure[15-19]. Children are particularly susceptible to these complications. For example, corticosteroids are potent inhibitors of linear growth, especially during the adolescent growth spurt[20]. Likewise, the incidence of corticosteroid-related osteonecrosis, a debilitating skeletal complication, is highest in adolescents, presumably reflective of the vulnerability of rapidly growing bone[21]. Acute complications of steroid treatment are less well studied but include more infections and reduced QOL[13,22-25]. Serious infections correlate with other steroid toxicities and thus can serve as a surrogate for overall steroid morbidity[26]. We quantified the risk of serious infections using data from 176 adult and pediatric MAGIC natural history trial patients with Minnesota standard risk GVHD that was low risk by biomarkers (see below). Serious infections were defined using the standardized criteria widely used for clinical trials at academic BMT centers, such as life-threatening fungal infections or hemorrhagic cystitis from BK viral infection [27] and included clinically significant CMV infections that required anti-viral treatment regardless of end-organ damage, given the toxicity of such treatments[28]. Systemic steroid treatment doubled the incidence of serious infections (56% vs 30%, p=0.002), a finding driven by serious viral infections (e.g., CMV colitis, HHV6 encephalitis, EBV-related PTLD, etc.) (42% vs 19%, p=0.003) [**Figure 1**]. The difference in serious infections remained statistically significant when we controlled for severity of target organ involvement (p=0.01).

3.4 GVHD Biomarker Algorithm Identifies Patients with Low Risk GVHD

MAGIC has validated a biomarker-based risk stratification system that is more accurate than clinical symptoms at classifying GVHD severity[7,29-31]. The MAGIC algorithm probability (MAP) define the Ann Arbor (AA) risk scores (1, 2 or 3) that identify patients at high risk for treatment failure as well as patients who respond well to steroids and would benefit from reductions in treatment. The MAP reflects the extent of GI crypt damage as measured by serum concentrations of ST2 and REG3α[29,32]. The presence of GI crypt damage portends a worse outcome, even when GI symptoms are minimal or absent, while the absence of GI crypt damage predicts response to steroid treatment, even when GI symptoms are present[6,29,33]. The MAP has also been validated as a response biomarker and more accurately predicts survival than clinical response[31].

Recently we validated the MAGIC algorithm at start of steroid treatment for GVHD in 194 children (median age 12y, range 0.3-21y). Ann Arbor 1 GVHD (65% of patients) represents the best risk group with 2% NRM and each increase in Ann Arbor score represented a highly significantly increase in risk for NRM **[Figure 2]**. An analysis restricted to children <12y yielded similarly significant results. The area under the curve (AUC) for NRM was significantly better for Ann Arbor scores than clinical severity (0.84 vs 0.63, p=0.007). Ann Arbor scores were predictive of outcomes regardless of onset GVHD severity and within subgroups such as graft type (marrow, peripheral blood, or cord blood), use of anti-thymocyte globulin during conditioning, or diagnosis.

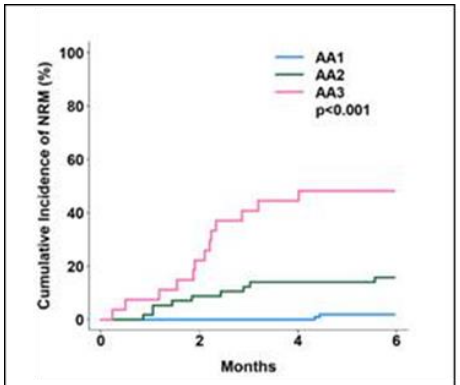

Figure 2. NRM in 194 pediatric patients from start of steroid treatment by Ann Arbor score.

Further analyses demonstrated that the combination of favorable clinical features (Minnesota standard risk) and biomarkers Ann Arbor 1 score defines a **low risk** population with a good overall response rate (ORR) to steroids (79%), but the risk posed by a 20% treatment failure rate is a barrier to the rapid tapers likely needed to reduce steroid toxicities.

3.5 Serial Monitoring Identifies Patients with Ultra-Low Risk GVHD

Given that the MAP can also act as a monitoring biomarker, we used both the clinical response and the MAP during the first two weeks of systemic steroid treatment to analyze 85 pediatric patients with Minnesota standard risk/AA1 GVHD. MAPs were categorized as high or low using the validated 0.29 threshold[7]. Changes in clinical severity were scored as either response, stable, or progression. Patients who responded by the end of week one and maintained both clinical response and a low MAP at week two (48% of patients), experienced 95% day 28 ORR. Importantly, serial monitoring demonstrated that **slow** clinical responders (17% of patients) have equally good outcomes with a 100% ORR; these patients have stable disease at week one, a response at week two and a low MAP at all three assessments. The remaining patients (35%) either lacked a treatment response or had an increase in their MAP above 0.29. Taken together, serial monitoring identifies 65% of patients with Minnesota standard risk/AA1 GVHD as an **ultra-low risk** group with higher response rates (96% vs 47%, p<0.001) than other patients. Furthermore, GVHD flares that required an increase in treatment occurred in only 5% of patients with ultra-low risk GVHD. Thus, these patients are excellent candidates for a GVHD treatment strategy that minimizes steroid exposure.

3.6 Patient Reported Outcomes in Children Treated for Acute GVHD

Patient-reported outcomes (PROs) refer to patient-perceived health-related quality of life (HRQOL), functional status, and symptom burden. PROs provide a direct way to capture the

burden of patient symptoms and emotional distress that are poorly quantified by traditional measures[34]. The United States Food and Drug Administration (FDA) now recognizes PROs as a valid measure of clinical benefit for new drug approval[35]. Improvement of QOL during treatment can reflect a meaningful benefit to the patient not captured by clinical response because PROs measure the symptom burden of both acute GVHD and its treatment[36].

Studies have clearly outlined the impact of chronic steroid use on QOL, physical functioning, and psychological distress in adult[37-40] and pediatric[41] HCT survivors with chronic GVHD. Less is known about the effect of steroid treatment of acute GVHD on QOL. In one study of acute GVHD in adults, reduced steroid exposure correlated with better QOL[25] but the impact of steroid treatment for acute GVHD in children is not yet described. In children treated for acute leukemia, steroid exposure decreased mood and increased behavior problems[42,43]. Resolution of the neuropsychiatric effects of steroid use in children is closely correlated with discontinuation of steroids[44].

Although multiple tools have been developed for the assessment of PROs, the Center for International Blood and Marrow Transplant Research (CIBMTR) and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) have called for the harmonization of the use of PRO measures in HCT studies[45]. The NIH PROMIS (Patient Reported Outcomes Measures Information System) tool is validated in HCT patients, free, and easy to administer and score[46]. PROMIS tests quantify clinically meaningful changes and have been validated for use in children as young as 5 years when using parental proxy[47-49]. In this study we will use PROMIS surveys to measure symptoms of poor QOL associated with steroid exposure (Global QOL, Physical Mobility, Anxiety, Depression, Fatigue, Sleep Disturbance). This trial will provide essential data lacking in the literature on HRQOL in children diagnosed with acute GVHD and treated with steroids. We will be able to analyze PROs as a function of steroid exposure, to further describe the impact of steroid use on HRQOL. Since measures within a PROMIS domain (such as physical or mental health) can be compared on the same t-score metric, regardless of number and items administered, this will allow for further use of this data for future comparisons across studies that may use different PROMIS measures.

3.7 Mount Sinai Acute GVHD International Consortium (MAGIC)

Multicenter biomarker-guided treatment trials require a detailed understanding of the natural history of GVHD, the ability to result biomarker scores within 24 hours, harmonized clinical staging and grading for accurate response measures, and strong communication between the Data Coordinating Center (DCC) and the participating sites. MAGIC was designed to provide these services and in the past few years has become recognized as a world-leader in GVHD clinical research. Recent accomplishments include the validation of the MAP to predict GVHD outcomes prior to and at the onset of GVHD[29], to identify a large good risk group of “slow responders” within steroid-resistant GVHD[7], as the first treatment response biomarker for GVHD with better accuracy after one week of treatment than clinical response after four weeks of treatment[31], and to provide guidance for immunosuppression tapers in patients without GVHD[30]. MAGIC also developed, tested, and validated standardized acute GVHD staging guidance[50], and its subsequent endorsement by the National Institutes of Health (NIH), European Blood and Marrow Transplant Group (EBMT), and CIBMTR led to its rapid adoption worldwide[51]. A free mobile phone app using MAGIC guidance for bedside clinical assessment, eGVHD, has been downloaded several hundred times[52].

