CLINICAL STUDY PROTOCOL

Protocol Title:	An Open Label, Non-Randomized Multicenter Phase 2b, Study with a Safety Run-in to Evaluate the Safety and Efficacy of RGI-2001 for the Prevention of Acute Graft-Versus-Host Disease (aGvHD) Compared to Contemporary Controls in Subjects Following Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)
Protocol Number:	RGI-2001-003
Investigational Product:	RGI-2001
IND Number/NCT Number:	102,285/ NCT04014790
Sponsor:	REGiMMUNE Corporation 35-3 Nihonbashi Hakozaki-cho BRICK GATE 5F, Chuou-ku, Tokyo 103-0015 Japan
Protocol Date and Version:	Original: 18 March 2019, Version 1.0 Amendment #1: 06 March 2020, Version 2.0

CONDUCT

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

CONFIDENTIAL INFORMATION

PROTOCOL APPROVAL SIGNATURE PAGE

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Protocol Number: RGI-2001-003

Date: 06 March 2020

[redacted] _____ _____

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open Label, Non-Randomized Multicenter Phase 2b, Study with a Safety Run-in to Evaluate the Safety and Efficacy of RGI-2001 for the Prevention of Acute Graft-Versus-Host Disease Compared to Contemporary Controls in Subjects Following Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

Date: 06 March 2020

Signature on this page assures the Sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board (IRB) operates in accordance with the governing regulations, and that the investigator understands, and agrees to conduct this study in accordance with the protocol and according to the Declaration of Helsinki, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements. All study site personnel involved in the study will be under their direction and informed about the contents of this study protocol and will receive all necessary instructions for conducting the study in accordance with the study protocol.

_____ _____

Investigator's Signature Date

_____

Name (printed)

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aGvHD	Acute Graft versus Host Disease
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
alloHSCT	Allogeneic hematopoietic Stem Cell Transplantation
α-GalCer	α-galactosylceramide
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cell
API	Active Pharmaceutical Ingredient
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATG	Anti-Thymocyte Globulin
AUC	Area Under the Curve
BMT	Bone Marrow Transplantation
BP	Blood Pressure
BUN	Blood Urea Nitrogen
cGvHD	Chronic Graft versus Host Disease
Cmax	Maximum Concentration
Cmin	Minimum Concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CRA	Clinical Research Associate
CR	Complete Remission
CRF	Comprehensive Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic Cell
DCregs	Regulatory Dendritic Cells
DLT	Dose-Limiting Toxicity
DST	Donor-Specific Transfusion
ET	Early Termination
ECGs	Electrocardiograms
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FIH	First-In-Human
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practice
GRFS	Graft vs Host disease free, relapse free survival

Abbreviation	Definition
GvHD	Graft versus Host Disease
GvL	Graft vs Leukemia
HBV	Hepatitis B Virus
Hct	Hematocrit
HEENT	Head, ears, eyes, nose and throat
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HNSTD	Highest non-severely toxic dose
HR	Heart Rate
HSCs	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IL	Interleukin
iNKT	Invariant Natural Killer T (cells)
INR	International Normalized Ratio
IP(s)	Investigational Product(s)
IRB	Institutional Review Board
iTCR	Invariant T-cell Receptor
IUD	Intra-uterine Device
IV	Intravenously
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
MHC	Major Histocompatibility Complex
MMF	Mycophenolate Mofetil
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NCI	National Cancer Institute
NKT	Natural killer T (cell)
NRM	Nonrelapse Mortality
OS	Overall Survival
OTC	Over-the-counter
PBSCT	Peripheral Blood Stem Cell Transplant
PBMC	Peripheral Blood Mononuclear Cell

Abbreviation	Definition
PD	Pharmacodynamic
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin Time
QTcF	QTc interval using Frederica's correction
RBC	Red Blood Cell
RR	Respiratory Rate
RRT	Regimen-related toxicity
SAEs	Serious Adverse Events
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SRC	Safety Review Committee
STD	Severely toxic dose
T1/2	Half-life
TEAE	Treatment emergent adverse event
TK	Toxicokinetic
Tmax	Time to C_{max}
TNF-α	Tumor Necrosis Factor-alpha
Tregs	Regulatory T Cells
ULN	Upper Limit of Normal
WBC	White Blood Cell

2 PROTOCOL SYNOPSIS

Name of Sponsor	REGiMMUNE Corporation (JAPAN) 35-3 Nihonbashi Hakozaki-cho BRICK GATE 5F, Chuou-ku, Tokyo 103-0015 Japan
Protocol Title	An Open Label, Non-Randomized Multicenter Phase 2b, Study with a Safety Run-in to Evaluate the Safety and Efficacy of RGI-2001 for the Prevention of Acute Graft-Versus-Host Disease Compared to Contemporary Controls in Subjects Following Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)
Name of Investigational Product	RGI-2001
Protocol Number	RGI-2001-003
Phase	Phase 2
Indication	Prevention of Acute Graft–versus-Host Disease following alloHSCT
Study Centers	This study will be conducted at 8-12 sites in the United States.
Study Rationale:	Despite efforts to date, the incidence of acute GvHD remains high. Thus, improvements in the prevention of the disease constitutes a high unmet medical need. Studies in both humans and mice have confirmed the pivotal role CD4+Foxp3+ Treg cells play in controlling GvHD (Socié 2009). However, the development of Treg cell-based therapeutic modalities has been hampered, in part, by the small numbers of these cells. RGI-2001 is a liposomal form designed to deliver RGI-7000, which is an immunomodulatory compound that may promote the proliferation of Tregs in donor bone marrow and the development of tolerance to alloantigens and therefore constitutes a novel approach to the prevention of GvHD.
Objectives	Endpoints
Primary	
• To assess the potential efficacy of RGI-2001 in addition to standard of care (SOC) vs SOC for the prevention of acute GvHD (aGvHD) • To characterize the safety and tolerability of 6 weekly intravenous (IV) infusions of	• Efficacy: Grades II-IV aGvHD by Day 100 according to the Modified Keystone Criteria (Przepiorka 1995) • Safety: Incidence, nature, and severity of treatment-emergent AEs, SAEs, laboratory test values, vital-sign measures, and graft failure

RGI-2001 in subjects following alloHSCT	
Secondary	
• To assess the potential efficacy of RGI-2001 in addition to SOC vs SOC for the prevention of chronic GvHD (cGvHD) according to the secondary endpoints listed • To assess the survival of subjects who received RGI-2001 in addition to SOC vs SOC • To evaluate the pharmacodynamics (PD) effects of weekly dosing of RGI-2001	• Grades II-IV aGvHD by Day 180 according to the Modified Keystone Criteria • Total and moderate-severe cGvHD at 6 months and 1 year according to the 2014 NIH criteria for cGvHD • Non-relapse mortality (NRM) rates at Day 100, 6 months and 1 year • Disease-free survival (DFS) at 6 months and 1 year • GvHD-free, relapse free survival (GRFS) at 6 months and 1 year • Overall survival (OS) at 6 months and 1 year • Change from baseline in the percentage of CD4+CD25+CD45RA+ CD127-LO T cells (naive Tregs) on Days 14, 28, 42, 60, 100, 180
[redacted]	
[redacted]	[redacted]
Study Design	This is an open-label, multi-center, single-arm study to evaluate six weekly doses of RGI-2001 in combination with SOC treatment for the prevention of aGvHD in subjects following alloHSCT. Study subjects will be compared to a contemporaneous set of controls from the Center for International Bone and Marrow Transplant Research (CIBMTR) that is derived using the same eligibility criteria

	used for this study. The study will include a Safety Run-in Phase and an Expansion Phase. Safety Run-in Phase: Subjects will receive open-label RGI-2001 at a dose of 100µg /kg, via 30-minute intravenous (IV) infusion on a weekly basis for 6 doses in addition to a standard of care (SOC) GvHD prophylactic regimen. The first dose will be administered on Day 0, approximately 30 minutes and no later than 1 hour after hematopoietic stem cell transplant (HSCT) infusion. Subsequent doses will be administered weekly, on Days 7, 14, 21, 28 and 35. Up to two cohorts of 3 subjects each will be enrolled to the Safety Run-in Phase. Initially, 3 subjects will be enrolled, treated and assessed for dose-limiting toxicities through Day 30 (dose limiting toxicity [DLT] window). A safety review committee (SRC) will examine all relevant safety data after the 3rd subject has reached Day 30. As a rough guide, a DLT rate on the order of 20% or less would be considered as acceptable. Therefore, if 0 subjects are reported to have a DLT among the first 3 subjects, consideration will be given to enrolling up to 3 additional subjects. However, this decision will not be made solely on the observed occurrence (or lack of) DLTs; rather the SRC will consider the totality of the safety data before arriving at a definitive conclusion regarding enrollment of additional subjects at the dose of 100µg /kg. If within the first 3 subjects, 1 or more DLT are observed, then consideration will be given to use of an alternative dose and/or dosing schedule, with the ultimate decision being made by the SRC. If an alternate dose and/or schedule is used, the same process as described above will be used. If the additional 3 subjects (beyond the initial 3) are allowed to enroll at the dose of 100µg /kg or a lower dose and/or alternative schedule, safety data after the 6th subject has completed all 6 doses, as well as initial efficacy, PK and PD data will be evaluated in coming to a recommendation regarding proceeding to the Expansion Phase, with this recommendation made by the SRC. Definition of Dose-limiting Toxicities The following DLT criteria apply to the Safety Run-in Phase of the study. A DLT is defined as any treatment-related AE that is not attributable to an extraneous cause (e.g., disease progression, preparatory regimen or HSCT infusion) and also excludes any signs and symptoms of GvHD. A DLT is an adverse event occurring in the period of 30 days after the first dose of RGI-2001 administration, and meeting at least 1 of the following NCI CTC (Version 5.0) criteria: • Grade 3+ infusion-related/cytokine release reactions

