A Proof of Concept Pilot Trial of Alpha-1-Antitrypsin for Pre-Emption Of Steroid-Refractory Acute GVHD
PI: John Levine, MD
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A PROOF OF CONCEPT PILOT TRIAL OF ALPHA-1-ANTITRYPSIN FOR PRE-EMPTION OF STEROID-REFRACTORY ACUTE GVHD

Principal Investigator:

John E. Levine, MD, MS
Bone Marrow Transplantation Program
The Tisch Cancer Institute
Division of Hematology/Medical Oncology
Icahn School of Medicine at Mount Sinai
1 Gustave L. Levy Pl, Box 1410,
New York, New York 10029
Phone: 212-241-6021
Fax: 212-241-8618
john.levine@mssm.edu

Co-Investigators:

James Ferrara, MD, DSc
Icahn School of Medicine at Mount Sinai
New York, New York 10029
Phone: 212-824-9365
Fax: 646-537-9576
james.ferrara@mssm.edu

Hannah Choe, MD
The Ohio State University
Columbus, Ohio
Phone: 614-293-3271
Fax: 614-293-7526
hannah.choe@osumc.edu

Karamjeet Sandhu, MD
City of Hope National Medical Center
Duarte, California
Phone: 626-256-4673
Fax: 626-218-6116
ksandhu@coh.org

Madan Jagasia, MBBS, MS
Vanderbilt University
Nashville, Tennessee
Phone: 615-936-8422
Fax : 615-936-1812
madan.jagasia@vanderbilt.edu

Zachariah DeFilipp, MD
Massachusetts General Hospital
Boston, Massachusetts
Phone: 617-726-0187
Fax: 617-643-5843
zdefilipp@mgh.harvard.org

Umut Özbek, PhD (**Biostatistician**)
Icahn School of Medicine at Mount Sinai
New York, New York
Phone: 212-659-9633
Fax: 212-241-2998
umut.ozbek@mountsinai.org

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TABLE OF CONTENTS

ABBREVIATIONS

Examples Include [the list should be inclusive of the entire protocol]:

6-MP	6-mercaptopurine
AAT	Alpha-1-antitrypsin
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
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
CD	Crohn's Disease
CMP	Comprehensive Metabolic Panel
CMV	Cytomegalovirus
CNS	Central Nervous System
Co-PI	Co-Principal Investigator
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
EBV	Epstein-Barr Virus
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GI	Gastrointestinal
GVHD	Graft-Versus-Host Disease
HCT	Hematopoietic Stem Cell Transplantation
HHV6	Human Herpes Virus 6
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
MS	Multiple Sclerosis
NCI	National Cancer Institute
NOS	Not Otherwise Specified

NR	No Response
NRM	Non-Relapse Mortality
OS	Overall Survival
PE	Physical Exam
PI	Principal Investigator
PJP	*Pneumocystis Jiroveci* Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PTLD	Post-Transplant Lymphoproliferative Disorder
REG3α	Regenerating islet-derived 3 alpha
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 the Mount Sinai Health System
TNFR1	Tumor necrosis factor receptor-1
UGI	Upper Gastrointestinal
VZV	Varicella-Zoster Virus

STUDY SYNOPSIS

Title	A Proof of Concept Pilot Trial of Alpha-1-Antitrypsin For Pre-Emption Of Steroid-Refractory Acute GVHD
Phase	Proof of Concept Pilot
Methodology	Open label single arm
Study Duration	2 years
Study Center(s)	Multicenter – Icahn School of Medicine at Mount Sinai, Mass General, Ohio State University, Vanderbilt University, City of Hope
Objectives	**PRIMARY:** To generate data for assessing the feasibility, safety and preliminary efficacy of alpha-1-antitrypsin (AAT) as pre-emptive therapy in patients at high risk for the development of steroid-refractory GVHD. **SECONDARY:** To generate a preliminary estimate of the 100 day incidence of clinically relevant GVHD states including steroid-refractory GVHD, grade II-IV GVHD, and grade III-IV in patients at high risk for the development of steroid-refractory GVHD treated with AAT. To generate a preliminary estimate of the non-relapse mortality, relapse, and survival rates in patients at high risk for the development of steroid-refractory GVHD treated with AAT. To generate a preliminary estimate of the incidence of severe toxicities, serious infections, and viral reactivations in patients at high risk for the development of steroid-refractory GVHD treated with AAT. To assess the safety of AAT as pre-emptive therapy in patients at high risk for the development of steroid-refractory GVHD. **EXPLORATORY:** To correlate GVHD biomarkers with clinical endpoints
Number of Subjects	30 subjects
Inclusion Criteria	1. High risk prediction score as determined by the MAGIC algorithm at either day 7 or day 14 post HCT. 2. Any donor type (e.g., related, unrelated) or stem cell source (bone marrow, peripheral blood, cord blood). 3. Related and unrelated donor and recipient match each other for at least 7/8 HLA-loci (HLA-A, B, C, and DR) 4. Cord blood donor(s) match recipient for at least 4/6 HLA-loci (HLA-A, B, and DR) 5. Subjects receiving either non-myeloablative or myeloablative or reduced intensity conditioning regimen are eligible. 6. Any GVHD prophylaxis is permitted. 7. The use of serotherapy to prevent GVHD (e.g.,antithymocyte globulin) prior to day 3 post-HCT is permitted. 8. Age 18 years and older 9. Direct bilirubin must be <2 mg/dL unless the elevation is known to be due to Gilbert syndrome within 3 days of enrollment. 10. ALT/SGPT and AST/SGOT must be <5 x the upper limit of the normal range within 3 days of enrollment. 11. Written informed consent from patient or legal representative.

Exclusion Criteria	1. Patients who develop acute GVHD prior to start of study drug 2. Patients at very high risk for primary disease relapse post HCT defined as very high disease risk index (Armand et al. 2014) 3. Patients participating in a clinical trial where prevention of GVHD is the primary endpoint 4. Uncontrolled active infection (i.e., progressive symptoms related to infection despite treatment or persistently positive microbiological cultures despite treatment or any other evidence of severe sepsis) 5. Patients who are pregnant 6. Patients on dialysis within 7 days of enrollment 7. Patients requiring mechanical respiratory support or patients requiring oxygen supplementation exceeding 40% FiO2 within 14 days of enrollment. 8. Patients receiving investigational agent within 30 days of enrollment However, the Principal Investigator (PI) may approve prior use of an investigational agent if the agent is not expected to interfere with the safety or the efficacy of alpha-1-antitrypsin 9. History of allergic reaction to alpha-1-antitrypsin
Study Product(s), Dose, Route, Regimen	Alpha-1-antitrypsin (Glassia) 90 mg/kg intravenous on day 0, then 45 mg/kg twice weekly for 15 more doses
Duration of Administration	Eight weeks
Statistical Methodology	This is a proof of concept pilot study intended to determine if sufficient evidence can be developed to warrant further study of pre-emptive treatment with AAT. The expected incidence of steroid refractory (SR) GVHD by **day 100** in patients who are high risk at either day 7 or 14 is 28%. We assume that the incidence of steroid refractory GVHD by day 100 among high risk patients treated pre-emptively will be 15% as a clinically meaningful incidence. Based on this assumption, a sample size of 30 achieves 85% power to detect a 13% improvement (28%-15%) in steroid refractory incidence rate using a one-sided exact test with a target significance level of 0.23. If we observe 6 or fewer cases of SR GVHD, we will consider this approach sufficiently promising to warrant further study.