The MAGIC DCC is skilled in GVHD clinical trial management, including a natural history study of acute GVHD that enrolls ~700 adult and pediatric allogeneic BMT recipients per year. Clinical trial data is entered through a remote data entry system that is accessible 24/7. The DCC uses

cost-efficient processes to minimize data errors both before and after data entry. These processes include: 1) rigorous data manager training with webinars, YouTube videos and testing; 2) standardized guidance embedded directly into data entry forms for on-demand reference; 3) real time alerts regarding values out of range, or missing/inconsistent data through instant cross checks; 4) reinforcement of best practices through monthly webinars; and 5) automated computation for complex data points such as response to treatment. Real-time biomarker scoring for clinical trials has been available since 2016 through the CLIA-certified GVHD laboratory at Mount Sinai with more than 700 adult patients screened and 165 patients enrolled on interventional clinical trials. Ann Arbor scores are reported to centers the same day as receipt by the GVHD laboratory 98% of the time. MAGIC has an excellent track record in clinical trial performance. We have successfully conducted three trials in adult GVHD meeting accrual goals on time.

3.8 Rationale to Changes to Study; 5/5/2023

Two changes to eligibility will be made. First, eligibility will be broadened to include stage 2 skin GVHD (Grade I), or isolated upper GI GVHD to better reflect current treatment practices. These patients were initially excluded because topical therapy alone is a treatment option. However, we analyzed treatment practices for 113 pediatric transplant recipients from 2019-2023 who developed GVHD. Systemic steroid treatment was initiated for 16/28 (57%) of patients who presented with skin stage 2 GVHD and for 10/14 (71%) of patients who presented with isolated upper GI GVHD. The subset with Ann Arbor 1 GVHD had a similar response rate to steroids (75%) as the overall Minnesota Standard risk/AA1 population, are appropriate to include in this study, and their inclusion will help meet accrual goals in a timely manner.

Second, we will remove exclusion criteria for organ function and performance score (with the exception that patients requiring mechanical ventilation and/or cardiac pressors will remain excluded). This change is being made because GVHD occurs in patients with a broad range of morbidities, and patients with organ dysfunction may benefit from reduction in steroid exposure. Inclusion of patients with serious comorbidities will improve the generalizability of the approach and given that this is a treatment de-escalation approach is unlikely to increase risk to subjects.

3.9 Summary of Study Rationale

Acute graft-versus-host disease (GVHD) that requires systemic treatment continues to be a problem for children who undergo allogeneic hematopoietic cell transplant with a cumulative incidence of 35%. High dose systemic steroid therapy for weeks to months remains the standard of care even though the majority of pediatric GVHD is low risk. The status quo persists for two reasons. First, initial GVHD severity does not reliably predict treatment response. Second, physicians are uncertain whether early treatment responses will be durable and delay steroid tapers. Thus, steroid-related short and long-term complications are common, even though most children are **over-treated** for steroid responsive GVHD. The aggressive steroid tapers needed to substantially reduce steroid exposure have not been successful in adults due to a fear of treatment failure, the absence of a validated steroid taper algorithm, and an uncertain risk/benefit ratio[53,54]. To the best of our knowledge, there have been no attempts to study aggressive steroid tapers in children with GVHD.

MAGIC developed and validated a biomarker risk stratification system that identifies the large population of children whose GVHD is **low-risk**. A real-time monitoring system that incorporates two additional clinical and biomarker response measurements over two weeks identifies an even lower risk group that comprises 40% of all pediatric GVHD cases and who are candidates for the

rapid tapers needed to reduce steroid complications. This trial will be the first ever aimed at decreasing the toxicity of GVHD treatment by **personalizing steroid dosing** based on serial assessments of clinical and biomarker responses. If successful, this trial has the potential to change the way acute GVHD is treated in children. This study also will improve the knowledge gap regarding the illness experience in children with acute GVHD by analysis of patient reported outcomes.

4.0 STUDY OBJECTIVES

4.1 Primary Objectives

4.1.1 To improve the proportion of pediatric patients whose low-risk GVHD is successfully treated with low cumulative doses of steroids from 14% to 42%.

4.2 Secondary Objectives

Secondary and exploratory objectives will be assessed in all study subjects and in the ultra-low risk patient subset

4.2.1 To determine the overall response rate at day 28 of treatment

4.2.2 To calculate the duration of response

4.2.3 To calculate the incidence of serious infections (overall, viral, bacterial, fungal, parasitic) by day 90 of treatment

4.2.4 To determine the cumulative steroid exposure through days 28 and 90 of treatment

4.2.5 To determine the incidence of 1 year NRM, relapse, overall survival, and chronic GVHD

4.2.6 To determine the incidence of steroid-refractory GVHD in patients by day 90 of treatment

4.3 Exploratory Objectives

4.3.1 To measure quality of life (physical functioning and neuropsychiatric well-being)

4.3.2 To calculate linear growth velocity in study patients

4.3.3 To calculate the MAP at day 28 of treatment

4.4 Primary Endpoint

Proportion of patients with low-risk GVHD (Minnesota standard risk/Ann Arbor 1) who are in CR, VGPR or PR on day 28 of treatment and whose cumulative prednisone (or other steroid equivalent) exposure during the first four weeks of treatment is ≤13.5 mg/kg (i.e., <50% of current practice).

4.5 Secondary Endpoints

1. Proportion of patients who achieve a treatment response by day 28 of treatment. Treatment responses are defined as complete response (CR), very good partial

response (VGPR), or partial response (PR). For a response to be scored as CR, VGPR, or PR on day 28, the patient must be in response on day 28 and have had no intervening systemic therapy for acute GVHD other than steroids.

2. Proportion of patients who develop serious infections (viral, bacterial, fungal, parasitic as defined in section 9.1.11)
3. Overall survival at 6 and 12 months
4. Cumulative incidence of NRM at 6 and 12 months
5. Relapse rate at 6 and 12 months
6. Cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year from enrollment
7. Cumulative steroid dose at days 28 and 90

4.6 Safety Endpoints

1. Proportion of patients who develop steroid refractory GVHD defined as GVHD that worsens by at least one stage in at least one target organ **and** requires systemic treatment with an agent other than steroids

4.7 Exploratory Endpoints

1. GVHD biomarker concentrations (ST2 and REG3) and their associations with clinical endpoints at day 28
2. Patient reported outcomes (QOL) through day 180
3. Linear growth velocity (change in height, relative to sex- and age-means)

5.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and none of the exclusion criteria to be eligible to participate in the study. Subjects can begin treatment with prednisone 0.5 mg/kg/day (or equivalent) during screening and prior to enrollment. Day 0 is the day an enrolled patient began systemic steroid treatment, even if prior to confirmation of eligibility.

5.1 Inclusion Criteria

5.1.1 Newly diagnosed GVHD that meets criteria for Minnesota standard risk (see section 9.0) except isolated skin rash <25% body surface area without other manifestations

5.1.2 Ann Arbor 1 GVHD by biomarkers

5.1.3 GVHD not previously treated systemically (topical therapies and non-absorbed steroids are allowed)

5.1.4 Any donor type, HLA-match, conditioning regimen is acceptable

5.1.5 Age 0-21 years at the time of screening

5.1.6 Signed and dated written informed consent obtained from patient or legal representative and assent from pediatric patients capable of providing assent

5.2 Exclusion Criteria

5.2.1 Patients treated for GVHD with >0.5 mg/kg/day prednisone for any duration or any steroid treatment for GVHD for more than 2 days prior to screening.*

5.2.2 Patients receiving corticosteroids >0.1 mg/kg prednisone (or other steroid equivalent) for any indication within 7 days before the onset of acute GVHD except for adrenal insufficiency, premedication for transfusions/IV medications, or intermittent use for symptom control such as nausea/vomiting

5.2.3 Relapsed, progressing, or persistent malignancy or other condition (e.g., known declining donor chimerism) requiring withdrawal of systemic immune suppression or donor leukocyte infusion (DLI)

5.2.4 Patients with uncontrolled infection (i.e., progressive symptoms related to infection despite treatment, persistently positive microbiological cultures despite treatment, viral reactivations unresponsive to treatment, or any other evidence of severe infection)

5.2.5 Patients requiring mechanical ventilation or cardiac pressor support

5.2.6 A clinical presentation resembling de novo chronic GVHD or overlap syndrome developing before or present at the time of enrollment

5.2.7 Patients who are pregnant

*Patients on ≤0.5 mg/kg/day prednisone for ≤2 days for new onset GVHD can be eligible as delineated in section 6.0

6.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

To be eligible for this study, patients must have newly diagnosed low risk acute GVHD defined as Minnesota standard risk based on symptoms and Ann Arbor 1 GVHD based on biomarkers.