	• Graft failure (as defined in Section 9.4.1) • Any Grade 4-5 non-hematological AE • Delay in dosing by > 2 weeks due to treatment-related AE that is not attributable to an extraneous cause Expansion Phase: Once a dose/schedule is determined by the SRC to have an acceptable safety/PK profile, enrollment will continue in the Expansion Phase and be extended to all sites. Accrual is targeted at 50 subjects who receive the dose deemed as acceptable from the Safety Run-in Phase (44 in the Expansion Phase, 6 from the Safety Run-in Phase at the dose used in expansion). Subjects will receive open-label RGI-2001 at a dose of 100µg/kg, via 30-minute intravenous (IV) infusion on a weekly basis for 6 doses (or an alternative dose/schedule as determined in the run-in phase) in addition to a SOC GvHD prophylactic regimen. The first dose will be administered on Day 0 at approximately 30 minutes and no later than 1 hour after HSCT infusion. Subsequent doses will be administered weekly, on Days 7, 14, 21, 28 and 35. Control Group: A non-randomized, contemporary control group from the CIBMTR database will be derived for comparison. Control subjects will be chosen so as to meet all eligibility requirements for the clinical trial, have received a transplant in the same time window as the study subjects, and have been transplanted in a center that participates in this study. Consent will be obtained via the CIBMTR to participate in this study.
Number of Subjects	A total of 50 subjects will be enrolled. It is anticipated that a minimum of 250 subjects will be included in the control group.
Study Duration	Individual subject participation is expected to last up to 1 year following alloHSCT, including a 6-week treatment period and a 42-week follow-up period. In addition, there is a screening period lasting approximately 2 weeks.
Inclusion Criteria	All subjects (including CIBMTR control group, except where noted) must meet the following criteria: 1. Ages $\geq$ 18 and $\leq$ 65 years of age 2. Has a hematologic malignancy as defined below and is considered a candidate for alloHSCT: a. Acute myelogenous leukemia (AML) in first or subsequent morphologic complete remission (CR) b. T or B cell acute lymphoblastic leukemia (ALL) in first or subsequent complete morphologic remission

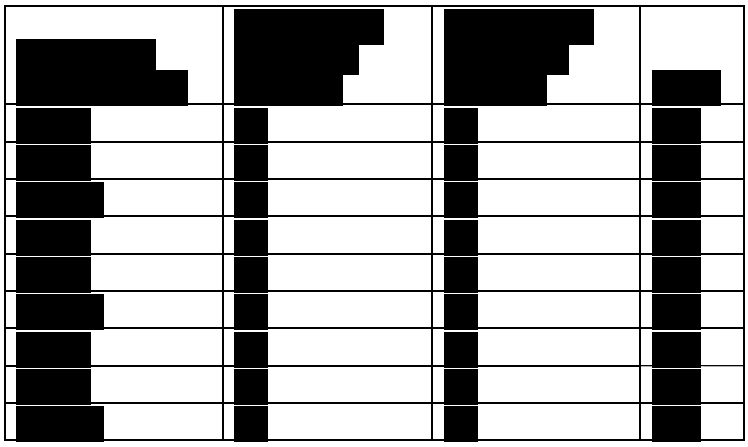
	c. Myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloproliferative disorder (MPD) including myeloid metaplasia and myelofibrosis and are currently with < 10% blasts in bone marrow d. CML subjects who have received prior treatment including at least one tyrosine kinase inhibitor and are currently in chronic phase or with a complete hematologic remission but with evidence of cytogenetic or molecular relapse 3. Must have adequate organ function as defined below (RGI-2001treatment group only): a. Cardiac function: Left ventricular ejection fraction at rest ≥ 45% b. Liver function: total bilirubin < 1.5 x upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x the ULN. Patients who have been diagnosed with Gilbert's Disease or malignant involvement are allowed to exceed the defined bilirubin value of 1.5 x the ULN c. Serum creatinine < 2 mg/dL or estimated creatinine clearance > 50mL/min calculated using the Cockcroft-Gault equation d. Pulmonary: DLCO (corrected for hemoglobin) and/or FEV1 ≥ 50 % 4. Considered suitable candidate for a myeloablative allogeneic or unrelated donor transplant based on institutional criteria 5. Subject must be receiving first allogeneic transplant from a single donor. Prior autologous transplant is acceptable 6. Transplant Donor: a. Matched related donor (8/8): Molecular identity at HLA-A, -B, -C and -DRB1 by high-resolution typing b. Unrelated donor (≥ 7/8 allelic match): high resolution molecular typing at the following loci is required HLA -A, -B, -C and -DRB1 c. Meets institutional criteria for bone marrow or PBSC donation (see Section 7.4) 7. Source of the allograft; unmodified bone marrow or mobilized peripheral blood stem cell (PBSC) transplant, using granulocyte colony stimulating factor

	(G-CSF) as the mobilizing agent. Cord blood is not allowed. 8. KPS ≥ 60 9. Is a candidate for anti-graft-vs-host-disease (GvHD) prophylaxis that includes a calcineurin inhibitor (either tacrolimus [FK 506] or cyclosporine A), in combination with either methotrexate (MTX), mycophenolate mofetil (MMF). 10. Ability to understand and willingness to sign a written informed consent form Inclusion criteria pertaining specifically for subjects scheduled to receive RGI-2001: 11. If female of childbearing potential, must have had a negative serum pregnancy test prior to enrollment and must have agreed to use a double barrier method of contraception for 90 days following the last dose of RGI-2001 12. If male, must be sterile or willing to use an approved method of contraception from the time of informed consent to 90 days after the last dose of RGI-2001
Exclusion Criteria	Any subjects (including CIBMTR control group) who meet any of the following criteria will be excluded from study entry: 1. Has had any other prior organ transplantation 2. Planned procedure to deplete regulatory T-cells from donor transplant materials 3. Planned reduced intensity conditioning 4. Planned use of any additional or alternative drug(s) for GvHD prophylaxis than listed in the inclusion criteria (e.g., rapamycin, cyclophosphamide, steroids) 5. Has had prior treatment with anti-CD3, other T cell depleting antibodies, or anti-thymocyte globulin within 12 months prior to alloHSCT procedure 6. Is participating in a trial (other than RGI-2001-003) involving an investigational agent/non-standard of care drug 7. Has progressive underlying malignant disease including post-transplant lymphoproliferative disease 8. Has evidence of active central nervous system (CNS) disease including known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of CNS involvement) 9. Patients with active bacterial, viral or fungal infections (currently taking medication(s) and with progression or no clinical improvement)

	10. Known history of human immunodeficiency virus (HIV) 11. Active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) (control group only). 12. Is female and pregnant or lactating Exclusion criteria pertaining specifically to subjects scheduled to receive RGI-2001: 13. Has undergone major surgery within 1 month before Day 0. Indwelling catheter placement is allowed 14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with viral load above the limit of quantification. Subjects that are on study with HBV or HCV infection should have titers checked regularly, as per institutional standard of care 15. Has had any other condition that, in the opinion of the Investigator, renders the subject unsuitable for study participation 16. Has a documented history of uncontrolled autoimmune disease or on active treatment 17. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 18. History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to receiving study drug 19. Has received an investigational agent within 4 half-lives or 14 days prior to HSCT, whichever is shorter
Investigational Product; Dose; Route of Administration	RGI-2001 for Injection is supplied as a sterile liquid suspension filled into depyrogenated USP Type 1, 5-mL glass vials with a 2.5 mL fill volume. All subjects will receive 6 weekly doses of RGI-2001, 100 µg/kg via IV administration over 30 minutes. The dosage of RGI-2001 will be diluted in 50 mL 0.9% normal saline and the first dose will administered intravenously (IV) at approximately 30 minutes and no later than 1 hour after completion of the alloHSCT on Day 0.

Conditioning, Prophylactic and Concomitant Therapy	Concomitant medications are any prescription or over-the-counter (OTC) preparations used from 2 days prior to the preparatory regimen before Day 0 through the end of the subject's study participation. Standard myeloablative preparatory regimens, (i.e., experimental regimens or drugs are not allowed), HSCT, and standard supportive care/ prophylactic treatments (including but not limited to colony stimulating factors, transfusions, antibiotics/ anti-virals/ anti-fungals) per institutional guidelines for optimal medical care shall be permitted during participation in this study. The dose of steroids that are required for reasons unrelated to the underlying malignancy or HSCT process or sequelae must not be higher than physiologic doses (the equivalent of 20 mg of prednisone). No anti-thymocyte globulin is allowed in the conditioning regimen. GvHD prophylaxis must consist of a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with MTX or MMF. Dosing, schedule and monitoring of the GvHD regimen should follow institutional guidelines. Please see respective prescribing information for safety information. Steroids, sirolimus, post-transplant cyclophosphamide, other GvHD prophylactic agents (including investigational agents) or manipulation of the graft to reduce GvHD are not allowed. Post transplant maintenance therapy that includes an investigational agent (ie, not an FDA approved drug for any indication), or any treatments that can be used for GvHD is not allowed. Maintenance therapy for actionable targeted mutations (e.g., FLT3 inhibitors) or with FDA approved agents in any indication, should not be initiated prior to Day 42 post alloHSCT. Treatment of GvHD should follow institutional guidelines and may include steroid treatment at supra-physiologic doses.
Statistical Considerations	The primary objective of this study is to assess the potential efficacy of RGI-2001. The primary endpoint for these purposes is grades II-IV acute GvHD, and the study subjects will be compared to a control group of subjects supplied by the CIBMTR. Control subjects will be chosen so as to meet all eligibility requirements for the clinical trial, have received a transplant in the same time window as the study subjects, and have been transplanted in a center that participates in this study. 