1.0 BACKGROUND AND RATIONALE

1.1 Acute GVHD

Hematopoietic cellular transplantation (HCT or BMT) is an important treatment for high-risk hematologic malignancies whose curative potential depends on the graft-versus-leukemia (GVL) effect. Graft-versus-host disease (GVHD), the major cause of non-relapse mortality (NRM) after HCT, is closely associated with GVL [1-3]. Pre-transplant clinical risk factors for GVHD include the degree of human leukocyte antigen (HLA) match between donor and recipient, recipient age, donor type, and conditioning regimen intensity [4,5]. Some centers use one or more of these risk factors to guide GVHD prophylaxis, such as the use of anti-thymocyte globulin when the donor is not an HLA-identical sibling [6], but such approaches are globally immunosuppressive and carry their own risks, in particular of opportunistic infections [7,8].

Acute GVHD affects 40% to 60% of patients and targets the skin, liver, and gastrointestinal (GI) tract [5,9]. The median onset of acute GVHD is approximately 1 month after transplant [10,11]. The initial treatment for GVHD is typically high doses of systemic corticosteroids, but up to 50% of patients do not respond to this approach. Steroid refractory (SR) GVHD, which most often involves the GI tract, is the primary driver of lethal GVHD, and by extension, non-relapse mortality after HCT [10]. However, until now there has been no reliable method to identify the patients at high risk for SR GVHD before GVHD develops.

1.2 GVHD Biomarker Algorithms Predict HCT Outcomes

The concentrations of several protein biomarkers (e.g., ST2, REG3α, IL2Rα, TNFR1, hepatocyte growth factor, and elafin) in the serum are increased in patients with GVHD [12-15]. Combinations of ST2 and REG3α, with or without TNFR1, have been proven to be prognostic for GVHD outcomes when measured at the time GVHD is diagnosed [10,16]. Recently, we used serum samples obtained from patients participating in the Mount Sinai Acute GVHD International Consortium (MAGIC) to develop and validate an algorithm that uses the combination of ST2 and REG3α concentrations, measured on Day 7 post-HCT, to predict the development of non-relapse mortality (NRM) [16]. We used samples from Day 7 post-HCT to develop the algorithm because GVHD rarely develops in the first week after HCT, providing sufficient time to test pre-emptive treatment strategies. The MAGIC algorithm identified a high risk (HR) group in the training set whose NRM (28%) was significantly greater ($p<0.001$) than that of the low risk (LR) group (7%) (Figure 1A). Application of this algorithm to the test set produced similar, highly statistically significant differences between HR and LR groups (Figure 1B). We performed a second validation in the multicenter set and again observed large differences between groups, with an HR 6-month NRM of 26% versus 10% in the LR group ($p<0.001$) (Figure 1C). The proportion of patients in the HR group was similar in all 3 patient sets (16% to 20%). Relapse rates were equivalent in both risk groups in all 3 sets (Figure 1, D–F), with the result that HR patients experienced significantly worse overall survival ($p<0.001$) (Figure 1, G–I). Importantly, GVHD was the driver of NRM. HR patients were 3 times more likely to die from GVHD than LR patients (HR 19% vs. LR 6%, $p<0.001$), a finding explained by the much higher 6-month incidence of SR GVHD in high risk patients compared to LR patients (35% vs 15%, $p<0.001$). It is likely that the blood biomarker concentrations on Day 7 reflect subclinical GI pathology, a notion that is reinforced by the fact that ST2 and REG3α, the two biomarkers that performed the best in the models, are closely associated with GI GVHD[12,17].

Several pre-HCT clinical risk factors predict a higher risk of NRM, such as HLA mismatch, non-family member donors, age of the recipient, and the intensity of the conditioning regimen[5,18]. Importantly, the MAGIC algorithm also stratified patients into distinct risk groups independently of patient age [≤21y: HR 27% vs LR 6%, $p<0.001$; >21y: HR 29% vs LR 8%, $p<0.001$], conditioning regimen [reduced intensity: HR 37% vs LR 8%, $p<0.001$; full intensity: HR 25% vs LR 8%, $p<0.001$] or the use of thymoglobulin in the conditioning regimen [ATG given: HR 31% vs LR 8%, $p<0.001$;

no ATG: HR 28% vs LR 8%, p<0.001]. Relapse rates were equivalent within all subgroups of clinical risk factors, resulting in a decrease of at least 20% in overall survival for HR patients