Biomarker assays will be performed at the Mount Sinai GVHD laboratory CLIA-certified laboratory according to established protocols[29,31]. Patients will be recruited from centers participating in the Mount Sinai Acute GVHD International Consortium (MAGIC) where the procedures for obtaining screening samples for biomarker scoring are already established. **Patients can be treated with 0.5 mg/kg/day prednisone (or equivalent) for new onset GVHD for up to 2 days prior to screening**

Consented patients will be registered into the remote data entry system using a unique study number automatically assigned by the database. Five mL of serum will be collected from patients after GVHD has been diagnosed and within 1 day of initiation of treatment. If shipping Monday-Thursday, use the **first overnight** shipping option**,** or if shipping on Friday, use the **priority overnight for Saturday delivery** shipping option, and send to the Mount Sinai GVHD laboratory for early AM arrival (**see Appendix A for detailed collection and shipping procedures**). Samples can be received Tuesday through Saturday. Once received in the laboratory, the GVHD biomarkers used to assign the Ann Arbor GVHD risk score will be measured by ELISA using standard technical procedures. Processing, measuring, and confirming the ELISA assay results take 4.5 hours (range 4-6 hours). Once the Ann Arbor GVHD risk score is confirmed, the investigator at the participating center will be notified of the score by telephone and written confirmation by email.

Patient registration for this trial will be centrally managed by the MAGIC Data Coordinating Center of the Icahn School of Medicine at Mount Sinai as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the electronic Screening and Enrollment Log provided by the MAGIC Data Coordinating Center (DCC).

It is the responsibility of the local site investigator to confirm patient eligibility for the clinical trial. Confirmation of the MAGIC GVHD risk score will be provided directly to the identified Primary Site contact at the participating site by the MAGIC DCC. All other eligibility criteria will be provided by the participating site. After patient eligibility has been determined, a copy of the **completed** Eligibility form will be submitted by the requesting site to the MAGIC Data Coordinating Center by email to MAGICDCC@mssm.edu with local site investigator signature and supporting source documentation.

The MAGIC Coordinator, who acts as the registrar, will review the submitted documents and process the registration. An email will be sent by the registrar to the requesting site registrar to confirm patient registration. Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not be followed on study.

7.0 TREATMENT PLAN

7.1 Treatment Dosage and Administration

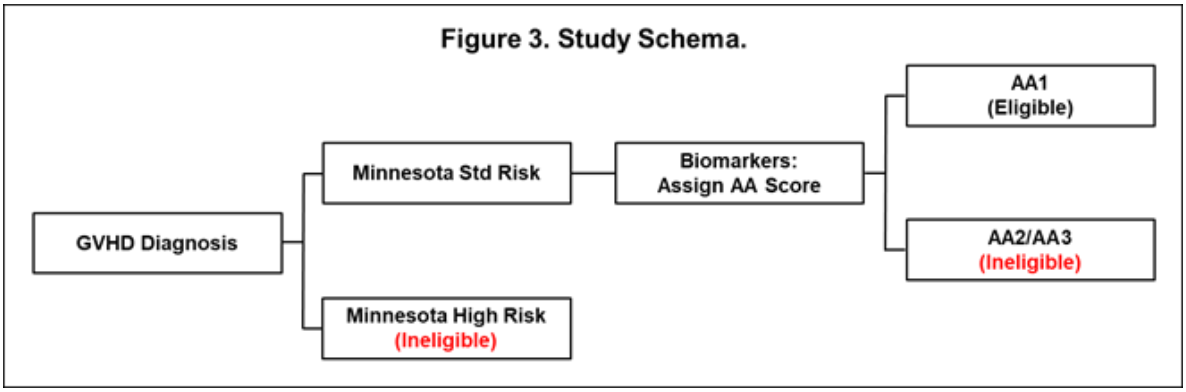

Table 1: Treatment Schema

TX		Week 1			Week 2			Week 3***	Week 4	Cumulative mg/kg
MAP	mg/kg	MAP	Response	mg/kg	MAP	Response	mg/kg	mg/kg	mg/kg	
		>0.29	All	1-2**	Ad lib or clinical trial					
			Progression							
AA1	**0.5**	**≤0.29**	**Responder**	**0.35**	**≤0.29**	**Responder**	**0.25**	**0.15**	**0.1**	**8.75 (↓68%)**
						Partial loss of response*	**0.35**	**0.25**	**0.15**	**10.9 (↓60%)**
						Flare	1-2**	Ad lib or clinical trial		
					>0.29	All				
AA1	**0.5**	**≤0.29**	**Stable**	**0.5**	**≤0.29**	**Responder**	**0.35**	**0.25**	**0.15**	**11.2 (↓59%)**
						Stable	1-2**	Ad lib or clinical trial		
					>0.29	All				

* partial loss of response = increase in GVHD stage from week 1 but less than baseline
** suggested dose
*** partial loss of response, delay taper, refer to protocol section (section 7.1.9)

7.1.1 To avoid delays in treatment and because steroid treatment is the standard of care for GVHD, the starting prednisone dose of 0.5 mg/kg/day (or oral or intravenous equivalent) can start before screening is complete. The initial dose is based on its proven effectiveness as a starting dose for grade II GVHD[54]. Dosing frequency can be daily or in divided doses as per institutional standard. For example, a patient who is diagnosed with Minnesota standard risk GVHD can begin prednisone treatment at 0.5 mg/kg/day pending Ann Arbor score results. If Ann Arbor 2/3 GVHD is confirmed, the patient will not be enrolled on the study, and the prednisone dose should be increased to 1-2 mg/kg/day and further treatment will be at physician discretion. If Ann Arbor 1 GVHD is confirmed, treatment should continue at the initial dose with further dose tapers or increases as specified in **Table 1**. In cases where treatment was not begun during

screening, treatment must begin within one day of confirmation of Ann Arbor 1 GVHD. Day 0 is the day that systemic treatment was begun.

7.1.2 Subsequent prednisone doses are determined based on the clinical response and MAPs as in **Table 1**.

7.1.3 Prednisone dose or equivalent can be rounded to nearest feasible dose based on formulation, dosing options, and institutional practice.

7.1.4 Prednisone dose is based on baseline weight.

7.1.5 Patients with an early and sustained response over all four weeks are tapered the most aggressively to 0.1 mg/kg/day by week 4.

7.1.6 Prednisone dose remains 0.5 mg/kg/day for patients with stable GVHD and a favorable MAP at the first assessment (week 1) do not taper. Slow responders, i.e., patients with response by week 2, begin the taper at week 2.

7.1.7 Patients who do not respond by week 2 are removed from study treatment schedule and it is recommended that the prednisone dose be increased to 1-2 mg/kg/day in order to produce a clinical response.

7.1.8 Patients with an initial response at week 1 but a partial loss of response at week 2 (e.g., increase in GVHD staging from week 1 but still improved compared to baseline) do not taper further until staging improves.

7.1.9 For patients who have a partial loss of response at week 3, delay taper until further improvement in stage.

7.1.10 Patients whose GVHD worsens compared to baseline, fails to improve by week 2, or who develop a MAP >0.29 are removed from study treatment schedule and it is recommended that the prednisone dose be increased to 1-2 mg/kg/day with further tapering per physician judgment.