We consider a one-sided significance level of .10 to be sufficient evidence of a signal for moving forward.



Based on these estimates, it is anticipated that a total of 50 subjects who receive at least one dose of RGI-2001 will be enrolled, this including subjects from the run-in stage treated at the dose moved forward to the Expansion Phase. It is anticipated that a minimum of 250 subjects will be included in the control group.

Demographics and Baseline Characteristics

Categorical factors will be summarized with proportions, and continuous variables will be summarized using means and medians.

Analysis Population, Handling of Dropouts, and Missing Data

All subjects who receive at least one dose of RGI-2001 will be used for comparison to the CIBMTR subjects.

Analysis of Efficacy Data

The primary endpoint grades II-IV acute GvHD by Day 100 according to the Modified Keystone Criteria will be compared between the study group and CIBMTR controls using logistic regression. The factors that will be considered for adjustment in this model include subject age, gender, donor age, type of donor (MRD, 8/8 URD 7/8 URD), source of allograft, diagnosis (AML, ALL, MDS, MPD including CMML), preparative regimen, GvHD prophylaxis regimen.

Secondary endpoints that will be modeled as binary outcomes will similarly be compared using logistic regression. Secondary endpoints that will be modeled as time-to-event outcomes will be compared using Cox regression.

Potential interactions of RGI-2001 and various factors will be examined by including appropriate factors into regression models.

Given that this is not a randomized study and that the intention is only to assess outcomes for a potential signal, no

	adjustments will be made for multiple comparisons. As such, a Type II error (or a false negative) is prioritized over a Type I error (or a false positive). Binary exploratory outcomes will be summarized with proportions, continuous outcomes with means and medians, and time-to-event outcomes with Kaplan-Meier estimates or cumulative incidence estimates for endpoints with competing risks.

3 SCHEDULE OF ASSESSMENTS

ASSESSMENTS	Screening[a]	Prior to HSCT	HSCT/ RGI-2001 Infusion	Treatment Period					Follow-up Safety Period						Early Termination (ET)[b]	Unscheduled Visit[c]
	Day															
	-14 to -1	0	0	7	14	21	28	35	42	60	100	180	274 (9mo)	365 (12mo)		
Visit Window		0	0	(± 1)	(± 1)	(± 1)	(± 1)	(± 1)	(± 3)	(± 3)	(± 5)	(± 5)	(± 7)	(± 7)		
Informed consent[d]	X															
Demographics	X															
Inclusion/exclusion criteria	X															
Medical/cancer/ surgical history[e]	X															
Vital signs/KPS[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/height[g]	X	X		X	X	X	X	X			X	X		X	X	
Physical exam[h]	X	X			X		X	X		X	X	X	X	X	X	X
Hematology[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation testing[k]	X	X														X
Urinalysis[l]	X															X
Serum pregnancy test[m]	X															X
12-lead ECG	X															X
Allogeneic HSCT			X													
RGI-2001 administration[o]			X	X	X	X	X	X								
RGI-2001 PK samples		[redacted]														
Blood for immunophenotyping																
[redacted]																
[redacted]																
GvHD assessment[p]					X	X	X	X	X	X	X	X	X	X	X	X
Tumor assessments[q]	X										X	X		X	X	X
Adverse events[r]	X	X													X	X
Concomitant medications[s]	X														X	X

Abbreviations: ET = early termination, HSCT = hematopoetic stem cell transplant, KPS = karnofsky performance status, ECG = electrocardiogram, PK= pharmacokinetics, GvHD = graft vs host disease

[a] Screening assessments must be performed within 14 days prior to initiation of any treatments related to the HSCT including the preparatory regimen unless otherwise

specified. Informed consent, results of screening hepatitis, HIV tests, and tumor assessment (provided that no intervening therapy for their malignancy has been administered) may be obtained up to 42 days before initiation of the preparatory regimen. PFTs and ECHO may be obtained as per institutional standard of care criteria within 84 days prior to the preparatory regimen provided no intervening therapy for their malignancy has been administered. Pregnancy test must be conducted within 7 days before preparatory regimen. Results of standard of care tests/procedures, performed prior to the subject signing the informed consent form (ICF) can be used as part of the screening assessments as long as the tests/procedures are performed within the appropriate screening window, unless otherwise specified. Screening assessments do not need to be repeated due to minor delays in procurement of donor HSC's.

[b] Subjects who are permanently discontinued from the study, either during the treatment period or follow up period, should complete the Early Termination Visit and, if applicable, monitor adverse event through 30 days of last RGI-2001 dose.

[c] Unscheduled visits and procedures may be performed as clinically indicated.

[d] Written informed consent must be signed by the subject before any protocol required procedures and assessments are performed. Results of standard of care tests/procedures, performed prior to the subject signing the informed consent form (ICF) can be used as part of the screening assessments as long as the tests/procedures are performed within the appropriate screening window unless otherwise specified. Screening assessments do not need to be repeated due to minor delays in procurement of donor HSC's.

[e] Prior cancer history includes: (i) date of diagnosis, (ii) prognostic score if applicable (iii) all previous therapies (i.e., chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (i.e., regimen, start and stop dates), (v) best response for each regimen.

[f] Vital signs, including temperature, blood pressure (systolic/diastolic), heart rate (HR), and respiratory rate (RR) should be taken in supine or seated position. Vital signs should be obtained within 15 minutes prior to RGI-2001 infusion and should be repeated within 30 minutes after the infusion. Additional vital signs measurements should be obtained as clinically indicated.

[g] Height (without shoes) should be obtained prior to initiation of the preparatory regimen only. Weight should be taken within one day of dosing and the dosage of RGI-2001 should be verified to be the same as the planned dose.

[h] A complete physical exam should be performed during screening and should include HEENT, dermatologic, cardiovascular, respiratory, GI (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems. Physical examinations at all other time points should be a limited review of body systems as well as symptom-directed physical examinations of an AE or SAE.

[i] A complete blood count including red blood cell (RBC) and white blood cell (WBC) count with differential, hemoglobin, hematocrit, and platelet count.

[j] A comprehensive chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, calcium, phosphorus, magnesium, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and gamma glutamyl transferase (GGT).

[k] Coagulation tests including prothrombin time (PT) or INR, and aPTT should be obtained at baseline and prior to HSCT infusion. Additional tests may be obtained as clinically indicated.

[l] Urinalysis, including protein, glucose, ketones, blood, bilirubin, urobilinogen, pH, specific gravity and nitrates, with microscopic examination of sediment in the event of an abnormal reading on the dipstick.

[m] Serum pregnancy test (women of child-bearing potential) – within 7 days prior to preparatory regimen.

[n] Single ECG to be performed. If abnormal, including QTc > 450 msec, perform in triplicate approximately 30 seconds apart, using the average of the three.

[o] RGI-2001 should be administered intravenously over 30 minutes. On Day 0, the infusion should occur approximately 30 minutes and no later than 1 hour following the completion of HSCT. If cytokine reaction occurs with HSCT, subject should have resolved symptoms prior to the administration of RGI-2001.

[p] Assessment for GvHD should be performed during every examination or per institutional guidelines from the time of engraftment to end of study. Documentation of the timing, severity is required including any biopsies obtained. Treatment for GvHD and outcome should be documented.

[q] Evaluation of status of hematologic malignancy should be conducted as per institutional guidelines but should include a bone marrow aspirate and biopsy with cytogenetics, molecular diagnostics and chimerism as appropriate based on disease histology at baseline, and at time intervals close to Days 100, 180 and 365.

[r] Adverse events (AEs) must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) where possible. The reporting period for non-serious AEs starts after the first administration of study drug on Day 0. The reporting period for serious AEs starts after the informed consent form (ICF) has been signed. Adverse event monitoring should be continued for at least 30 days following the last dose of study drug. Infections should be recorded throughout the study. See Section 10 for further details.

[s] Review of all medications, including over-the-counter (OTC) preparations and herbal products. Concomitant medications used from 2 days prior to the preparatory regimen before Day 0 through the end of the subject's study participation, should be recorded. Maintenance therapy should be documented as a concomitant medication.

4 INTRODUCTION

4.1 Background

4.1.1 Graft Versus Host Disease

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is an important therapeutic option, and, in some indications, the only potentially curative therapy, for the treatment of a variety of hematologic malignancies, including acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML) and myelodysplastic syndrome (MDS). In the U.S. approximately 8,500 subjects underwent allogeneic HSCT for a variety of indications in 2016.