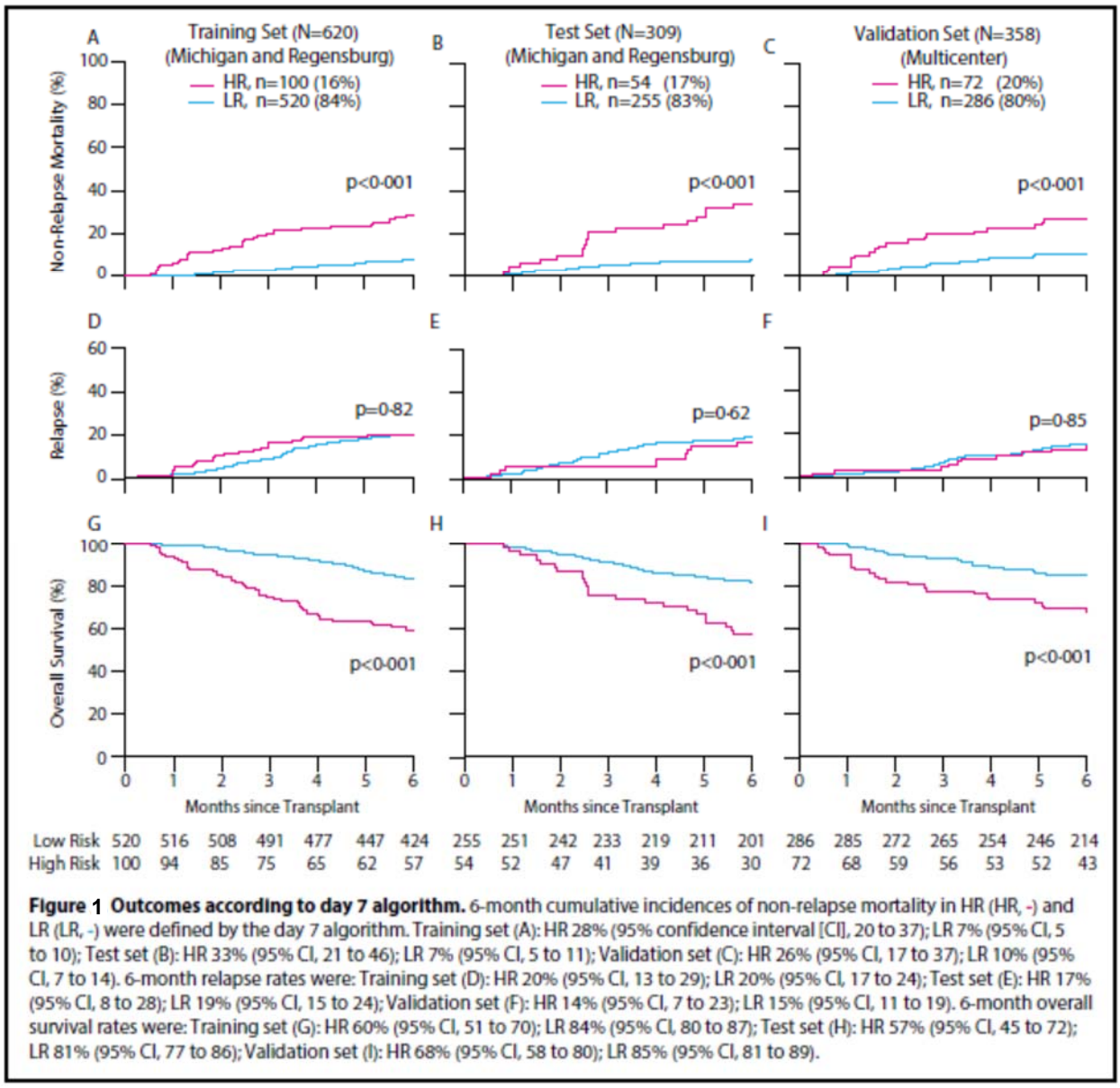

Figure 1 Outcomes according to day 7 algorithm. 6-month cumulative incidences of non-relapse mortality in HR (HR, -) and LR (LR, -) were defined by the day 7 algorithm. Training set (A): HR 28% (95% confidence interval [CI], 20 to 37); LR 7% (95% CI, 5 to 10); Test set (B): HR 33% (95% CI, 21 to 46); LR 7% (95% CI, 5 to 11); Validation set (C): HR 26% (95% CI, 17 to 37); LR 10% (95% CI, 7 to 14). 6-month relapse rates were: Training set (D): HR 20% (95% CI, 13 to 29); LR 20% (95% CI, 17 to 24); Test set (E): HR 17% (95% CI, 8 to 28); LR 19% (95% CI, 15 to 24); Validation set (F): HR 14% (95% CI, 7 to 23); LR 15% (95% CI, 11 to 19). 6-month overall survival rates were: Training set (G): HR 60% (95% CI, 51 to 70); LR 84% (95% CI, 80 to 87); Test set (H): HR 57% (95% CI, 45 to 72); LR 81% (95% CI, 77 to 86); Validation set (I): HR 68% (95% CI, 58 to 80); LR 85% (95% CI, 81 to 89).

We recently tested whether we could improve the sensitivity of the MAGIC algorithm by re-testing low risk patients one week later (Day 14), reasoning that the concentration of GVHD biomarkers would be higher one week closer to the onset of GVHD. Serum samples from both Day 7 and Day 14 were available for 768 MAGIC patients (Figure 2) We measured ST2 and REG3α on Day 7 in all patients and identified 145 (19%) as high risk and 623 (81%) as low risk with distinctly different NRM (26% vs 8%, p<0.001). Twenty low risk patients (3%) developed GVHD between Day 7 and Day 14 and were excluded from further analysis. When we repeated the test on Day 14 in the remaining 603 LR patients, we identified 60 additional HR patients whose NRM risk was similar to the day 7 HR patients and significantly higher than the 543 patients who remained LR (24% vs 6%, p<0.001). Compared to the Day 7 test alone, repeat testing on Day 14 resulted in a large improvement in sensitivity for NRM (46% to 61%) with only a modest loss of specificity (80% to

75%). Serial testing at both Days 7 and 14 significantly increases the proportion of patients potentially eligible to participate in a GVHD pre-emptive treatment trial from 19% (145/768) of the total population to 27% (205/768).

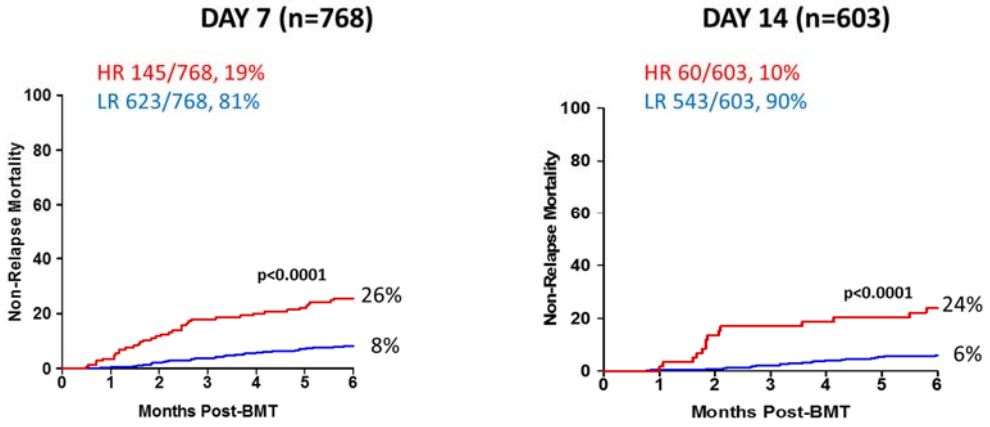

Figure 2: Serial monitoring of MAGIC biomarkers at Days 7 and 14 post-BMT. Patients who are low risk at Day 7 but high risk at Day 14 are significantly more likely to die from non-relapse causes than patients who are low risk at both Day 7 and Day 14.

For this proof of concept pilot trial we will use the incidence of SR GVHD by day 100 as the primary endpoint to determine whether pre-emption therapy with AAT warrants further study. **The cumulative incidence of SR GVHD by day 100 in patients who are HR at either Day 7 or 14 is 28%**.

1.3 Alpha-1-Antitrypsin

Few side effects and promising efficacy are desirable properties in an agent to be tested for GVHD preemption. Alpha-1-antitrypsin (AAT, A1PI, Glassia®) possesses these properties. Glassia is a stable, liquid, ready to use preparation of 2% human AAT that belongs to the family of serine protease inhibitors and is primarily produced in the liver and secreted into the circulation. In addition to its anti-protease activity, A1PI has anti-inflammatory, anti-apoptotic and immunomodulatory properties[19-22].

Glassia is an injection solution prepared from pooled human plasma collected from healthy volunteers in accordance with Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulations. It was approved in the United States (US) in July 2010 for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of AAT.

The mechanism of action of AAT for GVHD is not fully understood. However, animal studies provide strong evidence to support AAT's use in this setting. GVHD results when donor T cells are primed against host antigens in the context of a pro-inflammatory environment (e.g., high pro-inflammatory cytokines such as IL-1, TNF and IL-6, low anti-inflammatory cytokines such as IL-10, and decreased regulatory T cell numbers). First, the administration of exogenous AAT significantly reduced the incidence and severity of GvHD in murine bone marrow transplant models[23,24]. In one of these mouse GVHD models, Tawara et al showed that AAT administration before GVHD developed inhibited pro-inflammatory cytokine production, enhanced IL-10 production, and favorably altered regulatory T cell numbers[23]. These findings were confirmed in a separate murine study by Marcondes et al which developed evidence that AAT alters mitochondrial biogenesis in a cell-specific manner. Specifically, AAT exposed effector T cells (which cause GVHD related tissue damage) have significantly less respiratory reserve than T-regs and DCs. These cell specific differences favor survival of immune cells that promote tolerance[25]. Taken together, these data

show that AAT alters metabolism within immune system cells in an pro-tolerance, anti-inflammatory direction which supports its use in this trial of GVHD prevention.

Nonclinical PK studies in rabbits treated with a single bolus IV administration of AAT showed that the half-life of A1AT during the Phase 1 elimination was 16.3 hours; the maximum concentration, terminal half-life (Phase 2 half-life) and Phase 2 elimination rate constants were 42 264 ± 3443 ng/mL, 68.13 ± 13.53 hours and 0.0046 ± 0.0014 hours-1, respectively. Nonclinical toxicology studies have evaluated acute and repeated dosing with AAT in rats and rabbits; AAT was well tolerated with no overt toxicities reported.

Glassia has been evaluated in two clinical studies in adult subjects with AAT deficiency, one clinical study in subjects aged 9 to 18 years with type 1 diabetes mellitus and one Phase 4 clinical study in adult healthy volunteers. Glassia was generally safe and well tolerated in all 4 studies; the majority of adverse events (AEs) reported were of mild or moderate severity. All serious adverse events (SAEs) reported in the clinical studies were assessed by the investigator as unrelated to AAT.

The relationship between alpha-1-antitrypsin and GVHD has been examined in human studies. A study of 12 children with GI GVHD found a significant positive correlation between more rapid GI clearance of AAT and severe symptoms[26]. Higher donor AAT levels correlated with significantly less GVHD in recipients[25].