7.1.11 Physicians are permitted to increase steroid dosing whenever deemed in the best interest of the patient. The reason for increasing the steroid dose will be reported.

7.1.12 Prednisone dosing will be reported weekly through day 28 and then either weekly or whenever the dose is changed, whichever is less frequent, until study day 90. After week 4 prednisone tapering or dose increases will be determined by the treating physician.

7.1.13 To promote adherence to the steroid dosing schedule outlined in **Table 1**, the prednisone dose for the week will be communicated by the MAGIC DCC to the treating physician. For weeks 1 and 2 this communication will occur simultaneously with reporting of the biomarker results.

7.1.14 **GVHD Prophylaxis Medications**

Medications given for GVHD prophylaxis such as cyclosporine, tacrolimus, sirolimus, methotrexate, mycophenolate should be continued at therapeutic doses (according to institutional standards) and adjusted as necessary for renal,

central nervous system (CNS) or other toxicity using institutional guidelines. This study allows for changes in GVHD prophylaxis medication (e.g., replacement of cyclosporine with sirolimus for management of posterior reversible encephalopathy syndrome [PRES]) as per institutional standards. GVHD prophylaxis medications will be tapered according to local institutional tapering practices.

7.1.15 GVHD Topical Treatments

The preliminary data for this study were generated from patients transplanted at multiple centers with heterogeneous GVHD treatment practices. In order to develop "real world" experience in this study, institutional GVHD treatment practices such as topical steroid therapy for skin or upper GI GVHD are permitted.

7.1.16 Ancillary therapies

Ancillary/supportive care measures for acute GVHD such as the use of anti-motility agents for diarrhea is allowed at the discretion of the treating physician. Use of ursodiol to prevent/reduce gall bladder sludging or prevent hepatic transplant-related complications is allowed according to institutional guidelines.

7.1.17 Supportive Care Guidelines

All patients should receive the following:

- Transfusion support per institutional practice
- Anti-infective prophylaxis against viral infections (e.g., herpes virus) is required but institutional dosing and duration practices can be followed.
- Anti-infective prophylaxis against *Pneumocystis jiroveci*, bacterial and fungal infections according to standard institutional guidelines.
- Pre-emptive monitoring and treatment for CMV infections is required but otherwise institutional practice can be followed.

7.2 Toxicities and Dosing Delays/Dose Modifications

Steroid treatment is the standard of care for acute GVHD. The goal of this study is to reduce the toxicities of steroid treatment. Toxicities of steroid treatment that are not captured as study endpoints will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and reported according to the Time and Events Table (Section 6.2).

It is anticipated that prednisone doses not in accordance with **Table 1** may occur. For example, a patient with life-threatening steroid toxicities may require discontinuation of treatment. Prednisone dosing delays and dose modifications that deviate from the prescribed prednisone taper will be monitored and their reasons reported.

7.3 Concomitant Medications/Treatments

Concomitant use of investigational agents is not permitted during the treatment phase of the study without PI approval.

7.4 Other Modalities or Procedures

Patients who have undergone allogeneic HCT are often simultaneously being treated for other conditions and transplant-related complications. Such treatments will be considered distinct from the study treatment.

7.5 Duration of Therapy

The duration of protocol therapy on this study is four weeks. Protocol therapy will end after week 4, if any of the conditions for removal of therapy during the first 4 weeks as defined in section 7.1 are met, or if any of the following criteria apply:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

7.6 Off Treatment Criteria

Patients will be removed from study treatment when any of the criteria listed in Section 7.1 or 7.5 apply. The reason for ending study treatment and the date the patient was removed from treatment will be documented in the study record. All patients who discontinue treatment should continue to comply with protocol specific follow-up procedures and remain On Study as outlined in Section 8.2. The only exception to this requirement is when a subject withdraws consent for all study procedures or dies.

7.7 Duration of Follow-Up

Patients will be followed until 1 year post-enrollment, withdrawal of consent or until death, whichever occurs first. HCT patients are followed closely and frequent clinical evaluations are the norm. While the following outlines the minimum frequency of follow-up evaluations, it is anticipated that the majority of patients will be evaluated more frequently.

During the first 4 weeks of participation, patients will be seen at least weekly for assessment of their GVHD. Patients will also be evaluated at days 42, 56, 90, 180 and 365. Additionally, patients will be evaluated if GVHD flares.

7.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

7.8.1 Patient withdraws consent (termination of treatment and follow-up);

7.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

7.8.3 Patient is unable to comply with protocol requirements;

7.8.4 The subject has any disorder or condition that in the investigator's judgment may impede the participant's participation in the study, pose increased risk to the participant, or confound the results of the study

7.8.5 Termination of the study;

7.8.6 Patient completes protocol treatment and follow-up criteria.

Discontinuation of study treatment (such as subsequent to starting systemic steroids) does not remove the patient from other aspects of study participation including providing follow-up data. Participants will be encouraged to provide this information whether or not they complete the anticipated course of study treatment.

7.9 Patient Replacement

Patients who enroll in the study but (1) do not receive prednisone treatment or (2) initiate prednisone at a dose higher than 0.5 mg/kg (rounding to achieve a feasible dose is allowed) will be replaced. The number of patients and reason(s) for replacement will be reported and will be used to assess the feasibility of the study design. Patients who withdraw consent or are lost to follow-up prior to day 28 will also be replaced. Patients who do not follow the protocol defined steroid dosing will be considered evaluable and not replaced. Reasons for not following the protocol defined steroid dosing will be reported.

8.0 STUDY PROCEDURES

8.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. Frequent monitoring of clinical chemistry and hematology is routine in HCT patients. This study does not require specific laboratory monitoring other than specified below.

8.1.1 **Informed consent** (**and assent from children when applicable)**

8.1.2 **Demographics**

8.1.3 **Review subject eligibility criteria**

8.1.4 **Review concomitant medications** (immunosuppressants and GVHD prophylaxis medications only)

8.1.5 **Baseline PRO Assessment**

8.1.6 **Adverse event assessment**

Baseline adverse events will be assessed and preexisting conditions will be reported. See Section 10.0 for Adverse Event monitoring and reporting.

8.1.7 **Serum chemistries (within 3 days prior to enrollment)**

ALT/SGPT, AST/SGOT, total and direct bilirubin are required for assessment of exclusion criteria within 3 days prior to enrollment.

8.2 Follow-Up Procedures

The following outlines the **minimum** frequency of follow-up evaluations, it is anticipated that the majority of patients will be evaluated more frequently.

During the first 4 weeks of participation (i.e., through the primary endpoint), patients will be evaluated at least weekly for assessment of their GVHD. Patients will also be evaluated at study

day 42, 56, 90, 180, 1 year and at the time of GVHD flares. Telehealth visits are permitted when in-person visits are not feasible.

Patient compliance with self-administration of prednisone will be assessed by pill diary. Patients will record whether they took their prescribed dose daily for the first 28 days of treatment. Pill diaries will be reviewed at specified study visits and discrepancies with prescribed and actual administration resolved.

PRO tests will be administered at baseline, day 28, day 90 and day 180 visits. Participants will complete the study assessments in-person during their follow-up visits. We will use email, paper copies by US mail, or verbal completion by video or telephone visits when in-person assessment is not feasible. In some cases the baseline PRO will be administered prior to confirming eligibility. If this is the case and patient is a screen fail, the PRO survey will be destroyed. PRO tests are provided in Appendix B.

Infections, as defined in sections 9.1.11 will be closely monitored on this study. In our preliminary data, all patients who developed at least one serious infection did so within 90 days. Given these data, we will monitor for serious infections from start of study treatment through study day 90.