The success of myeloablative alloHSCT derives both from the ability to treat subjects with intensive chemo radiotherapy and from potent graft-versus-leukemia (GVL) effects mediated by donor immunity. Donor T cells in the infused stem cell graft are used to attack malignant cells, but may also strike normal host tissues and organs, resulting in graft versus host disease (GvHD). Despite the use of immunosuppressive agents, GvHD, acute or chronic, is one of the leading causes of morbidity and mortality from alloHSCT.

Five phases of the development of acute GvHD have been described (Socié 2019). The first phase, priming of the immune response, is initiated by the underlying disease and the conditioning regimen used to prepare for transplantation. Damage to host tissues results in the secretion of pro-inflammatory cytokines that can increase the expression of adhesion molecules, co-stimulatory molecules, major histocompatibility complex (MHC) antigens and chemokines - all of which activate host antigen presenting cells (APCs). The second phase, T-cell activation and co-stimulation occur when donor T cells proliferate and differentiate in response to host APCs. The incidence of acute GvHD is directly related to the degree of mismatch in human leukocyte antigen (HLA) determinants such as MHC class II and I and minor histocompatibility antigens (MiHA). Additional donor/host differences, such as polymorphisms in proteins connected with innate immunity (NOD2), in the Toll-like receptor family, and in cytokine genes, are also believed to contribute to acute GvHD risk. The third and fourth phases of acute GvHD include alloreactive T-cell expansion and differentiation followed by the migration of activated T-cells to GvHD target tissues such as the gut, liver, skin, and lung and the recruitment of other effector leukocytes. In the last phase of acute GvHD development, effector T-cells initiate the destruction of target tissues via exposure to the cell surface and the release of soluble immune effectors. The resultant tissue damage leads to an increase in inflammatory signals and propagation of the cytokine storm.

Classic acute GvHD generally develops within the first 100 days after myeloablative HSCT and typically affects the skin, gastrointestinal (GI) tract, and liver. In the setting of prophylaxis with immunosuppressants, Grade II-IV acute GvHD occurs in 25-60% of matched related transplant recipients and in 45-70% of matched unrelated recipients (Ho 2001). Although less common with myeloablative transplants, late onset acute GvHD may occur after 100 days post HSCT. The incidence of acute GvHD increases with increasing HLA mismatch between donor and recipient, unrelated donor transplant, female donor to male recipient and use of a total body irradiation (TBI) containing preparatory regimen. The development of Grade III/IV acute GvHD is

associated with a decrease in survival in subjects undergoing allogeneic transplantation. Steroids, primarily prednisone and methylprednisolone, constitute the first line of treatment for Grade III-IV acute GvHD. Complete responses can be expected in 25-35% of subjects, with an additional 15% achieving a partial response. Failure to respond to steroid therapy portends a poor prognosis. Second line treatment for acute GvHD include other immunosuppressive agents, such as tacrolimus, and anti-thymocyte globulin (ATG), as well as agents targeting TNF-α and the IL-2 receptor (Paczesny 2010). These therapeutic approaches are complicated by broad immunosuppression that results in enhanced susceptibility to infection and the risk of recurrence of the underlying malignancy.

4.1.2 CD4+Foxp3+ Regulatory T-cells

A number of approaches, both pharmaceutical and cellular, in the prophylaxis of acute GvHD are being studied. The mainstay of prophylaxis therapy is a combination of a calcineurin inhibitor (cyclosporine and tacrolimus) plus either a short course of methotrexate or mycophenolate mofetil. More recently, sirolimus, which has been successful in the prevention of organ transplantation, has been utilized for acute GvHD. To date, no single combination has proved superior in the prevention of acute GvHD, and the incidence of acute GvHD remains high. Cellular approaches have included T-cell depletion, either ex vivo or in vivo and the positive selection of stem cells (to facilitate the exclusion of T-cells). While these efforts have had an impact on the incidence of acute GvHD, when used aggressively, these techniques have been associated with higher disease relapse rates (Paczesny 2010).

More recently, efforts have been made to understand the function of regulatory T cells in transplantation. CD4+Foxp3+ Treg cells are considered a key player in maintaining peripheral tolerance (Wing 2001, Sagoo 2008, Paczesny 2010). Animal studies have demonstrated that these cells prevent or ameliorate various T-cell mediated diseases, including autoimmune disease and GvHD, by restoring immune tolerance to self-antigens as well as alloantigens (Wolff 2009). Studies in both humans and mice have confirmed the pivotal role Treg cells play in controlling GvHD (Socié 2019). However, the development of Treg cell-based therapeutic modalities has been hampered, in part, by the small numbers of these cells. RGI-2001 can expand these Treg cells in vivo and thus constitutes a novel approach to the treatment of GvHD.

The relationship between Treg cells and acute GvHD in clinical allogeneic bone marrow transplantation (BMT) recipients has been assessed clinically. A prospective analysis of peripheral blood Treg cells as determined by the frequency of CD4+CD25hiFoxp3+ lymphocytes was conducted in 215 BMT subjects (Magneau 2010). Autologous BMT subjects (N = 90) and allogeneic BMT subjects without GvHD (N = 65) had similar cell frequencies, whereas allogeneic subjects with GvHD (N = 60) had Treg cell frequencies that were 40% less than those without GvHD. Treg cell frequencies decreased linearly with increasing grades of GvHD at onset, and correlated with the eventual maximum grade of GvHD ($P < 0.001$). In addition, the number of Treg cells at onset of GvHD predicted the response to GvHD treatment ($P < 0.003$). Subjects with Treg cell frequencies less than the median had higher non-relapse mortality than subjects with Treg cells greater than the median, but experienced equivalent relapse mortality, resulting in an inferior survival at 2 years (38% versus 63%, $P < 0.03$). Treg

cell frequency may therefore have important prognostic value as a biomarker of acute GvHD (Magneau 2010).

4.2 Investigational Product

RGI-2001 is a liposomal formulation of the compound known as RGI-7000. RGI-7000 is a synthetic glycolipid composed of a galactose and a ceramide moiety linked in an α-configuration, a derivative of α-galactosylceramide (α-GalCer), a glycolipid originally extracted from a marine sponge (Natori 1993). It serves as a ligand for the CD1d molecule, expressed on APCs (Kawano 1997, Brossay 1998). The CD1d molecule is a non-polymorphic, MHC class I–like antigen-presenting molecule with an antigen-binding groove adapted for the presentation of lipid antigens (Moody 2005, Brigl 2004). [redacted]

Refer to the current edition of the Investigator's Brochure (IB) for additional information related to the physical, chemical and pharmaceutical properties and formulation of RGI-2001.

4.3 Study Rationale

Despite efforts to date, the incidence of acute GvHD remains high. Thus, improvements in the prevention of the disease constitutes a high unmet medical need.

Studies in both humans and mice have confirmed the pivotal role CD4+Foxp3+ Treg cells play in controlling GvHD (Socié 2009). However, the development of Treg cell-based therapeutic modalities has been hampered, in part, by the small numbers of these cells. RGI-2001 is a liposomal form designed to deliver RGI-7000, which is an immunomodulatory compound that may promote the proliferation of Tregs in donor bone marrow and the development of tolerance to alloantigens and therefore constitutes a novel approach to the prevention of GvHD.

Preclinical studies suggest that the effects of RGI-2001 treatment are immunologically selective, affecting responses against specific antigens without causing generalized immunosuppression or the depletion of B- or T-cell function or numbers, and that RGI-2001 does not compromise beneficial GvL. In vitro and in vivo studies using model antigens have determined the mechanism for RGI-2001's immunomodulatory activity. These studies have shown that RGI-2001 activates a tolerogenic cellular pathway, which ultimately leads to the activation of cellular cascades including regulatory dendritic cells (DCreg) and Tregs. These antigen-specific Tregs have been shown to down regulate the immune response directed toward specific antigens without causing generalized immunosuppression. In vivo experiments have also shown that primary antibody (humoral) responses were suppressed when mice were exposed to a prototypic preparation of liposomal RGI-7000 at or around the time an antigen was introduced (Ishii 2008). Furthermore, in a murine model of acute GvHD, treatment with RGI-2001 resulted in a statistically significant prolongation of survival in animals treated at doses ranging from 0.1 to 100 µg/kg. In the treated animals, significantly higher levels of host alloantigen-specific Tregs

were observed after hematopoietic cell transplantation when compared with untreated animals. Immune responses against host alloantigens were suppressed in these treated mice, but responsiveness to third-party alloantigens remained intact. Additionally, in a mouse model of graft-versus-leukemia (GvL), treatment with RGI-2001 at the time of allogeneic bone marrow transplant was clearly shown to suppress GvHD without abrogating GvL effects (Duramad 2011).

4.4 Summary of Nonclinical Data

RGI-2001 is anticipated to elicit antigen-specific immune tolerance. In vitro and in vivo studies have demonstrated the biological activity of RGI-2001 as follows:

- RGI-2001 has been shown in vitro to be effectively taken up by B cells.
- In peripheral blood mononuclear cell (PBMC) and whole blood studies to assess cytokine induction, RGI-2001 at clinically relevant concentrations, did not induce significant levels of pro-inflammatory cytokines in either human PBMCs or whole blood, demonstrating the low potential for inducing cytokines that may play an inciting role in GvHD (e.g., IL-12, IFN-γ or TNF-α).
- In an acute GvHD model, RGI-2001 induced host-specific tolerance by promoting significant and dose dependent expansion of donor-derived CD4+Foxp3+ Tregs following allogeneic bone marrow and whole spleen cell (WSC) transplantation. The expansion of Tregs was also associated with a significant survival benefit and improvement in clinical signs of GvHD without compromise of GvL effects.
- Concurrent treatment of normal mice with RGI-2001 and allogeneic donor spleen cells resulted in tolerance specific to the donor alloantigens through expansion of DCreg and Treg cells in a donor-specific transfusion (DST) mouse model (REGiMMUNE internal report.
- In the GvHD efficacy studies a highly significant survival benefit was seen in mice treated with single injections of RGI-2001 at doses as low as 0.1 µg/kg. A dose-dependent donor derived CD4+Foxp3+ Treg expansion was observed at doses ranging from 0.01 to 100 µg/kg. The survival benefit in these models reached significance at approximately 0.1 ug/kg. Thus, the minimum pharmacologically active dose (PAD) in the mouse GvHD model was defined as 0.1 µg/kg based on both survival and Treg expansion.