One recent clinical trial tested the safety and efficacy of Glassia in 12 patients with SR- GVHD [27]. Subjects received a loading dose of AAT of 90 mg/kg IV on Day 1, followed by either 30 or 60 mg/kg every other day through Day 15. In the analysis, most AEs were of mild or moderate severity. Two subjects experienced bowel perforation 3 weeks and 2 months, respectively, after the last dose of AAT. Neither AE resulted in death and the study Data Safety Monitoring Board concluded that the 2 bowel perforation events were not related to AAT, but instead were related to viral infections. One fatal case of liver failure occurred <30 days after the last dose of AAT and was assessed by the investigator as possibly related to AAT. Further assessment by Kamada considered the case as unrelated. Other adverse events during the study were consistent with those expected in subjects undergoing HCT or experiencing GvHD. The efficacy data from this study showed that 8 of the 12 subjects had overall responses, 4 of which were CRs, and 4 of which were PRs. Six of the 12 subjects (50%) were alive at follow-up of up to 820 days at the time of the interim analysis.

A second clinical trial tested the efficacy AAT in 26 patients with SR GVHD. Subjects received 60mg/kg of AAT twice weekly for four weeks. A high overall response rate (CR+PR) of 62% at four weeks was reported[28]. Taken together, the preclinical and clinical data demonstrate that AAT has a favorable safety profile and is potentially beneficial as a treatment for GVHD.

The AAT dosing for this study (90 mg/kg loading dose followed by 45 mg/kg twice weekly) is similar to the two dosing regimens used for SR-GVHD. Normal AAT levels in adults are 150-200 mg/dL, which is the equivalent of a total circulating amount of AAT of 7.5-10 gr based on typical adult blood volumes. Given the half-life of AAT (approximately five days) the dosing regimen in this study should increase plasma levels of AAT to 1.5 to 2 times normal for a 70 kg person.

1.4 Correlative Studies

Serial serum biomarkers. GVHD biomarkers are prognostic early after HCT, at diagnosis, and during treatment[10,13,16], but the relationship between changes in GVHD biomarker concentrations measured serially over time and outcomes is not yet well understood. We expect that larger increases in GVHD biomarker concentrations over time will correlate with worse outcomes. We will collect and store serum samples in subjects receiving AAT treatment for the purpose of exploratory analyses according to the study calendar in Section 6.3.

1.5 Summary of Study Rationale

The MAGIC algorithm identifies patients at high risk for developing steroid-refractory GVHD as early as seven days after HCT, which is days to weeks before GVHD symptoms develop. A second test at day 14, applied to subjects still at risk, and still two weeks before the median time of GVHD onset, dramatically improves the sensitivity of the test, which will facilitate rapid accrual. Targeting HR patients allows experimental approaches to be tested in patients most likely to benefit, reducing exposure for low risk patients. A shift to objective laboratory measures from imprecise clinical symptoms has the potential to transform GVHD therapy and represents a key step towards a precision medicine approach for GVHD. Alpha-1-antitrypsin has an excellent safety profile as observed in other clinical settings, including as a treatment for SR GVHD, but it has not yet been tested in this context. Importantly, AAT has no effect on clinical chemistry or hematologic parameters in either animal or human studies. The absence of notable toxicities increases its attractiveness for use in HCT. This proof of concept pilot study will develop the safety and efficacy data needed for further clinical development.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To generate data for assessing the feasibility, safety and preliminary efficacy of alpha-1-antitrypsin (AAT) as pre-emptive therapy in patients at high risk for the development of steroid-refractory GVHD.

2.2 Secondary Objectives

2.2.1 To generate a preliminary estimate of the 100 days incidence of clinically relevant GVHD states including steroid-refractory GVHD, grade II-IV GVHD, and grade III-IV in patients at high risk for the development of steroid-refractory GVHD treated with AAT.

2.2.2 To generate a preliminary estimate of the non-relapse mortality, relapse, and survival rates in patients at high risk for the development of steroid-refractory GVHD treated with AAT.

2.2.3 To generate a preliminary estimate of the incidence of severe toxicities, serious infections, and viral reactivations in patients at high risk for the development of steroid-refractory GVHD treated with AAT.

2.3 Primary Endpoint

1. Proportion of HR patients who develop steroid refractory GVHD by day 100 post HCT.

   GVHD is defined as steroid refractory if CR or PR is not achieved by day 28 of systemic steroid treatment **OR** if additional immunosuppression beyond steroids was given for treatment of GVHD prior to 28 days of steroid treatment.

Secondary endpoints:

1. Overall survival at 6 months
2. Cumulative incidence of NRM at 6 months and 1 year
3. Relapse rate (see section 2.2.1)

4. 100 days incidence of clinically relevant GVHD states including steroid-refractory GVHD, grade II-IV GVHD, and grade III-IV GVHD (See section 2.2.1).
5. For patients who develop GVHD prior to day 100 post-HCT, the overall response rate (CR + PR) 28 days after initiation of systemic steroid treatment. PR is defined as improvement in one or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR on day 28, the patient must be in PR on day 28 and have had no intervening systemic therapy for acute GVHD other than steroids.
6. Cumulative incidence of severe GI GVHD stage 3 or 4 by day 100 post-HCT
7. Cumulative incidence of chronic GVHD requiring systemic steroid treatment by one year
8. Number of serious infections (defined as grade 3 by the Blood and Marrow Transplant Clinical Trials Network)

Safety endpoints

1. Number and proportion of patients developing reportable AEs and SAEs according to relatedness to study drug and stratified by severity
2. Percentage of infusions for which the infusion rate was reduced and/or the infusion interrupted or stopped for tolerability concerns or for adverse events (AEs)

Exploratory endpoints

1. Correlation of GVHD biomarkers with clinical endpoints

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and none of the exclusion criteria to be eligible to participate in the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 High risk prediction score as determined by the MAGIC algorithm at either day 7 or day 14 post HCT.

3.1.2 Any donor type (e.g., related, unrelated) or stem cell source (bone marrow, peripheral blood, cord blood).

3.1.3 Related and unrelated donor and recipient match each other for at least 7/8 HLA-loci (HLA-A, B, C, and DR)

3.1.4 Cord blood donor(s) match recipient for at least 4/6 HLA-loci (HLA A, B, and DR)

3.1.5 Any conditioning regimen (non-myeloablative, myeloablative, or reduced intensity) is acceptable.

3.1.6 Any GVHD prophylaxis is permitted.

3.1.7 The use of serotherapy to prevent GVHD (e.g., antithymocyte globulin) prior to day 3 post-HCT is permitted.

3.1.8 Age 18 years and older

3.1.9 Direct bilirubin must be <2 mg/dL unless the elevation is known to be due to Gilbert syndrome within 3 days prior to enrollment.