TABLE 2: TIME AND EVENTS TABLE

	Screening	Study day 0	Study day 7	Study day 14	Study day 21	**Study day 28**[1]	Study day 42	Study day 56	Study day 90	Study day 180	Study day 365	GVHD Flare[8]
Windows	*Newly diagnosed acute GVHD in need of systemic treatment +/- 1 day*	*Start of prednisone (or equivalent) therapy*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	***+/- 2 day***	*+/- 3 days*	*+/- 3 days*	*+/- 7 days*	*+/- 14 days*	*+/- 21 days*	*+/- 3 days*
Eligibility Review	X											
Concomitant Medication Review[2]	X	X	X	X	X	X	X	X	X			
Steroid Dose Collection	X	Steroid dose will be collected at each study visit during the first 90 days of study **and** changes occurring outside of the defined timepoints will be captured on an ad hoc form through study day 90										
Adverse Event Evaluations[3]	X	Adverse events will be reported from study day 0 through day 56. Report serious adverse events as they occur.										
Infections		Infections as defined in sections 9.1.11 will be reported from study day 0 through study day 90										
Serum Chemistry	X											
GVHD Staging[4]	X	X	X	X	X	X	X	X	X			X
Height and Weight	X					X		X	X	X	X	
Survival, Relapse & Chronic GVHD Status										X	X	
Patient Reported Outcomes		X[6]				X[6]			X[6]	X[6]		

(PRO) Assessment[5]												
	CORRELATIVE STUDIES											
5 ml serum[7]	X		X	X	X	X						X

[1] The primary endpoint is assessed on day 28 ±2 days

[2] Concomitant medication review will report **only** immunosuppressants and other drugs administered during the reporting period for GVHD prevention and treatment.

[3] Serious adverse events are reported as they occur. Other adverse events can be batch reported after day 56 of study.

[4] GVHD staging will follow the detailed guidelines provided in the MAGIC Acute GVHD Staging Guidance. GVHD staging and treatment should be reported weekly through day 100 post-HCT for patients co-enrolled on the MAGIC natural history study as per the natural history study calendar of events. Steroid dose changes occurring outside of the defined timepoints will be captured on an ad hoc form through study day 90.

[5] PRO tests consist of 7-10 questions that can be administered within 15-20 minutes. These should be completed during in-person visits. When an in-person follow-up is not available, PROs are permitted to be administered via email, paper copies by US mail, or verbal completion by video or telephone visits. PRO measures are included in Appendix B.

[6] The windows to administer PROs are 4 days for the baseline, 7 days for the day 28 assessment, 21 days for the day 90 assessment, and 28 days for the day 180 assessment.

[7] Serum samples will be banked for correlative studies. (For patients co-enrolled on the MAGIC natural history trial: To avoid unnecessary sample collection, when GVHD driven samples are collected within 3 days of a scheduled calendar based sample, the calendar based sample should not be collected).

[8] Collect GVHD staging data and a serum sample at the time of the first GVHD flare during the follow-up period, if needed

9.0 GVHD CLINICAL STAGING

GVHD clinical staging will be according to the established MAGIC criteria[50].

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Plus bullae and desquamation >5% BSA
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl
GI tract	Adult: < 500 ml/day Children <10 mg/kg/day	Adult: 500–1000 ml/day Children 10-19.9 mg/kg/day	Adult: 1001-1500 ml/day Children 20- 30 mg/kg/day	Adult: >1500 ml/day Children > 30 mg/kg/day	Severe abdominal pain +/- ileus, frank blood or melena (regardless of stool volume)
UGI		Severe nausea/vomiting			

- For GI GVHD, children is defined as <18 years of age and <50 kg weight
- For stage 4 GI GVHD, severe abdominal pain is defined as (1) pain that requires opioid use **and** (2) pain that significantly impacts on performance status as determined by the treating physician
- Comprehensive GVHD staging guidance is provided in the MAGIC GVHD Staging Guidance.

Overall Clinical Grade:

Grade 0 No stage 1-4 of any organ

Grade I Stage 1-2 skin and no liver or GI involvement

Grade II Stage 3 skin and/or Stage 1 liver and/or Stage 1 GI

Grade III Stage 0-3 skin with Stage 2-3 liver and/or Stage 2-3 GI

Grade IV Stage 4 in any target organ (skin, liver, GI)

Minnesota Risk Scoring[5]:

Standard Risk:

Stage 1-3 skin (single organ system)
Stage 1 GI (single organ system)
Stage 2 lower GI (if upper GI is absent)
Stage 1 upper GI + Stage 1-2 lower GI
Stage 1-3 skin + Stage 1 GI (two organ system involvement)
Stage 1-3 skin + Stage 1-4 liver (two organ system involvement)

High Risk: Any other combination of single or dual organ aGVHD stages

Minnesota risk scoring calculator: http://z.umn.edu/MNAcuteGVHDRiskScore

9.1 Endpoint and Response Criteria

9.1.1 Definitions

Treatment Response is defined as a patient's weekly clinical GVHD response due to systemic treatment, typically systemic steroids, without taking into account if new lines of treatment were given.

Study Response is defined as a patient's day 28 clinical GVHD response due to systemic treatment, with also taking into account if new lines of treatment were given.

Complete Response (CR): All evaluable organs (skin, liver, GI tract) stage 0. For a response to be scored as CR on day 28, the patient must be in CR on that day and have had no intervening additional GVHD therapy.

Partial Response (PR): An improvement in one or more organ involved with GVHD symptoms without worsening in others. For a response to be scored as PR on day 28, the patient must be in PR on that day and have had no intervening additional GVHD therapy.

Very Good Partial Response (VGPR): Any response that approximates a CR with the exception of rash <25% body surface area[55]. For a response to be scored as VGPR on day 28, the patient must be in response on day 28 and have had no intervening systemic therapy for acute GVHD other than steroids.

No response (NR): All responses that are not CR, PR, or VGPR. Patients who receive any systemic GVHD therapy other than the continuation or modification of GVHD prophylaxis, systemic steroids, and topical/non-absorbable oral steroid therapy, will be scored as NR on day 28 regardless of organ staging.

9.1.2 Earliest response

Earliest response, or first response, is defined as the first date from start of systemic treatment when CR, PR or VGPR occurs. Further improvement may

occur, but the initial date of response will be reported and used to determine duration of response

9.1.3 Steroid refractory GVHD

Steroid refractory GVHD is defined as either an increase by at least one GVHD stage that requires initiation of an additional line of therapy beyond steroids or a lack of response (i.e., NR) by day 28. Escalation of steroid doses during treatment for GVHD are not considered in the definition of steroid refractory GVHD. The resumption or addition of tacrolimus, sirolimus, or cyclosporine will not be considered a new line of treatment.

9.1.4 GVHD Flare

An increase in GVHD symptoms of at least 1 stage after CR, PR or VGPR on day 28 that requires a change in treatment. Change in treatment includes increase in steroid dose of >0.25 mg/kg/day or initiation of another systemic immunosuppressive therapy. The resumption or addition of tacrolimus, sirolimus, or cyclosporine will not be considered a new line of treatment.

9.1.5 Duration of response

Duration of response is calculated as the number of days from first response to steroid treatment until GVHD flare, development of steroid refractory GVHD, initiation of additional systemic treatment for GVHD, or death, whichever comes first.

9.1.6 Steroid discontinuation

The date of discontinuation of steroid therapy will be reported.

9.1.7 Lines of GVHD therapy

Any additional systemic immunosuppression treatment to steroid therapy for acute GVHD will be considered 2nd line therapy and considered a failure to respond to steroid treatment. Resumption or changes in GVHD prophylaxis (e.g., substitution of mycophenolate for tacrolimus due to PRES) are not considered new lines of therapy. The addition of tacrolimus, sirolimus, or cyclosporine will not be considered a new line of treatment. Topical steroids and non-absorbable oral steroids are not considered new lines of therapy.

9.1.8 Non-Relapse Mortality (NRM)

Any death that occurs after HCT not attributable to relapse of the underlying disease will be considered a non-relapse death.

9.1.9 Chronic GVHD

The occurrence of chronic GVHD as defined by NIH consensus criteria requiring systemic treatment, including date of diagnosis, will be reported.

9.1.10 Relapse

Relapse, including date of relapse, of the underlying malignancy will be reported.

9.1.11 Serious Infections

Serious infections are defined using the standardized criteria widely used for clinical trials at academic BMT centers, such as life-threatening fungal infections or hemorrhagic cystitis from BK viral infection[27] and include clinically significant CMV infections that require anti-viral treatment regardless of end-organ damage, given the toxicity of such treatments[28]. Serious infections include any viral, bacterial, fungal or parasitic infections that requires systemic treatment.