In good laboratory practice (GLP) toxicology studies in the mouse (doses of 0.25, 3.5, or 50 mg/kg every 3 days) and monkey (doses of 0.1, 1.5, or 20 mg/kg every 3 days), doses up to 50 mg/kg and 20 mg/kg of RGI-2001 respectively, the maximum feasible doses (MFD), did not result in significant toxicity or dose limiting adverse effects. RGI-2001 was administered intravenously every 3 days to mice and monkeys for a period of up to 2 weeks, for a total of 5 doses. These repeat dose studies included complete clinical, as well as morphological evaluations in addition to immunophenotypic analyses. Although the severely toxic dose – 10 (STD-10) or the highest non-severely toxic dose (HNSTD) was not reached in the mouse or monkey repeat dose toxicology studies, the highest dose was considered the no observed adverse

effect level (NOAEL). The human equivalent dose (HED) of the NOAEL in the mouse (50 mg/kg) is 4400 µg/kg and the HED of the NOAEL in the monkey (20 mg/kg) is 6450 µg/kg. These HEDs are 44- to 65-fold higher than the dose planned in study RGI-2001-003 (100 µg/kg),

To supplement the general toxicology studies a single primate GLP safety pharmacology study encompassing CNS, cardiovascular, and respiratory evaluations was conducted. This study assessed intravenous doses of up to 20 mg/kg (the same doses evaluated in the definitive toxicology study in the monkey), employing telemetry to monitor cardiovascular responses. Cardiovascular parameters were also monitored in the repeat-dose GLP toxicology study in monkeys.

RGI-2001 administration did not result in any mortality and was without effect on functional observational battery (FOB) parameters. In addition, there were no significant effects on; body weight, body temperature, PR interval, QRS duration, QTc interval, QT vs. RR or QTc vs. RR interval plots, electrocardiographic morphology evaluations, respiratory rate, minute volume, or tidal volume.

Toxicokinetic (TK) evaluations were performed for each of the pivotal toxicology studies in mice and monkeys and demonstrated adequate exposure throughout the course of the studies. Mass balance (i.e., excretion into urine and feces) studies were conducted in mice and monkeys using radiolabeled RGI-2001. In addition, a tissue distribution and expired air study was conducted in mice.

In both mice and monkeys, radioactivity following [^{14}C]RGI-2001 administration was associated more with plasma than blood cells over the first several hours post-treatment, but the terminal half-life (T ½) in cells (> 250 hours) was much longer than in plasma (~ 50 hours).

After administration of [^{14}C]RGI-2001 to mice, different tissues reached peak radioactivity levels at different times with widespread distribution of radioactivity to tissues still observed at 168 hours post-dose. Tissues with notably high radioactivity levels were the spleen, liver, bone marrow, lung, and adrenal gland. These distribution data were consistent with established clearance mechanisms for liposomes through the reticuloendothelial system (Ishida 2002). Some of the tissues with the highest radioactivity were those associated with histopathologic alterations in the mouse toxicology study. Tissues with notably low radioactivity were the central nervous system (CNS), ocular tissues, bone, skeletal muscle and reproductive tissues.

Excretion studies in both mice and monkeys demonstrated that very little RGI-2001 was eliminated in the urine and feces. In monkeys, 2.88% was eliminated in the urine and 0.91% in the feces. In mice < 6% was eliminated in urine and feces combined. In bile duct-cannulated mice, it was shown that only 0.11% of the injected radioactivity was collected in bile over 24 hours. Collection of expired air yielded 64.68% of the injected dose as CO_2, indicating the major route of elimination was conversion of [^{14}C]RGI-2001 to CO_2.

The species used in the absorption, distribution, metabolism and excretion (ADME)/toxicokinetic evaluations of RGI-2001 were the same species employed in the pharmacological evaluations (mouse, cynomolgus monkey) and definitive toxicology studies. To date, no metabolism studies of RGI-2001 have been conducted. The expected consequence of the metabolism of liposomal products such as RGI-2001 is degradation to the individual phospholipid components and/or triglycerides (Seltzer 1984).

An in vitro study was performed with appropriate positive and negative controls to determine if RGI-7000, the active pharmaceutical ingredient (API) of RGI-2001, inherited human cytochrome P450 enzymes. This study was conducted with RGI-7000 rather than RGI-2001 because it was considered a more sensitive means with which to assess inhibitory potential. Under experimental conditions, there was little or no evidence that RGI-7000 inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 in either a direct, time-dependent without metabolism or metabolism-dependent manner.

The protein binding capacity of RGI-2001 and RGI-7000 was assessed in mouse, monkey, and human plasma.

[redacted]

Refer to the current edition of the RGI-2001 IB for additional information related to RGI-2001 clinical experience.

4.5 Summary of Clinical Data

The first in human (FIH) study of RGI-2001 was a Phase 1/2a multicenter, open-label, dose escalation study whose primary objective was to evaluate the safety, tolerability, and pharmacokinetic profile of a single dose of RGI-2001 in subjects undergoing alloHSCT, with radiation or non-radiation containing myeloablative or reduced intensity preparative treatments based on institutional practices. GvHD prophylaxis consisted of a calcineurin inhibitor and one of the following (based on institutional practices): methotrexate, mycophenolate mofetil, or sirolimus. The study was divided into 2 parts: Part 1 was the dose-escalation phase and Part 2 was the dose-expansion Phase. Eligible subjects were enrolled at 7 centers. A total of 68 subjects, 57 RGI-2001 treated subjects as well as 11 control subjects participated in the study.

In Part 1 of the study, a total of 28 subjects with a variety of hematologic diseases received a single dose of RGI-2001, administered approximately 30 minutes and no later than 1 hour after alloHSCT with an unrelated peripheral blood or bone marrow donor graft. The dose ranged from 0.001 ug/kg to 100 ug/kg. Based on the results of the Part 1 study, 2 doses, were selected to further study in the Part 2 for the dose-expansion. The maximal administered dose that had no significant toxicity and had some signal of effect was 100 µg/kg. A dose 2 logs lower (1 µg/kg) was chosen to evaluate the potential dose response between the 1 µg/kg and 100 µg/kg doses in an effort to see a dose response in Part 2 of the study.

In the Part 2 dose-expansion phase of the study, 29 subjects receiving matched related or unrelated donor grafts were randomized to receive a single infusion of either 1.0 ug/kg or 100 ug/kg RGI-2001 administered approximately 30 minutes and no later than 1 hour after alloHSCT. Fourteen subjects received a dose of 1.0 ug/kg and 15 subjects received a dose of 100 ug/kg of RGI-2001. An additional 11 subjects were enrolled as control subjects. A subset of subjects comprised of 4 subjects from each cohort, (8 of 29, 28%) responded to RGI-2001 by inducing a markedly increased number of cells with a Treg phenotype. The Treg had a high

Ki-67 index and were almost exclusively Helios+ and Foxp3+, indicating that their accumulation was due to expansion of natural Tregs. Notably, the incidence of grade 2 to 4 GvHD in the 8 subjects who responded to RGI-2001 was 12.5%, compared with 52.4% in the 21 subjects who did not respond. No grade 3 or 4 GvHD was observed in the responder group, compared with a 9.5% incidence among nonresponders (Chen 2017).

The expansion of Treg cells was observed through Day 22 relative to the control group. Treg increases appeared to be inversely related to the severity of GvHD. There was no impact on myeloid or platelet engraftment noted.

In general, the mean Cmax was increased as the dose of RGI-2001 increased. For most cohorts and for the subjects who received either the 1 µg/kg or 100 µg/kg dose of RGI-2001 in Part 2, the median times to Tmax were between 0.5 and 0.7 hours.

RGI-2001 was well tolerated and without infusion reactions or cytokine release syndrome up to a dose level of 100 µg/kg administered as a single intravenous infusion in subjects who underwent allogeneic transplantation. There were no notable adverse effects across a variety of conditioning regimens and regimens for GvHD prophylaxis.

This study served as the proof of concept for further exploring the potential of RGI-2001 for repeat administration to reduce or prevent GvHD during the critical phase post-transplantation.

Refer to the current edition of the RGI-2001 IB for additional information related to RGI-2001 clinical experience.

4.6 Risks/Benefits

Despite utilization of doublet prophylactic regimens, GvHD remains the largest factor influencing outcome from HSCT. Transplant related mortality rates increase with increasing severity of acute GvHD. Thus, additional treatments are needed. RGI-2001 has demonstrated the potential for Treg expansion and a subsequent decrease in acute GvHD without significant toxicity.