3.1.10 ALT/SGPT and AST/SGOT must be <5 x the upper limit of the normal range within 3 days prior to enrollment.

3.1.11 Signed and dated written informed consent obtained from patient or legal representative.

3.2 Exclusion Criteria

3.2.1 Patients who develop acute GVHD prior to start of study drug

3.2.2 Patients at very high risk for relapse post HCT as defined by very high disease risk index[29]

3.2.3 Patients participating in a clinical trial where prevention of GVHD is the primary endpoint

3.2.4 Uncontrolled active infection (i.e., progressive symptoms related to infection despite treatment or persistently positive microbiological cultures despite treatment or any other evidence of severe sepsis)

3.2.5 Patients who are pregnant

3.2.6 Patients on dialysis within 7 days of enrollment

3.2.7 Patients requiring ventilator support or oxygen supplementation exceeding 40% FiO2 within 14 days of enrollment.

3.2.8 Patients receiving investigational agent within 30 days of enrollment. However, the Principal Investigator (PI) may approve prior use of an investigational agent if the agent is not expected to interfere with the safety or the efficacy of alpha-1-antitrypsin

3.2.9 History of allergic reaction to alpha-1-antitrypsin

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Study Schema

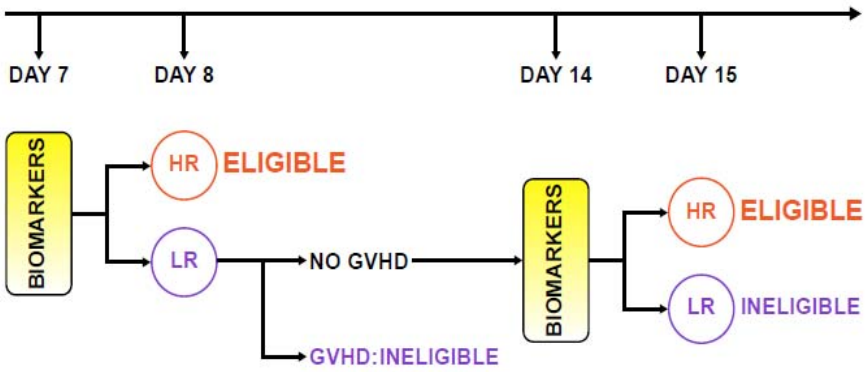

Figure 3: Study Schema

To be eligible for this study, patients must have a high MAGIC GVHD risk score on day 7 or 14 post-HCT (see Appendix). 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.

The pre-screening process is outlined in Figure 3 above. Consented patients will be registered into the remote data entry system using a unique study number assigned by the MAGIC DCC. Five mL of serum will be collected from patients on day 7 post-HCT (+/- 1 day) and shipped priority overnight to the Mount Sinai GVHD laboratory for early AM arrival (**see MAGIC Sample Collection and Storage manual for shipping procedures**). Samples can be received Tuesday through Saturday. Once received in the laboratory, the GVHD biomarkers used to assign the MAGIC 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 MAGIC GVHD risk score is confirmed by Dr. Ferrara (or Dr. Levine in Dr. Ferrara's absence), the investigator at the participating center will be notified of the MAGIC score by telephone and written confirmation by email.

Patients who are low risk on day 7, who have not already developed GVHD requiring systemic treatment, and who meet the other eligibility criteria will be re-screened on day 14 (+/- 1 day). Patients who were low risk on day 7 but high risk on day 14 are also eligible for this study provided they have not already developed GVHD requiring systemic treatment. Only patients with confirmed high MAGIC GVHD risk scores will be eligible to enroll on the clinical trial.

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 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 a high MAGIC GVHD risk score will be provided directly to the identified Primary Site contact from the participating site by Dr. Ferrara, Dr. Levine or designee. 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 magic@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 receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within **2 days of confirmation of a high MAGIC GVHD risk score**. For example, a patient whose Day 7 post-HCT falls on a Friday (day 7), who has a research sample shipped to the Ferrara Lab that day, will have their MAGIC GVHD risk

score assigned on Saturday (day 8). Such a patient **must** begin study treatment no later than Monday (day 10). **There are no exceptions to this requirement**.

5.1.1 Alpha-1-antitrypsin (Glassia) will be supplied by Kamada. Each participating site will have a sufficient supply of alpha-1-antitrypsin on hand to begin treatment, additional doses will be shipped to the participating site to complete treatment. See section 9.1 for preparation, dispensing, and administration information.

5.1.2 Study treatment will consist of alpha-1-anti-trypsin administered intravenously at a loading dose of 90 mg/kg (study day 0) followed by twice weekly doses of 45 mg/kg for 15 more doses (total of 16 doses over 8 weeks).

5.1.3 The *planned* schedule of subsequent doses (Mondays and Thursdays, Tuesdays and Fridays, Wednesdays and Saturdays) can be adjusted as necessary so long as the time between doses is not shorter than two days or longer than four days.

5.1.4 Missed doses will be made up as soon as possible and the schedule resumed until all sixteen doses have been administered or ten weeks from first dose, whichever comes first.

5.1.5 Subjects who miss more than two doses due to non-compliance will be analyzed for safety but considered inevaluable for efficacy assessment and replaced.

5.1.6 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. The initiation of medications other than AAT for the purpose of intensifying GVHD prophylaxis in high risk patients is prohibited. GVHD prophylaxis medications will be tapered according to local institutional tapering practices.

5.1.7 GVHD treatment

The preliminary data for this study was 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 are permitted unless their use is explicitly prohibited.

Patients who develop GVHD will be treated as per institutional standards with systemic and non-systemic treatments such as topical steroids or non-absorbable steroids for GI GVHD. If systemic steroid treatment is initiated the recommended starting dose is **prednisone 2 mg/kg/day**. Centers may use a starting dose of 2 mg/kg of methylprednisolone if that is their institutional practice. Additional agents for the purpose of treating GVHD (e.g., etanercept, extracorporeal photopheresis, ATG) are not allowed. The initiation of systemic GVHD treatment beyond continuation or adjustment of GVHD prophylaxis medications (see section 5.1.6) and corticosteroids will be considered the initiation of second line GVHD treatment and considered a treatment failure. **Study treatment with alpha-1-antitrypsin continues during GVHD treatment until all 16 doses have been administered or ten weeks have elapsed from the start of AAT, whichever comes first.**

GVHD treatment will be tapered according to local institutional tapering practices. A recommended taper is provided in the appendices.

5.1.8 Ancillary therapies

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

5.1.9 Supportive Care Guidelines

All patients should receive the following:

- Transfusion support per institutional practice
- Anti-infective prophylaxis against herpes virus is required but otherwise institutional practice 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.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The dose of Glassia will not be modified. In the event of a SAE causally related to study drug, Glassia should be discontinued and the patient will be included in all analyses of safety and efficacy.

5.3 Concomitant Medications/Treatments

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

5.4 Other Modalities or Procedures

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

5.5 Duration of Therapy

The duration of protocol therapy on this study is eight weeks (16 doses). Protocol therapy will end after the 16th dose of alpha-1-antitrypsin has been administered or if any of the following criteria apply:

- 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 **OR**
- Ten weeks has elapsed since the first dose of AAT

5.6 Off Treatment Criteria

Patients will be removed from receiving the investigational drug when any of the criteria listed in Section 5.5 apply. The reason for ending investigational drug therapy and the date

the patient was removed from treatment will be documented in the study record. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures.

5.7 Duration of Follow-Up

Patients will be followed until 1 year post-HCT, withdrawal of consent or until death, whichever occurs first. HCT patients are followed closely and frequent clinical evaluations are the norm. 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 8 weeks of participation (i.e., through the last dose of alpha-1-antitrypsin), patients will be seen twice weekly for study drug administration. GVHD staging should be performed approximately weekly through day 100 post-HCT as part of the standard of care for HCT recipients. Patients will be evaluated at least monthly until 6 months post-HCT than again at one year post-HCT. If GVHD develops during the first six months post-HCT, staging and treatment response should be evaluated at least weekly for four weeks as part of the standard of care for patients who develop GVHD.

5.8 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:

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

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

5.8.3 Patient is unable to comply with protocol requirements;

5.8.4 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

5.8.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.8.6 Termination of the study;

5.8.7 Patient completes protocol treatment and follow-up criteria.

The informed consent documents will emphasize the importance of collecting outcome data from individuals who choose to discontinue treatment during the study, and participants will be encouraged to provide this information whether or not they complete the anticipated course of study treatment.

5.9 Patient Replacement

Patients who enroll in the study but do not receive any study treatment will be replaced. Patients who initiate study treatment but miss more than two doses due to non-compliance will also be replaced. The number of patients and reason(s) for replacement will be recorded and will be used to assess the feasibility of the study design.

6.0 STUDY PROCEDURES

6.1 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.