All grade 2 or 3 infections as defined by the Blood and Marrow Transplant Clinical Trials Network must be reported through day 90.

9.1.12 **Linear growth velocity:** The change in linear growth (height) from baseline to last contact, corrected for age and duration of observation.

9.2 Safety/Toxicity Definitions

9.2.1 Safety/Tolerability

The study will use the CTCAE version 5.0 for reporting of adverse events (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

10.0 ADVERSE EVENTS

10.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar strategies. Data on adverse events will be collected from the time of the initiation of study treatment until day 56 as defined in section 10.2. Any serious adverse event that occurs after day 56 that is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE (CTCAE grade 3 or higher) or SAE, as defined in Section 10.2.2, occurring from the initial study treatment administration through study

day 56 days must be reported as an adverse event in the patient's source documents and on the CRF.

10.2 Definitions

10.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- Event reporting for GVHD treatment protocols can be complicated and confusing for investigators, data managers, and regulatory oversight bodies because patients typically develop numerous complications as part of the typical treatment course not related to study therapy. Furthermore, transplant-related complications often occur both simultaneously and in series, as one complication leads to a series of downstream events. Therefore, a well-conceived event reporting plan separates background transplant and GVHD noise as might be seen with any transplant where GVHD develops from study related events that are relevant to patient safety. On this study, we will not report any CTCAE grade 1 and 2 adverse events (which make up the majority of events) unless the investigator determines the event should be reported to protect subject safety. Furthermore, because vast experience with corticosteroid treatment for GVHD in children already exists, and this is a de-escalation study, with the exception of infections (which are also a study endpoint), adverse events deemed not related or unlikely related to tapering steroids (e.g., symptomatic hypoglycemia or steroid withdrawal symptoms) are also not required to be reported. Changes in GVHD staging, treatment response, will be reported as study endpoints and are not considered adverse events on this trial with the exception of the development of steroid refractory GVHD.

- After study day 56, adverse events should only be reported if they are unexpected or fatal regardless of attribution. All serious adverse events. Reporting of such events should include the investigator's assessment as to whether the event should be attributed to any of the HCT procedure itself, GVHD, or its treatment. An event may be attributable to all, some, or one of these categories.

- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy and otherwise meet the criteria for a reportable adverse event as defined above. They are to be captured under the signs, symptoms or diagnoses associated with them.

- All serious adverse event reporting will cease if patient has relapse or second transplant.

10.2.2 **Serious Adverse Event**

An adverse event is considered “serious” if it results in any of the following outcomes:

- Death
- A life-threatening adverse event
  An adverse event is considered ‘life-threatening’ if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

  As additional guidance, preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient’s medical history at the time of study enrollment should not be considered SAEs.

  The development of steroid-refractory GVHD at any time from study entry to study day 100 will be considered an SAE for the purposes of this study.

10.2.3 **Expected Adverse Events**

In this protocol, an adverse event (AE) is considered “expected” if it is described in the Package Insert, in published medical literature, in the protocol, or in the informed consent document.

10.2.4 Unexpected Adverse Event

In this protocol, an adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, in published medical literature, in the protocol, or in the informed consent document.

10.3 Adverse Event Characteristics

10.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site. (http://ctep.cancer.gov)

10.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

10.4 Serious Adverse Event Reporting Guidelines

The Sponsor Investigator will report SAEs to regulatory bodies and to the participating sites in the following manner:

SAE Reporting

	DCC Reports SAE to:		
	DSMB	**Single IRB (NMDP)**	**Consortium**
Note: Sites report these SAEs to DCC from patient consent to study day 56			
All SAEs; ✓ Expected or Unexpected ✓ Not Related, Unlikely, Possible, Probable, or Definite	With scheduled submissions	In summary fashion at the time of IRB continuing review	Monthly
Note: Sites report these SAEs to DCC for events occurring after 56 days			
SAEs – ✓ Unexpected ✓ Probable or Definite	5 days from knowledge AND	Within 10 working days after the investigator becomes aware of the event	Monthly

	With scheduled submissions		
Note: Sites report these SAEs to DCC for events occurring at any time on study			
SAEs – ✓ All deaths not meeting criteria in above two categories	With scheduled submissions	Within 10 working days if the death meets the criteria for an unanticipated problem as defined in Section 10.5	Monthly

10.4.1 The Principal Investigator must be notified within 3 business day of study team's knowledge of any event meeting the criteria and definition per this protocol in section 10.1 of a serious adverse event, occurring during the study.

10.4.2 The investigator must report all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible to study treatment administration) to the local IRB as per local IRB policy.

10.4.3 All reportable Serious Adverse Events will be reported using the Serious Adverse Event form within 3 days of first awareness of the event to the MAGIC Data Coordinating Center. A copy of the form should be sent to the MAGIC Coordinator via email to **magicdcc@mssm.edu**.

The MAGIC Data Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 3 days of review of the information by the PI or designee if the event(s) is believed to be related (i.e. probably or definitely) to the study treatment. All other Serious Adverse Events will be discussed on monthly webinars held with all participating centers.

The Principal Investigator will be responsible for reporting of events to the FDA and supporters, as appropriate and defined in the regulations under 21 CFR 312.32.

10.5 Reporting of Unanticipated Problems

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem involving risks to subjects or others, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes are considered unanticipated if it meets all of the following criteria:

1. Unexpected (not previously documented in terms of nature, severity, or frequency);
2. Causally related or possibly related to participation in the study; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the MAGIC Data Coordinating Center within 3 days of first awareness of the events, and to the local IRB as per local IRB policy.

10.6 Stopping Rules

The primary risk from a rapid steroid taper is the possibility of steroid-refractory GVHD. We will monitor the study subjects for the development of steroid-refractory GVHD. We will allow continuous accrual on to the study unless a stopping rule is met or the target accrual is reached. The study may also be stopped based on the recommendation of the investigators, the TCI DSMC, or the single IRB.

Steroid-refractory GVHD:

We expect a rapid steroid taper to be safe for ultra-low risk patients given the high response rates and very low NRM observed in our preliminary data from patients treated with standard steroid doses. The primary risk to patients is the possibility that a rapid taper of steroids will result in GVHD that is non-responsive even to higher doses of steroids. In order to protect study subjects we have designed a stopping rule that will terminate the trial early if a rapid taper leads to an unacceptable incidence of steroid-refractory GVHD. Our preliminary data show that the incidence of steroid-refractory GVHD by day 100 of treatment using the definition in section 9.1.3 in pediatric patients with low risk (Minnesota standard risk/Ann Arbor 1) GVHD is 15%.

We will monitor the number of cases of steroid-refractory GVHD by day 100 in the entire study population and accrual will be halted if there is sufficient evidence that the rate of steroid refractory GVHD exceeds the acceptable target rate of 15% by more than 20% (35% unacceptable rate). If the cumulative number of patients that experience treatment failure is greater than the associated boundary value b_k listed in the table below, among the k patients enrolled in the trial, then accrual will be halted for safety considerations. Specifically, if more than 4 of the first 11 patients or more than 5 of the first 15, etc. develop steroid refractory GVHD, the trial will be halted for safety considerations.

Maximum # of Patients, k	Up to 11	12-15	16-19	20-23	24-27	28-32	33-36	37-41	42-46	47-50
Boundary, b_k	4	5	6	7	8	9	10	11	12	13

The operating characteristics of this stopping rule are as follows:

	True Steroid Refractory Rate		
	15%	**30%**	**35%**
Probability of Early Stopping	**0.05**	**0.75**	**0.92**

Using these boundaries, if the true steroid refractory rate is 15%, 30%, or 35%, the probability of stopping the trial early is 0.05, 0.76, and 0.92 respectively.

All the stopping rules were computed using the toxbdry function in R and calculations of this function are based on methods described in Chapter 12 of Jennison and Turnbull and in the illustrative paper by Ivanova, Qaquish and Schell[56,57]. The boundary crossing probabilities under

the acceptable and unacceptable toxicity rates are 0.05 and 0.90 respectively and the boundaries are calculated starting from 10th patient.