Clinical experience consists of the Phase 1 study which is described in Section 4.5. The MTD was not reached in doses ranging from 0.001 µg/kg to 100 µg/kg.

There were no notable adverse effects across a variety of conditioning and GvHD prophylaxis regimens. The expansion of regulatory T-cells was observed up through Day 22 as compared to the control group. Correlation of regulatory T cell increase appeared to be in inverse relation with severity of GvHD.

All subjects achieved myeloid engraftment within 30 days following RGI-2001 administration. Two subjects (both in cohort 2 [0.01 µg/kg]) did not achieve platelet engraftment within the time period; platelet engraftment for 2 other subjects was unknown (1 in the 1.0 µg/kg group and 1 in the 100 µg/kg group). Three subjects in the control group did not have platelet engraftment within 30 days following RGI-2001 administration.

All of the subjects who received RGI-2001 reported at least 1 treatment-emergent adverse event (TEAE) during the protocol-specified reporting period. There were no TEAEs that led to

discontinuation from the study. No cytokine reactions or infusion-related reactions were observed.

The most frequently reported adverse events for all cohorts (those occurring in > 15% of the subjects who received RGI-2001) were diarrhea (63.2%); nausea (61.4%); mucosal inflammation (56.1%); fatigue (54.4%); febrile neutropenia (43.9%); vomiting (36.8%); hypertension (33.3%); rash and headache (31.6% each); peripheral edema (29.8%); constipation (28.1%); muscular weakness (24.6%); dyspnea, abdominal pain, and increased AST (22.8% each); pyrexia and stomatitis (21.1% each); tachycardia and chills (19.3% each); decreased appetite and myalgia (17.5% each); and increased blood creatinine and hypomagnesemia (15.8% each).

The TEAEs considered related to RGI-2001 (those occurring in ≥ 4 subjects in the all RGI-2001 group) were nausea (10/57 subjects, 17.5%); diarrhea and increased AST (9/57 subjects each, 15.8% each); febrile neutropenia (8/57 subjects, 14.0%); vomiting, increased ALT, and increased alkaline phosphatase (6/57 subjects each, 10.5% each); chills, fatigue, increased bilirubin, increased creatinine, and headache (5/57 subjects each, 8.8% each); and peripheral edema, myalgia, dizziness, and rash (4/57 subjects each, 7.0% each)

Grade 3 TEAEs (those occurring in ≥ 4 subjects in the all RGI-2001 group) were febrile neutropenia (24/57 subjects, 42.1%), mucosal inflammation (13/57 subjects, 22.8%), hypertension (10/57 subjects 17.5%), diarrhea (7/57 subjects, 12.3%), stomatitis (6/57 subjects, 10.5%), and nausea (5/57 subjects, 8.8%). Grade 4 TEAE included sepsis in 1 subject (100 µg/kg group), and septic shock and respiratory failure in another subject (100 µg/kg group).

The following SAEs occurred in ≥ 2 subjects in the all RGI-2001 group: pyrexia, GvHD, and venoocclusive disease (3 subjects each); and diarrhea, sepsis, and staphylococcal bacteremia (2 subjects each).

Based on the nonclinical safety data available for RGI-2001, potential side effects associated with the administration of RGI-2001 include:

- Extramedullary hematopoiesis and splenomegaly; observed in animals receiving multiple high dose injections of RGI-2001. Although extramedullary hematopoiesis is rare in humans, subjects will be monitored closely with complete blood counts (CBC) and physical exam for evaluation of splenomegaly.
- Microgranulomas; observed in the liver of animals receiving multiple high dose injections of RGI-2001. Subjects will have liver function tests monitored frequently throughout the course of the study.
- Changes in RBCs, reticulocytes, WBC, leukocytes and various T- and B-cell lymphocyte subsets. Decline in RBCs may result in anemia, while decline in lymphocyte subsets may increase susceptibility to some types of infection. Subjects will have frequent CBCs to monitor for significant changes in red and white blood cell populations.
- A mild decline in triglycerides; observed in preclinical safety studies. It is anticipated that such a decline will have little impact on safety in subjects.

The pharmacologic actions of RGI-2001, manifested by a decrease in iNKT cells, could result in an impaired immune response to various pathogens and in absolute changes in T-cell or B-cell lymphocyte counts. Additionally, the ability of RGI-2001 to induce a tolerogenic state could result in undesirable tolerance to antigens to which subjects are exposed in the interval surrounding the administration of RGI-2001.

Literature reports have linked the activation of iNKT cells with the progression of atherosclerosis in murine models of atherogenesis (Tupin 2004). The role of iNKT cells in the development of atherosclerotic lesions in humans is unknown; however, inflammation and the innate immune response are believed to contribute to the progression of atherosclerosis. Pharmacologically active doses of RGI-2001 are expected to activate iNKT cells and theoretically could, as a result, aggravate underlying atherosclerotic disease. Only subjects with adequate cardiovascular function without ischemia or myocardial infarction in the previous six months will be enrolled in the clinical study.

4.7 Dose Regimen and Treatment Period Rationale

The dose and dose schedule for the Phase 2 study is 100 µg/kg, weekly for a duration of 5 weeks (6 doses). This dose was selected based on nonclinical pharmacology and toxicology information and the safety and exploratory efficacy results of the Phase 1/2a FIH study.

In murine models of GvHD, doses as low as 2 µg/mouse (approximately 100 µg/kg) prolonged the survival of mice. Additional studies showed prolongation of survival in these murine models was noted over a dose range of 0.1 to 10 µg/kg. As there was no sign of decreasing efficacy with dose, these mouse models suggested a dose of 100 µg/kg was toward the top of a wide range of effective doses.

In 2-week GLP toxicity studies of RGI-2001 in the mouse and monkey, the NOAEL was the highest dose tested in each species, 50 and 20 mg/kg, respectively. The HED of these doses are 44-fold and 65-fold higher than the planned dose of 100 µg/kg in study RGI-2001-003. Exposure of mice and monkeys at the NOAEL, based AUC0-t was very large, 2,155,000 ng*h/mL and 12,950,000 ng*h/mL, respectively. These exposures are over 10,000-fold higher than the human AUC0-t associated with a dose of 100 µg/kg (133 ng*h/mL, n = 15, study RGI-2001-002, Part 2).

Longer term toxicity of the active agent (RGI-7000) given by daily IV injection has been evaluated in GLP studies in rats (50, 100, 200, and 400 µg/kg/day for 26 weeks) and monkeys (30, 60, 200, and 600 µg/kg/day for 15 weeks), with a toxicity pattern similar to that of RGI-2001 suggesting there is no change in the toxicity of the active agent of RGI-2001 with longer duration of treatment.

Further support for the selection of 100 µg/kg comes from the clinical safety seen in study RGI-2001-002, in which RGI-2001 was safe and well tolerated up to 100 µg/kg administered as a single intravenous infusion for subjects who received allogeneic transplantation. There were no notable adverse effects across a variety of conditioning regimens and GvHD prophylaxis. Possible efficacy was observed in subjects during Part 1 (dose escalation) of the study but the differences between doses were not clear because of the small sample sizes. In Part 2 (dose expansion), both doses at 1.0 µg/kg and 100 µg/kg dose level showed some signal of effect and

there was no increase toxicity at the highest dose evaluated. There were no trends in toxicity with dose escalation across all the cohorts. Therefore, RGI 2001 at 100 ug/kg was selected to further evaluated for repeat dosing for the clinical development program.

Potential signals of efficacy from a single dose of RGI-2001 in study RGI-2001-002 support further testing of repeated (weekly) doses of RGI-2001 in this study. The weekly interval was selected to extend the exposure seen in the single dose clinical trial RGI-2001-002, while minimizing subject inconvenience with clinic visits.

5 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the potential efficacy of RGI-2001 in addition to standard of care (SOC) vs SOC for the prevention of aGvHD • To characterize the safety and tolerability of 6-weekly IV infusions of RGI-2001 in subjects following alloHSCT	• Efficacy: Grades II-IV aGvHD by Day 100 according to the Modified Keystone Criteria (Przepiorka 1995) • Safety: Incidence, nature, and severity of treatment-emergent AEs, SAEs, laboratory test values, vital sign measures, and graft failure
Secondary	
• To assess the potential efficacy of RGI-2001 in addition to SOC vs SOC for the prevention of chronic GvHD (cGvHD) according to the secondary endpoints listed • To assess the survival of subjects who received RGI-2001 in addition to SOC vs SOC • To evaluate the pharmacodynamics effects of weekly dosing of RGI-2001	• Grades II-IV aGvHD by Day 180 according to the Modified Keystone Criteria • Total and moderate-severe cGvHD at 6 months and 1 year according to 2014 NIH criteria • Non-relapse mortality (NRM) rates at Day 100, 6 months and 1 year • Disease-free survival (DFS) at 6 months and 1 year • GvHD-free, relapse free survival (GRFS)[a] at 6 months and 1 year • Overall survival (OS) at 6 months and 1 year • Change from baseline in the percentage of CD4+CD25+CD45RA+ CD127-LO T cells (naive Tregs) on Days 14, 28, 42, 60, 100, 180
[redacted]	
• [redacted]	[redacted]

Objectives	Endpoints
	• [redacted]
	[redacted]

[a] A GRFS event includes grade III-IV acute GVHD, chronic GvHD requiring systemic immunosuppressive treatment, disease relapse or progression, or death by any cause.