The screening procedures include:

6.1.1 **Informed Consent** (informed consent can be obtained any time up to Day 7 post-HCT).

6.1.2 **Demographics**

6.1.3 **Review subject eligibility criteria** (Eligibility criteria must be assessed between days 4-7 post-HCT. For patients who are screened again at day 14, eligibility criteria must be re-assessed between days 11-14 post-HCT).

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

6.1.5 **Adverse event assessment**

Baseline adverse events will be assessed and preexisting conditions will be recorded. See Section 8.0 for Adverse Event monitoring and reporting.

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

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

6.2 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 8 weeks of participation (i.e., through the last dose of alpha-1-antitrypsin), patients will be seen twice weekly for study drug administration. GVHD staging should be performed weekly during the first eight weeks at intervals at the visit closest to 7 day interval from Study Day 0 (i.e., Study Day 7, 14, 21, etc). Between Study Day 56 and Study Day 100, GVHD staging should be performed no less than every other week. Weekly staging is preferred and if performed should be reported on the case report forms. Patients will also be evaluated at six months and one year post-enrollment for survival, relapse, acute and chronic GVHD. If acute GVHD develops during the first 100 days post enrollment, the staging, immunosuppression medications and treatment response should be determined at least weekly for four weeks to assess the primary study endpoint.

Follow-up studies are detailed in the Time and Events Table is section 6.3.

6.3 Time and Events Table

	CALENDAR BASED ASSESSMENTS														GVHD DRIVEN ASSESSMENTS [1]	
	Screening HCT Day 7 HCT Day 14 [2]	Study day 0	Study day 7	Study day 14	Study day 21	Study day 28	Study day 35	Study day 42	Study day 49	Study day 56	Every other week to HCT Day 100	HCT Day 100	HCT Day 180	1 Year Post HCT	GVHD Diagnosis or Treatment	Weekly x 4 from start of GVHD Diagnosis or Treatment
Windows	*+/- 1 day*	*Within 2 days of Risk Score Notification*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	*+/- 3 days*	*+/- 3 days*	*+/- 3 days*	*+/- 3 days*	*+/- 6 days*	*+/- 3 days*	*+/- 14 days*	*+/- 14 days*	*+/-2 days*	*+/-2 days*
Eligibility Review	X															
Concomitant Medication Review [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluations	X	Adverse events will be reported from the time of the study day 0 through 30 days after the last dose of study drug. Report serious adverse events as they occur.														
Serum Chemistry	X															
GVHD Staging [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alpha-1-antitrypsin Administration		90 mg/kg Once	45 mg/kg Twice weekly for 15 more doses for a total of 16 doses.												**If GVHD occurs, continue AAT treatment. Complete 16 doses as per protocol.**	
Survival, Relapse & Chronic GVHD Status												X	X	X		
	CORRELATIVES STUDIES															
Serum Sample (10 mL) [5]	X	X	X	X	X	X		X (HCT day 56 +/- 3 days, not study day 56)							X	X

[1] When GVHD driven assessments and sample collections occur within 3 days of a calendar based assessment/collection, the calendar assessment/collection is not required.

[2] Screening occurs on day 7 post-HCT and, if still eligible for screening, again on day 14 post-HCT. Screening samples are sent via overnight shipping to the MAGIC laboratory in New York. Patients who do not meet eligibility by high risk biomarkers will be followed for minimum data collection: GVHD onset date, maximum GVHD severity, steroid refractory GVHD by day 100 (Y/N), chronic GVHD requiring treatment (Y/N), relapse and death with reporting once at one year post-BMT.

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

[4] GVHD staging will follow the detailed guidelines provided in the MAGIC Acute GVHD Staging Guidance.

[5] Serum samples will be banked for correlative studies. 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.

7.0 GVHD CLINICAL STAGING

GVHD clinical staging will be according to the established criteria used for Blood and Marrow Transplant Clinical Trials Network GVHD staging (modified Glucksberg criteria).

	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	Adult: 500–1000 ml/day	Adult: 1001-1500 ml/day	Adult: >1500 ml/day	Severe abdominal pain +/- ileus, flank blood or melena (regardless of stool volume)
UGI		Severe nausea/vomiting			

- 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)

7.1 ENDPOINT AND RESPONSE CRITERIA

7.1.1 Definitions

Evaluable for response: Safety, tolerability, and efficacy of AAT will be assessed from the initiation of the first AAT treatment

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.

No response (NR): All responses that are not CR or PR. 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.

7.1.2 Proportion of CR and CR+PR

CR and PR on day 28 are scored in comparison to the patient's acute GVHD staging on the day systemic steroid treatment began.

7.1.3 **Steroid refractory GVHD**

Patients who are scored as no response on day 28 of systemic steroid treatment for GVHD **or** who receive additional systemic immunosuppression prior to day 28 (i.e., no response) will be considered steroid refractory. Escalation of steroid doses during treatment for GVHD are not considered in the definition of steroid refractory GVHD.

7.1.4 **Steroid discontinuation**

The date of discontinuation of steroid therapy will be recorded.

7.1.5 **Lines of GVHD therapy**

Systemic steroids are the first line of GVHD treatment. 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. Topical steroids and non-absorbable oral steroids are not considered new lines of therapy.

7.1.6 **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.

7.1.7 **Chronic GVHD**

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

7.1.8 **Relapse**

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

7.2 SAFETY/TOXICITY DEFINITIONS

7.2.1 Glassia was generally safe and well tolerated in clinical studies of healthy adult subjects, subjects with AAT deficiency, and type 1 diabetes mellitus. Headache (6%) and dizziness (3%) were reported by >1 subject in two clinical studies in patients with AAT deficiency. There were no toxicities observed in a study of AAT Glassia therapy in patients with steroid-refractory acute GVHD that were felt to be related to AAT administration. Although not previously reported, AAT has potential immunomodulatory activity that theoretically could increase the risk for infection. Known or plausible toxicities that may be related to alpha-1-antitrypsin will be reported.

7.2.2 **Systemic Infections**

Infections are common in patients who undergo HCT and generally respond to treatment. Any grade 3 infection as defined by the Blood and Marrow Transplant Clinical Trials Network will be reported. The full table can be referenced in Appendix B.

Grade 3 Bacterial Infections:

a. Bacteremia with deep organ involvement
b. Severe sepsis with bacteremia
c. Fasciitis requiring debridement
d. Pneumonia requiring intubation
e. Brain abscess or meningitis without bacteremia

f. Clostridium difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea.

Grade 3 Fungal Infections:
a. Fungemia, including candidemia
b. Proven or probable invasive fungal infections (e.g. Aspergillus, Mucor, Fusarium, Scedosporium)
c. Disseminated fungal infections (e.g. multifocal pneumonia, presence of urinary/blood antigen, CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis or Cryptomycosis
d. Pneumocystis jiroveci pneumonia

Grade 3 Viral Infections:
a. Severe VZV infection with either associated coagulopathy or organ involvement
b. CMV end organ involvement (e.g. pneumonitis, enteritis, retinitis)
c. EBV Post-transplant lymphoproliferative disorder (PTLD)
d. Adenovirus with end organ involvement (except adenoviral conjunctivitis or upper respiratory tract disease)
e. All lower respiratory tract viruses
f. Viral encephalitis or meningitis

Grade 3 parasitic infections:
a. Toxoplasmosis involving the CNS
b. Strongyloides hyperinfection

Non-microbiologically documented infections:
a. Any acute pneumonia requiring mechanical ventilation
b. Severe sepsis without an identified organism

7.2.3 Viral Reactivations

Because viral reactivations often require treatment in the HCT population, even in the absence of end organ disease, the following viral infections/reactivations will be reported:

The date, anatomical site or body fluid (e.g., blood, nasopharyngeal swab, stool, etc.), and method of detection for CMV, EBV, HHV6, VZV, HSV and adenovirus will be reported.