11.0 DRUG INFORMATION

11.1 Predniso(lo)ne

(Deltasone®, PrediniSONE Intensol®, Rayos®, Meticorten®, Liquid Pred®, Pediapred®, Millipred®, OraPred ODT®)

11.1.1 Source and Pharmacology

Prednisone and prednisolone are synthetic compounds closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells that are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with a plasma $t_{½}$ of 3.2 to 4 hours. (Biologic half-life is 12-36 hours.)

Predniso(lo)ne Toxicities:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (that may be reversible on discontinuation of prednisone in children)	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Corticosteroids cross the placenta (prednisone has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. Prednisone is excreted into breast		

	milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ≤ 20 mg/day.

(L) Toxicity may also occur later.

11.1.2 **Formulation and Stability**

Prednisone is available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets and as a solution in 1 mg/mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

Prednisolone is available as 5 mg scored tablets (base) and 10 mg, 15 mg, and 30 mg orally disintegrating tablets (ODT; sodium phosphate [strength expressed as base]). Liquid formulations of prednisolone are available as 15 mg/5 mL oral solution (base); 5 mg/5 mL, 10 mg/5 mL, 15 mg/5 mL, 20 mg/5 mL oral solution (sodium phosphate [strength expressed as base]; and 15 mg/5 mL oral syrup (base). Inactive ingredients vary depending on manufacturer. Tablet formulations may contain dyes and liquid formulations may contain edetate disodium, methylparaben, saccharin sodium.

11.1.3 **Guidelines for Administration**

See Treatment and Dose Modifications sections of the protocol.
PredniSONE and prednisoLONE are equipotent corticosteroids.

11.1.4 **Supplier**

Commercially available from various sources. See package insert for further information

12.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to improve our understanding of the biological processes that drive GVHD and its clinical outcomes.

12.1 Sample Collection Guidelines

The correlative sample collection schedule is detailed in section 8 above. Serum will be collected in no additive, silicone coated glass or plastic tubes containing no anticoagulant (red or gold top tube). Non-real time samples (i.e., those that do not require overnight MAP analysis – screening, week 1, and week 2) will be processed at the participating center and batch shipped to GVHD Laboratory semi-annually for storage (in January and July). Further details are provided in Appendix A.

12.2 Assay Methodology

Assays will be performed according to the published MAGIC protocols[29].

12.3 Specimen Banking

Patient samples collected for this study will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. In addition to the biomarker studies planned as part of this study, additional studies studying the underlying disease may be performed on the banked research samples as part of collaborations with other institutions and entities.

The specimens and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by the Icahn School of Medicine at Mount Sinai, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

13.0 DATA COLLECTION PLAN

13.1 Data Coordinating Center (DCC)

Patients will be registered at the time of screening through an electronic data collection system (Electronic Research Application Portal, eRAP) maintained by the Icahn School of Medicine at Mount Sinai and used by the MAGIC DCC for clinical trials management. At the time of registration each subject, regardless of screening results, is assigned a unique six alphanumeric character identifier. Identifiers are used instead of subject names ensuring patient confidentiality with regard to all collected data and samples. Files that permit biospecimens, data, and records can be linked back to living individuals are available only at the enrolling site; the MAGIC DCC and laboratory personnel have no access to these files. All study correspondence and redacted source documents are electronically imaged and stored on a routinely backed-up, encrypted, password secured, computer server that sits behind a VPN-secured firewall that requires two-factor authentication to prevent intrusion. Research data files are stored within a clinical trial database created for this specific clinical trial, maintained by a dedicated information technology support team and protected by the same robust computer security protocols described above. Paper records are maintained in a locked file by the DCC regulatory team until they can be securely destroyed. All HIPAA protected information is maintained behind password-protected files at all times again using the same robust computer security protocols described above. Only HIPAA-certified personnel have access to individually identifiable information about human subjects. The private information and/or samples collected as part of this research will never be used or shared for future research unrelated to the study of GVHD or BMT, even if the identifiable information is removed.

13.2 Case Report Forms (CRF)

All data required to determine the safety, efficacy, and calculate each endpoint in section 9.1 will be submitted using the electronic case report forms located within the clinical trial subsection of the eRAP database for this trial.

13.3 Patient Reported Outcomes (PRO)

Patient reported outcome data will be obtained according to the schedule provided in the time and events table. Patients age 8 and older (and parental proxy surveys for patients age 5 to 17) will be administered six PROMIS surveys (see Appendix B) at each time point, thereby building the first multicenter quality of life dataset for pediatric patients with GVHD[47,48]. Each test consists of 4 to 10 questions and the completion of all surveys will take less than 20 minutes. Surveys will be preferentially administered on paper and in-person but study staff will follow-up with patients

and parents to complete any missed surveys or missed questions by mail, email, telehealth, or telephone and surveys can be finalized by email, verbally, or by US mail.

Study staff at all sites will receive virtual training to ensure consistent procedures for collection of PROs. Staff will be trained regarding: 1) approaching participants; 2) administering PROs in-person, electronically, or via telehealth; 3) tracking study participants; and 4) minimizing missing data through timely review and persistent follow-up. PRO scores will be integrated into the database using a specifically designed module that includes the response to each survey question, as well as both the raw and standardized scores for each survey.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design/Study Endpoints

This is a phase II, single arm, open-label, multicenter clinical trial to determine the effectiveness of a structured steroid taper, guided by serial biomarker and clinical response in pediatric patients with newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1). The primary study measure is the proportion of low-risk GVHD patients who achieve clinical response (CR, VGPR, or PR) on day 28 after being exposed to low cumulative dose of prednisone (≤13.5 mg/kg) or other steroid equivalent during the first 4 weeks of therapy. A single arm phase II design was selected due to the relatively small numbers of allogeneic transplants performed in children.

To further investigate the treatment regimen, we will determine the proportion of patients who achieve a treatment response (CR, VGPR, or PR) by day 28, duration of response, the incidence of steroid refractory GVHD by day 100, and the cumulative steroid dose at days 28 and 90. Secondary endpoints will also include the cumulative incidence of serious infections, patient reported outcomes at days 28, 90, and 180, overall survival at 6 and 12 months, cumulative incidence of NRM at 6 and 12 months, relapse rate, and cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year.

14.2 Sample Size and Accrual

In this phase II clinical trial, our aim is to determine the effectiveness of a structured steroid taper, guided by serial biomarker and clinical response in pediatric patients with newly diagnosed, low-risk acute GVHD defined by standard risk clinical criteria (Minnesota) and low risk biomarkers (Ann Arbor 1). Under current practice, the mean cumulative steroid dose during the first four weeks of treatment is 27.1 mg/kg. A substantial reduction in steroid exposure by 50% or more would likely result in clinical benefit from less treatment-related toxicity. The expected proportion of low-risk acute GVHD patients whose cumulative prednisone (or other steroid equivalent) exposure during the first four weeks of treatment is ≤13.5 mg/kg (i.e., <50% of current practice) is 14%. MAGIC preliminary data indicates that 65% of patients with low risk GVHD ultimately have the ultra-low risk form of GVHD that should be amenable to substantial reductions in steroid exposure. A three-fold increase in the proportion of patients (from 14% to 42%) whose cumulative steroid exposure is ≤13.5 mg/kg would be clinically significant. A sample size of 50 low risk patients provides 90% power with an alpha of 0.001 to detect a difference of 0.28 (0.14 to 0.42) using a two-sided exact test in the proportion of low risk patients treated successfully with low steroid exposure.

The combination of the primary efficacy endpoint (overall response rate) and the secondary endpoints (response rate, duration of response, steroid-refractory GVHD, NRM, and serious infections) will be used to determine if this approach should be compared to the current standard

of unstructured steroid tapers in a phase III trial for patients with low risk GVHD. We will continuously monitor these outcomes and if at any point during this trial sufficient evidence emerges that the structured steroid taper is not likely to result in improvement in any of these parameters, the protocol committee will terminate the trial for futility.