6 STUDY DESIGN

This is an open-label, multi-center, single-arm study to evaluate six weekly doses of RGI-2001 in combination with SOC treatment for the prevention of aGvHD in subjects following alloHSCT. The study will include a Safety Run-in Phase of up to 6 subjects to assess the safety and tolerability of 6 weekly doses of RGI-2001. If the safety profile in this run-in is deemed acceptable (see Section 6.1), an Expansion Phase in which the potential efficacy of 6 weekly doses of RGI-2001 in addition to SOC for GvHD prophylaxis will be assessed. Comparison will be made to a contemporaneous control group of subjects from the CIBMTR database in which SOC GvHD prophylaxis was administered (details in Section 11).

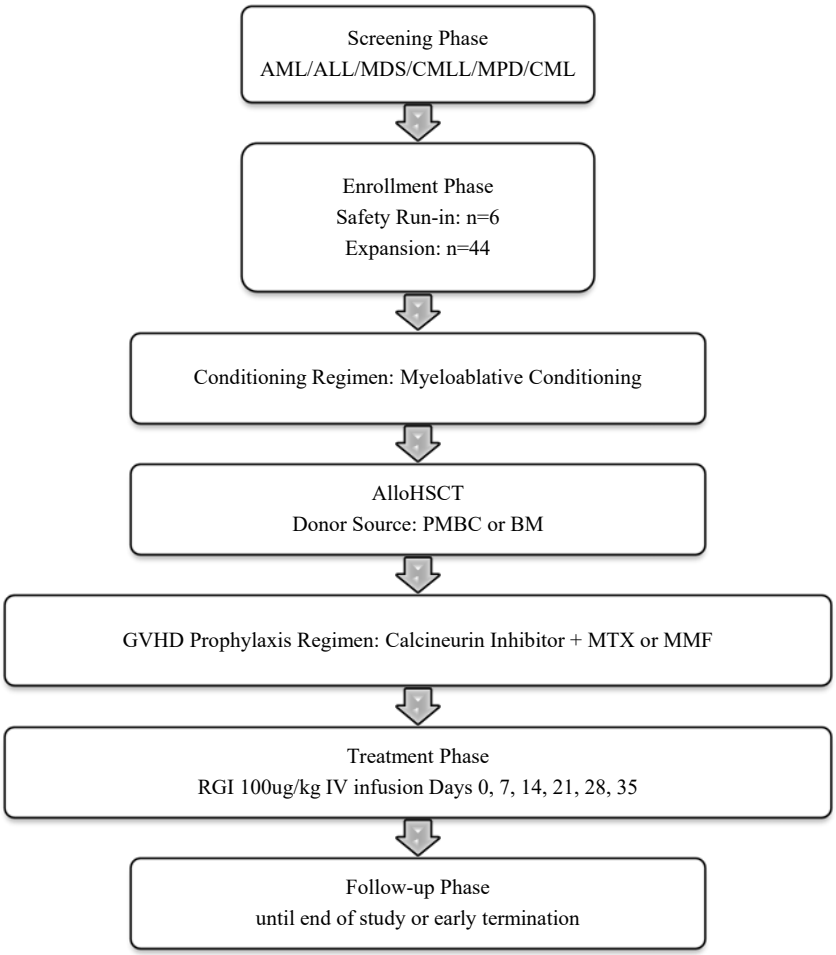
All subjects will be assessed for suitability of alloHSCT based on institutional practice, using either a matched-related donor (MRD) or unrelated donor (URD), and will be enrolled after meeting inclusion/exclusion criteria for this study. Preparatory regimens will be based on institutional practice for the disease subtype. Either bone marrow or peripheral stem cell grafts mobilized with G-CSF will be used. GvHD prophylaxis must consist of a calcineurin inhibitor (tacrolimus or cyclosporine) and a second agent (methotrexate or mycophenolate mofetil.

All subjects will be assessed for GvHD as per institutional practices but at minimum Day +100, +180 and 1-year post alloHSCT. Assessment of cGvHD will likewise occur at regular intervals as per institutional guidelines. Similar to the methodology employed by CIBMTR for the control subjects, cumulative data will be captured at regular intervals as outlined in the Schedule of Assessments (SoA).

- Safety will be assessed with periodic vital signs, physical exams, laboratory assessments and by reporting of AEs.
- Disease status will be assessed via regular laboratory and bone marrow assessments.

The study design is presented in Figure 1.

Figure 1 Study Design Schema



6.1 Safety Run-in Phase

A Safety Run-in Phase will be used to assess the safety profile and tolerability of repeat doses of RGI-2001 prior to the Expansion Phase. This portion of the study will be conducted at a limited number of sites.

Subjects will receive open-label RGI-2001 at a dose of 100µg /kg, via 30-minute intravenous (IV) infusion on a weekly basis for 6 doses in addition to a SOC GvHD prophylactic regimen. The first dose will be administered on Day 0 at approximately 30 minutes and no later than 1 hour after HSCT infusion (see Section 8.6 on Dose Administration). Subsequent doses will be administered weekly, on Days 7, 14, 21, 28 and 35.

Up to two cohorts of 3 subjects each will be enrolled to the Safety Run-in Phase. Initially, 3 subjects will be enrolled, treated and assessed for dose-limiting toxicities (as defined below in Section 6.1.1) through Day 30 (DLT window). A safety review committee (SRC) will examine all relevant safety data after the 3rd subject has reached Day 30. As a rough guide, a DLT rate on the order of 20% or less would be considered as acceptable. Therefore, if 0 subjects are reported

to have a DLT among the first 3 subjects, consideration will be given to enrolling up to 3 additional subjects. However, this decision will not be made solely on the observed occurrence (or lack of) DLTs; rather the SRC will consider the totality of the safety data before arriving at a definitive conclusion regarding enrollment of additional subjects at the dose of 100 µg /kg. If within the first 3 subjects, 1 or more DLTs are observed, then consideration will be given to use of an alternative dose and/or dosing schedule, with the ultimate decision being made by the SRC. If an alternate dose and/or schedule is used, the same process as described above will be used. If the additional 3 subjects (beyond the initial 3) are allowed to enroll at the dose of 100 µg /kg or a lower dose and/or alternative schedule, safety data after the 6th subject has completed all 6 doses, as well as initial efficacy, PK and PD data will be evaluated in coming to a recommendation regarding proceeding to the Expansion Phase, with this recommendation made by the SRC. Once the study extends to the Expansion Phase, enrollment will be open to all sites (Figure 2).

6.1.1 Definition of Dose-limiting Toxicities

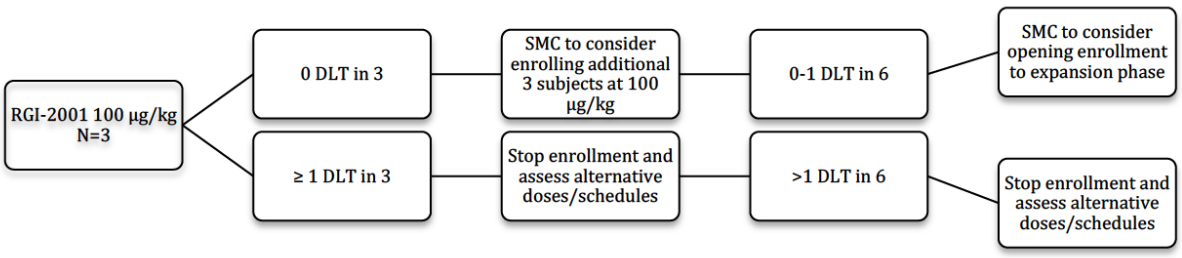
All subjects are expected to experience hematologic toxicity as part of the myeloablative alloHSCT procedure. Therefore, hematologic toxicities (e.g., leukopenia and thrombocytopenia) will not be useful measures of drug-induced toxicity, and DLTs are defined by non-hematologic toxicities.

The following DLT criteria apply to the Safety Run-in Phase of the study. A DLT is defined as any treatment-related AE that is not attributable to an extraneous cause (i.e., disease progression, preparatory regimen or HSCT infusion) and also excludes any signs and symptoms of GvHD. DLT is an adverse event occurring in the period of 30 days after the first dose of RGI-2001 administration, and meeting at least one of the following NCI CTC (Version 5.0) criteria:

- Grade 3+ infusion-related/cytokine release reactions
- Graft failure (as defined in Section 9.4.1.)
- Any Grade 4-5 non-hematological AE
- Delay in dosing by > 2 weeks due to treatment-related AE that is not attributable to an extraneous cause as defined above

Subjects who do not complete the DLT window for reasons other than toxicity may be replaced. Similarly, if a subject receives ≤ 50% of planned doses of RGI-2001 for reasons other than toxicity considered related to RGI-2001, this subject may be replaced.

Figure 2 DLT Schema



6.2 Expansion Phase

Once a dose/schedule is determined by the SRC to have an acceptable safety/PK profile, enrollment will continue in the Phase 2 Expansion Phase and be extended to all sites.

Accrual is targeted at 50 subjects who receive the dose deemed as acceptable from the Safety Run-in Phase (44 in the Expansion Phase, 6 from the Safety Run-in Phase at the dose used in expansion). All subjects in the Expansion Phase who receive at least one dose will be considered in all efficacy and safety analyses.