7.3 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE EVENTS

8.1 ALPHA-1-ANTITRYPSIN

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.1 Contraindications

Patients who have had an allergic reaction to alpha-1-antitrypsin

8.1.2 Special Warnings and Precautions for Use

Severe hypersensitivity and anaphylactic reactions may occur in IgA deficient patients with antibodies against IgA and in patients with a history of hypersensitivity to other Alpha1-AT products. These reactions are not expected in this study because of the immunosuppressive nature of the transplant procedure.

May carry a risk of transmitting infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

8.2 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 agents. Data on adverse events will be collected from the time of the initial study treatment (day 0) through 30 days after the last dose of alpha-1-antitrypsin. Any serious adverse event that occurs more than 30 days after the last alpha-1-antitrypsin dose and 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 administration 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 8.3, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment or study intervention must be recorded as an adverse event in the patient's source documents and on the CRF.

8.3 Definitions

8.3.1 **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 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.

- It is common for HCT recipients to experience multiple complications as part of the transplant itself that are unrelated to exposure to investigational agents. Symptoms of the original or targeted disease are not to be considered adverse events for this study except that all BMT CTN grade 3 infections will be reported (see Appendix B). Symptoms related to the conditioning regimen or GVHD will not be reported unless the event is serious (see section 8.3.2) and considered by the investigator to be possibly, probably, or definitely related to AAT. Events that are unlikely or unrelated to AAT are not required to be reported. 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, exposure to immunosuppressive agents other than AAT, and AAT. 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.

8.3.2 **Serious Adverse Event**

An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- 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.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. 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. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.3.3 **Expected Adverse Events**

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 **Unexpected Adverse Event**

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

8.4 Adverse Event Characteristics

8.4.1 **CTCAE Term**

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.4.2 **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.

8.5 Serious Adverse Event Reporting Guidelines

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

Sponsor SAE Reporting

Event occurring from Day 0 to 30 Days post last AAT infusion	**Report to:**		**Event occurring after 30 Days post last AAT infusion**	**Report to:**	
	FDA / IRB	**Consortium**		**FDA / IRB**	**Consortium**
All SAEs; ✓ Expected or Unexpected ✓ Possible, Probable, or Definite	3 Days from knowledge	Monthly	SAEs – ✓ Expected ✓ Probable or Definite **OR** ✓ Unexpected ✓ Possible, Probable or Definite	3 Days from knowledge	Monthly
			SAEs – ✓ Expected ✓ Possible	Annually	Monthly

8.5.2 The Principal Investigator must be notified within 3 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the AAT. Kamada should be notified within 3 days to enable reporting to regulatory authorities as required.

8.5.3 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.

8.5.4 All Serious Adverse Events whether expected or unexpected and possibly related (definite, probable or possible) to study treatment administration 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 **magic@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 Dr. Levine only in the case that the event(s) is believed to be related (i.e. probably or definitely) to the study medication. All other Serious Adverse Events will be discussed on monthly webinars held with all participating centers (see section 12).

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.

8.6 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.

8.7 Stopping Rules

Although alpha-1-antitrypsin is generally safe, its use as a pre-emptive therapy for acute GVHD has not been previously studied. We will continuously monitor the incidence of BMT CTN grade 3 infections occurring within 8 weeks of study administration and accrual will be halted if there is sufficient evidence that the infection rate exceeds the acceptable target rate of 24% (the incidence in patients with high risk GVHD) by more than 30%. If the incidence of BMT CTN grade 3 infections occurring within 8 weeks of study administration 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.

Maximum # of Patients, k	**6**	**7-12**	**13-18**	**19-24**	**25-30**
Boundary, b_k	**3**	**5**	**7**	**9**	**11**

Specifically, if more than 3 out of the first 6 patients, 5 out of the first 12 patients, 7 out of the first 18 patients, 9 out of the first 24 patients, or 11 out of the first 30 patients, experience grade 3 infections occurring within 8 weeks of study administration, the trial will be halted for safety considerations.

The operating characteristics of this stopping rule are as follows:

	True Toxicity Rate				
	24%	**30%**	**40%**	**50%**	**54%**
Probability of Early Stopping	**0.09**	**0.25**	**0.61**	**0.89**	**0.94**

Using these boundaries, if the true toxicity rate is 24%, 30%, 40%, 50% or 54%, the probability of stopping the trial early is 0.09, 0.25, 0.61, 0.89, and 0.94 respectively. This stopping rule was computed using the toxbdry function in R and calculations of this function are based on methods described in Chapter 12 of Jennison and Turnbull (2000)[30] and in the illustrative paper by Ivanova, Qaquish and Schell[31].

An enrollment rule to prevent an excessive number of toxicities as described in Song and Ivanova[32] will be used to inform us of the number of additional patients we can recruit when the current patient has not yet completed cycle 1. Formally, the trial can enroll *m* new patients such that $r + x + m \leq b_{n+m}$, $r + x + m - 1 < b_{n+m-1}$, and $n + m \leq K$ where *r* is defined as the number of patients that have not completed follow-up and are still being followed for toxicity; *x* is the number of patients that have experienced toxicity and *n* is the total number of patients enrolled to date. This enrollment rule is conservative in that it assumes the worst case scenario, that every patient in the follow-up will experience a dose-limiting toxicity.

The study may also be stopped based on the recommendation of the investigators, the TCI DSMC, or at Kamada's discretion for any reason.

9.0 DRUG INFORMATION

9.1 ALPHA-1-ANTITRYPSIN (AAT, AAT, A1PI)

- Commercial names for the drug: GLASSIA®

- Classification - type of agent: Human Alpha-1 Proteinase Inhibitor

- Description: AAT (Glassia) is supplied as contains a single use vial containing approximately
  1 gram of functional Alpha1-PI in 50 mL of solution and a sterile filter needle

- Mode of action: The mode of action of AAT in graft-versus-host disease is not well understood, but appears to be related to its anti-inflammatory, anti-apoptotic and immunomodulatory properties[19-22].

- Pharmacokinetics: A prospective, open-label, uncontrolled multicenter pharmacokinetic trial was conducted in 7 females and 11 males with congenital Alpha-1 antitrypsin deficiency, ranging in age from 40 to 69 years. Subjects received a single dose of GLASSIA either 30 mg/kg, 60 mg/kg or 120 mg/kg. Blood samples for pharmacokinetic study were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days and 7 days. The mean results for pharmacokinetic parameters in the 60 mg/kg dosage group are shown in the Table. The pharmacokinetics of GLASSIA were linear over the dose range of 30-120 mg/kg.

Pharmacokinetic Parameter	60 mg/kg Dose Group
Terminal Half-Life (h) *	111 ± 33
Area under the curve 0-168 hrs (mg·hmL)	89 ± 10
Clearance (mL/h/kg)	0.68 ± 0.1
Volume of Distribution (L)	3.2 ± 0.3

- Adverse reactions: The most common adverse reactions (>0.5% of infusions) in clinical trials were headache and upper respiratory infection.

  GLASSIA may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing severe hypersensitivity and anaphylactic reactions.

  Because this product is made from human plasma, it may carry a risk of transmitting

infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmitting an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process. Despite these measures, such products may still potentially transmit human pathogenic agents.

- Drug Interactions: Alpha-1-antitrypsin may interact with immunosuppressant agents and increase the risk of infection.

- Storage and stability: GLASSIA must be refrigerated between 2°C to 8°C (36°F to 46°F). Do not freeze. Product may be stored at room temperatures not exceeding 25°C (77°F) for up to one month. Once removed from refrigeration use within one month.