Sample size calculations were performed using PASS 2020 Power Analysis and Sample Size Software (2020) NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

The centers participating in this clinical trial collectively perform >300 allogeneic HCT per year. Based on data from the MAGIC database, we expect 105 patients will develop GVHD per year, including 90 with Minnesota standard risk GVHD. Although it is likely we will accrue faster, a conservative estimate is that we will consent and screen 50% of these cases (n=45), 65% of whom will have Ann Arbor 1 GVHD, which should result in 30 patients enrolled per year (approximately 2.5 per month). We also conservatively estimate that up to 5 patients will need to be replaced. We do not expect all centers to open to enrollment simultaneously and therefore we realistically expect to meet our accrual goals within three years.

14.3 Data Analysis Plans

The primary endpoint is the proportion of patients who (1) achieve CR, VGPR, or PR by day 28 of treatment without additional immunosuppressive therapy and (2) whose cumulative prednisone exposure is ≤13.5 mg/kg. The proportion of patients who are successfully treated with ≤13.5 mg/kg cumulative prednisone dose will be compared to the historical control rate of 14% using a Chi-squared test.

All study patients will be analyzed and when appropriate, subset analyses by ultra-low risk and other patients will be performed. We expect 33 ultra-low risk patients and 17 other patients out of our sample size of 50 study patients, which will be sufficient for subset analyses.

Secondary outcomes such as the overall response rate, duration of response, cumulative incidence of steroid-refractory GVHD, incidence of serious infections (viral, bacterial, fungal, and parasite), cumulative steroid exposure at day 28 and day 90, overall survival at 6 and 12 months, cumulative incidence of NRM at 6 and 12 months, relapse rate at 6 and 12 months, and cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year will be estimated and compared to historical controls.

Continuous variables will be summarized using standard summary statistics such as number of observations (n), mean, standard deviation (SD), minimum and maximum values, median, and 1st and 3rd quartiles. Categorical variables will be summarized in frequency tables as counts and percentages.

Cumulative incidence of non-relapse mortality will be estimated by Gray's method[58] and relapse will be considered as a competing risk. Disease free and overall survival, defined as the time from the transplantation to death or to last follow-up if alive, will be estimated by the method of Kaplan-Meier and the probability curves and 95% confidence intervals will be provided based on the method of Brookmeyer and Crowley[59].

The exploratory endpoints of linear growth velocity and patient reported outcomes as per Appendix B will be described for patients whose cumulative steroid exposure is ≤13.5 mg/kg and >13.5 mg/kg. Linear growth velocity will be expressed as a standard deviation score of the sex- and age-specific mean.

Data from a randomized adult acute GVHD treatment trial suggests that QOL (both physical and mental functioning) diverges around day 90 among patients with different steroid exposures[25]. We expect our measures to show greater and faster improvement in QOL in patients with less steroid exposure, but for completeness, we will track PROs until 180 days from GVHD onset. The day 180 time point may be confounded by steroid treatment for chronic GVHD in some patients, and subsets may thus need to be analyzed. Formal comparisons between groups are not planned but we will explore the possibility of creating groups according to cumulative steroid dose. If groups can be created, we will compare groups using the difference of half of a standard deviation (5 points) in PRO scores which has been validated as clinically meaningful[60,61]. PROMIS instruments will be scored in accordance with the manuals (https://www.healthmeasures.net/index.php?option=com_content&view=article&id=180&Itemid=994) and the scores will be analyzed using generalized linear models. General hierarchical random effects linear mixed model will be employed with repeated measures nested within site to assess the change between groups in outcomes of interest across multiple time points. The model will also include a random intercept. Determination of model fit will be aided by diagnostics for model residuals. We expect that there will be some minor and major missing data. Minor missing data include missing values on individual survey items. Although we will endeavor to check all questionnaires upon their return and call the participants to try to complete missing items, some data may still be missing. These individual items will be imputed. The imputed values will then be used to obtain point estimates for the missing data. Since the proposed study is longitudinal, major missing data from participant attrition is more likely and, potentially, more problematic. Two different attrition strategies will be employed. In the first, a binary variable for dropout (Yes or No) will be created and we will develop a hierarchic logistic regression model for clustered data (hospital is the clustering variable) using generalized linear mixed models with a logit link function. Any demographic or medical variables identified during initial data screening predicting dropout will be entered first. In the next step, any PRO measures will be assessed as predictor of dropout. These analyses will address the generalizability of study results. Patient and parental proxy scores will be compared for the subsets where both scores are available (ages 8-17y). The QOL analyses will be conducted in collaboration with Dr. Carlton Dampier, co-investigator and an expert in the interpretation of pediatric PRO data at Emory University.

15.0 DATA AND SAFETY MONITORING

The safety of subjects is paramount and supersedes all other concerns. This study employs several layers of oversight to ensure that patient safety is protected.

1. The Protocol Committee, composed of the individual site PI's, will review all facets of study conduct at all sites on monthly webinars
2. The Tisch Cancer Institute Data and Safety Monitoring Committee (TCI DSMC) of the Mount Sinai Health System is the DSMB of record for this study. The DSMB will be compliant with the NIH approved DSMP Charter. This committee will be responsible for monitoring the safety and data integrity of the trial. It is a DSMB entirely composed of members with no connection to this clinical trial.
3. Annual reviews and safety reporting will be provided to the single IRB and to each participating site.

Protocol Committee safety reviews: The centers participating in this study are collaborating centers in MAGIC (Mount Sinai Acute GVHD International Consortium). The local site principal investigator, data manager, and study coordinator will participate in monthly webinars where all facets of study conduct (e.g., screening rate, accrual, AEs, SAEs, and deviations) are discussed,

as is MAGIC standard practice, thereby facilitating early recognition and troubleshooting of potential problems.

The MAGIC Data Coordinating Center is responsible for collating all data and safety reports from all the participating sites, and providing the information to the TCI Data Safety Monitoring Committee.

TCI DSMC: The TCI DSMC serves as the data and safety monitoring board (DSMB) for investigator initiated studies conducted under the auspices of the Tisch Cancer Institute (TCI) at the Mount Sinai Health System. It is compliant with the National Institutes of Health and National Cancer Institute charter for DSMBs. This board will be responsible for monitoring the safety and data integrity of the trial and the DSMB for this study will be entirely composed of members with no connection to this clinical trial.

15.1 Multisite Clinical Monitoring Procedures

This clinical study will be coordinated by the MAGIC Data Coordinating Center (DCC). As such it will be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the DCC. This will be done as an actual site visit, teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his/her study staff will attend the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate DCC personnel until they have been answered and resolved.

This study will be monitored by a representative of the MAGIC Data Coordinating Center. Monitoring visits, whether remote or in person, will be made during the conduct of the study and at study close-out. The following issues will be monitored.

- Signed and dated ICF and assent
- Adherence to the protocol
- Completeness and accuracy of study data and laboratory samples collection

Any issues identified during these visits will be communicated to the site and are expected to be corrected by the site in a timely manner. For review of study-related documents at the DCC, the site will be required to ship, fax, or email documents to be reviewed, ensuring compliance with HIPAA and other privacy regulations.

Participating sites will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities.

16.0 DISSEMINATION OF RESULTS PLAN

Study results will be submitted for presentation at scientific meetings such as the American Society of Hematology or the Tandem BMT annual meetings. A study manuscript will be prepared and submitted to a high-impact scientific journal such as *Blood* or *Journal of Clinical Oncology.*

In addition to publication and presentations, study results will be posted to ClinicalTrials.gov no later than one year from completion date of the primary endpoint. Study participants will be informed that trial results will be posted to ClinicalTrials.gov and this will be documented in the informed consent document for the trial.

17.0 QUALITY ASSURANCE AND AUDITS

The Data Safety Monitoring Board can request a 'for cause' audit of the trial if the board identifies a need for a more rigorous evaluation of study-related issues. A "for cause" audit would be conducted by the Project Manager of the MAGIC Data Coordinating Center.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the MAGIC Data Coordinating Center that such a request has been made.

18.0 CONFLICT OF INTEREST

Drs. Levine and Ferrara are co-inventors of a GVHD biomarkers patent which will be disclosed in the informed consent and in all presentations and publications.

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