- Preparation:
  1. Use aseptic technique.
  2. Allow the product to reach room temperature prior to infusing and administer within three hours of entering the vials.
  3. Inspect the vial of GLASSIA. The solution should be clear and colorless to yellow-green and may contain a few protein particles. Do not use if the product is cloudy.
  4. The product is suitable for infusion directly from the vial or pooled into a sterile container for intravenous infusion.
  5. For pooling the product, use a vented spike (not supplied) to withdraw the solution from the vial and then use the supplied 5 micron filter needle to transfer the solution into the intravenous infusion container. NOTE: Do not use the 5 micron filter needle to withdraw GLASSIA from the vial.

- Administration:
  For intravenous infusion only.
  GLASSIA should be administered by a healthcare professional or self-administered by the patient/caregiver after appropriate training. For self-administration, provide the patient/caregiver with detailed instructions and adequate training for infusion in the home or other appropriate setting.

  1. Use aseptic technique.
  2. Inspect parenteral products visually for particulate matter and discoloration prior to administration whenever solution and container permit.
  3. Administer GLASSIA alone. Do not mix with other agents or diluting solutions.
  4. When infusing directly from the vials, use a vented spike (not supplied). If the contents of vials have been pooled to a sterile intravenous container, use an appropriate intravenous administration set.
  5. Always use a 5 micron in-line filter (not supplied) during infusion.
  6. Administer GLASSIA within three hours of entering the vials to avoid the potential ill effect of any inadvertent microbial contamination.
  7. Administer GLASSIA at room temperature through an appropriate intravenous administration set at a rate not to exceed 0.2 mL/kg body weight per minute, and as determined by the response and comfort of the patient.
  8. The recommended dosage of 90 mg/kg at a rate of 0.2 mL/kg/min will take approximately 22 minutes to infuse and dosage of 45 mg/kg will take 11 minutes to infuse.

9. Monitor the infusion rate closely during administration and observe the patient for signs of infusion related reactions. If infusion related adverse reactions occur, reduce the rate or interrupt the infusion as appropriate until the symptoms subside. Resume the infusion at a rate tolerated by the patient, except in the case of severe reaction
10. Monitor the patient for 30 minutes after completion of infusion for any adverse reactions.
11. Following administration, discard all open vials, unused solution and administration equipment.

- Availability: Provided by Kamada, Ltd.

- Return and Retention of Study Drug:

  Any remaining/expired/used is to be destroyed on site according to the institution standard operating procedure for drug destruction and documented on the drug accountability logs.

- Drug Accountability:
  The principal investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug, alpha-1-antitrypsin. The drug accountability records will capture drug receipt, drug dispensing, drug return, and final disposition.

10.0 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.

10.1 Sample Collection Guidelines

The correlative sample collection schedule is detailed in section 6.3 above. Serum will be collected in no additive, silicone coated glass or plastic tubes containing no anticoagulant (red or gold top tube). Samples will be processed at the participating center and batch shipped to Ferrara Laboratory quarterly for storage. Sample processing details are found in Appendix A. Instructions for quarterly batch shipping are found in the MAGIC Sample Collection and Storage Manual.

10.2 Assay Methodology

See Appendix A.

10.3 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 may be performed on the banked research samples as part of collaborations with other institutions and entities.

The specimens, DNA, 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

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is a proof of concept pilot single arm, open label multicenter clinical trial. The primary study measure of efficacy is the incidence of steroid-refractory GVHD by Day 100 after HCT. GVHD is defined as steroid refractory if CR or PR is not achieved by day 28 of systemic steroid treatment **OR** if additional immunosuppression beyond steroids was given for treatment of GVHD prior to 28 days of steroid treatment. Subjects who start treatment for GVHD within 28 days of Day 100 (i.e., on or after Day 72 post-HCT) must be followed for a full 28 days of systemic steroid treatment for the purposes of assessing the primary study measure of efficacy.

Because we expect improvements in the incidence of steroid refractory GVHD to translate into better long-term outcomes, secondary endpoints include 6 month NRM and 6 months overall survival. Additional secondary endpoints related to efficacy will include, in subjects who develop GVHD, time to discontinuation of steroid therapy, number of lines of GVHD therapy, and cumulative incidence of chronic GVHD. Secondary endpoints related to safety include 6 month and 1 year relapse rates and incidence of serious (BMT CTN grade 3) infections by day 100.

The historical control population for this study consists of patients who met the criteria for a high MAGIC GVHD risk score at either day 7 and 14 (see Background).

11.2 Sample Size and Accrual

This is a proof of concept pilot study intended to determine if sufficient evidence can be developed to warrant further study of pre-emptive treatment with AAT. The expected incidence of steroid refractory GVHD by day 100 in patients who are high risk at either day 7 or 14 is 28%. We assume that the incidence of steroid refractory GVHD by day 100 among high risk patients treated pre-emptively will be 15% as a clinically meaningful incidence. Based on this assumption, a sample size of 30 achieves 85% power to detect a 13% improvement (28%-15%) in steroid refractory incidence rate using a one-sided exact test with a target significance level of 0.23. It is suggested in the literature that in pilot studies, false positive rates up to 0.25 could be used as those studies are not designed to provide definite evidence but are designed to provide guidance to whether a larger study should be conducted[33]. If we observe 6 or fewer cases of SR GVHD, we will consider this approach sufficiently promising to warrant further study.

Sample size calculations were computed using the binomial enumeration of all possible outcomes method in PASS 14 Power Analysis and Sample Size Software (2015) NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

The five centers participating in this clinical trial collectively perform >600 allogeneic HCT per year, of whom >90% should meet the eligibility criteria for this trial. We will need to screen approximately 120 eligible patients in order to enroll 30 high risk patients onto this clinical trial. We expect to be able to meet our accrual goals within one year.

11.3 Data Analyses Plans

The primary endpoint is incidence of steroid-refractory GVHD by day 100. Death, lack of GVHD response to systemic steroids by day 28 of treatment, or initiation of additional systemic immunosuppressive therapy for GVHD will be considered failures for this

endpoint. The incidence of steroid-refractory GVHD by day 100 in the study patients will be compared to the historical control rate of 28%.

Secondary outcomes such as the overall response rate (CR+PR), the incidence of severe GI GVHD (stage 3 or 4), non-relapse mortality, relapse rates, overall survival, 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 and relapse will be considered as a competing risk[34]. 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[35].

12.0 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 local Data and Safety Monitoring Committee (DSMC) at each site which will be responsible for monthly reviews of patient data at each site
2. The Protocol Data and Safety Monitoring Committee (DSMC), composed of the individual site PI's which will review all facets of study conduct at all sites on monthly webinars
3. 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.
4. Annual reviews and safety reporting will be provided to the IRBs at each participating site, the Mount Sinai Health System, and the FDA as required by IND regulations (21 CFR 312.3).

Protocol DSMC: 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 participates in monthly webinars where all facets of study conduct are discussed, thereby providing an additional layer of safety oversight.

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. It is a DSMB entirely composed of members with no connection to this clinical trial.

12.1 Multisite Clinical Monitoring Procedures

This clinical study will be coordinated by the MAGIC Data Coordinating Center (DCC) of the Icahn School of Medicine at Mount Sinai. 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 should make every effort in attending 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
- Adherence to the protocol
- Completeness and accuracy of study data and laboratory samples collection
- Proper storage, dispensing and inventory control of investigational drug
- Compliance with state and local regulations

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. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit if all of the following apply:

- No patient has signed the Informed Consent Form and has enrolled into the study
- Investigational agent has not been dispensed
- All investigational agent and materials have been returned as defined for the study or destroyed and accounted for properly.

13.0 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.

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15.0 APPENDICES

Appendix A: High Risk MAGIC Scoring Manual

Appendix B: BMT CTN Infection Severity Grading Table

Appendix C: Suggested Steroid Taper for GVHD