Subjects will receive open-label RGI-2001 at a dose of 100µg/kg (unless an alternative dose and/or schedule is chosen by SRC), via 30-minute intravenous (IV) infusion on a weekly basis for 6 doses (or an alternative dose/schedule as determined in the run-in phase) in addition to a SOC GvHD prophylactic regimen. The first dose will be administered on Day 0 at approximately 30 minutes and no later than 1 hour after HSCT infusion. Subsequent doses will be administered weekly, on Days 7, 14, 21, 28 and 35.

6.3 Control Group

A non-randomized, contemporary control group from the CIBMTR database will be derived for comparison. Control subjects will be chosen so as to meet all eligibility requirements for the clinical trial, have received a transplant in the same time window as the study subjects, and have been transplanted in a center that participates in this study. Consent will be obtained via the CIBMTR to participate in this study (Section 11).

6.4 Safety Review Committee

As noted above, a safety review committee will be used in this study. The SRC will serve
3 primary roles: 1) assessment of DLTs, other safety measures, and PK/PD in the initial
3 subjects to determine whether dose and schedule appropriate to enroll another 3 subjects
2) assessment of safety and PK/PD data to determine suitability to proceed to dose expansion
3) ongoing monitoring of both safety and aggregated efficacy data. The SRC will develop and follow a data and Safety Monitoring Plan and charter.

The SRC will be composed of, at a minimum the Sponsor or designee members including the Medical Monitor, Statistician, Safety Scientist, and the Lead Principal Investigator (PI). SRC meetings will occur in accordance with the SRC charter.

Depending on the results of safety reviews, the SRC may provide recommendations on the future continuation of the study and other relevant steps, including prophylactic pre-medications in all or some current and future subjects.

6.5 Number of Sites

This study will be conducted at 8-12 sites in the United States.

6.6 Number of Subjects

Anticipated accrual is 50 patients who receive at least one dose of RGI-2001, with at least 6 subjects in the Safety Run-in Phase, and up to 44 subjects in the Expansion Phase. It is anticipated that a minimum of 250 subjects will be included in the control group.

6.7 Study Duration

Individual subject participation is expected to last up to one year following alloHSCT, including a 6-week treatment period and a 42-week follow-up period. In addition, there is a screening period lasting approximately 2 weeks.

7 SUBJECT POPULATION

7.1 Inclusion Criteria

All subjects (including CIBMTR control group, except where noted) must meet the following criteria:

1. Ages > 18 and ≤ 65 years of age
2. Has a hematologic malignancy as defined below and is considered a candidate for allo HSCT:
    a. Acute myelogenous leukemia (AML) in first or subsequent morphologic complete remission
    b. T or B cell acute lymphoblastic leukemia (ALL) in first or subsequent complete morphologic remission
    c. Myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), myeloproliferative disorder (MPD) including myeloid metaplasia and myelofibrosis and are currently with <10% blasts in bone marrow
    d. CML subjects who have received prior treatment including at least one tyrosine kinase inhibitor and are currently in chronic phase or with a complete hematologic remission but with evidence of cytogenetic or molecular relapse
3. Must have adequate organ function as defined below (RGI-2001treatment group only):
    a. Cardiac function: Left ventricular ejection fraction at rest ≥ 45%
    b. Liver function: total bilirubin < 1.5 x upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x the ULN. Patients who have been diagnosed with Gilbert's Disease or malignant involvement are allowed to exceed the defined bilirubin value of 1.5 x the ULN
    c. Serum creatinine < 2 mg/dL or estimated creatinine clearance >50mL/min calculated using the Cockcroft-Gault equation
    d. Pulmonary: DLCO (corrected for hemoglobin) and/or FEV_1 ≥ 50 %
4. Considered suitable candidate for a myeloablative allogeneic or unrelated donor transplant based on institutional criteria
5. Subject must be receiving first allogeneic transplant from a single donor. Prior autologous transplant is acceptable
6. Transplant Donor:
    a. Matched related donor (8/8): Molecular identity at HLA-A, -B, -C and -DRB1 by high-resolution typing
    b. Unrelated donor (≥ 7/8 allelic match): high resolution molecular typing at the following loci is required HLA -A, -B, -C and -DRB1
    c. Meets institutional criteria for bone marrow or PBSC donation (see Section 7.4)

7. Source of the Allograft:
    a. Unmodified bone marrow or mobilized peripheral blood stem cell (PBSC) transplant, using granulocyte colony stimulating factor (G-CSF) as the mobilizing agent. Cord blood is not allowed
8. KPS ≥ 60
9. Is a candidate for anti-graft-vs-host-disease (GvHD) prophylaxis that includes:
    a. A calcineurin inhibitor (either tacrolimus [FK 506] or cyclosporine A), in combination with either methotrexate (MTX), mycophenolate mofetil (MMF)
10. Ability to understand and willingness to sign a written informed consent form

Inclusion criteria pertaining specifically for subjects scheduled to receive RGI-2001:

11. If female of childbearing potential, must have had a negative serum pregnancy test prior to enrollment and must have agreed to use a double barrier method of contraception for 90 days following the last dose of RGI-2001
12. If male, must be sterile or willing to use an approved method of contraception from the time of informed consent to 90 days after the last dose of RGI-2001

7.2 Exclusion Criteria

Any subjects (including CIBMTR control group) who meet any of the following criteria will be excluded from study entry:

1. Has had any other prior organ transplantation
2. Planned procedure to deplete regulatory T-cells from donor transplant materials
3. Planned reduced intensity conditioning
4. Planned use of any additional or alternative drug(s) for GvHD prophylaxis than listed in the inclusion criteria (e.g., rapamycin, cyclophosphamide, steroids)
5. Has had prior treatment with anti-CD3, other T cell depleting antibodies, or anti-thymocyte globulin within 12 months prior to alloHSCT procedure
6. Is participating in a trial (other than RGI-2001-003) involving an investigational agent/non-standard of care drug.
7. Has progressive underlying malignant disease including post-transplant lymphoproliferative disease.
8. Has evidence of active central nervous system (CNS) disease including known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of CNS involvement).
9. Known history of human immunodeficiency virus (HIV)
10. Active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) (control group only)

11. Is female and pregnant or lactating
12. Patients with active bacterial, viral or fungal infections (currently taking medication(s) and with progression or no clinical improvement)

Exclusion criteria pertaining specifically for subjects scheduled to receive RGI-2001:

13. Has undergone major surgery within 1 month before Day 0. Indwelling catheter placement is allowed
14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with viral load above the limit of quantification. Subjects that are on study with HBV or HCV infection should have titers checked regularly, as per institutional standard of care.
15. Has had any other condition that, in the opinion of the Investigator, renders the subject unsuitable for study participation
16. Has a documented history of uncontrolled autoimmune disease or on active treatment
17. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
18. History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to receiving study drug
19. Has received an investigational agent within 4 half-lives or 14 days prior to HSCT, whichever is shorter

7.3 Eligibility for the Control Arm

Subjects in the control arm will be identified from subjects reported to the CIBMTR from U.S. centers and which agree to participate in this study. Control subjects must satisfy the inclusion and exclusion criteria of this study according to Section 7.

Data for all eligible subjects in centers agreeing to participate in the study will be used to constitute the control database for this study.

7.4 Donor Screening

Stem cell or bone marrow donors will be evaluated according to institutional protocol. A bone marrow transplant physician and/or nurse practitioner will perform a complete medical history and physical exam, donor health history questionnaire and Zika virus screening. Required testing will include hematology studies, evaluation of risk for hemoglobinopathy as clinically indicated, chemistry studies, infectious disease testing, EKG, and chest x-ray. Bone marrow donors will also require evaluation and clearance by an anesthesiologist as per institutional practices.

Donors will be considered eligible if screening shows that the donor is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases, and is free from communicable disease risks associated with transplantation (test results for relevant communicable disease agents are negative or nonreactive).

7.5 Withdrawal/Discontinuation from Treatment, Procedures and Study

7.5.1 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study overall or at a specific study site may include, but are not limited to the following:

1. The incidence or severity of adverse events (AEs) in this or other RGI-2001 studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Data recording is inaccurate or incomplete
4. Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
5. The safety review committee (SRC) recommends termination of the study due to revealed safety concerns.

7.5.2 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate process for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments and collection of data, including endpoints and adverse events. The investigator must document the level of follow-up that is agreed to by the subject (e.g., in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent from a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after two attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. Attempts to contact the subject should be documented in the study records.

7.5.3 Discontinuation of Study Treatment and/or Withdrawal of Subjects Prior to Study Completion

The investigator and/or Sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion. Reasons for removal from protocol-required investigational product or procedural assessments include any of the following:

1. Subject withdrawal of consent
2. Safety concern (e.g., due to an adverse event including those defined as DLT criteria, ineligibility determined, significant protocol deviation, noncompliance, requirement for alternative therapy, pregnancy)
3. Death
4. Lost to follow-up

If a subject develops acute GvHD prior to completing all six RGI-2001 doses, the subject is still permitted to receive any remaining RGI-2001 doses with written approval by the Medical Monitor and if no experimental GvHD treatment is planned.

Subjects who permanently discontinue RGI-2001 prior to receiving all six doses should be encouraged to remain in the study and follow the SOA (see Section 3) for all remaining study visits primarily for assessment of secondary endpoints.

Subjects who are permanently discontinued from the study, either during the treatment period or follow up period, should complete the Early Termination Visit as per the SOA (Section 3) and, if applicable, monitor adverse event through 30 days of last RGI-2001 dose.

7.6 Replacement of Subjects

Subjects in the Safety Run-in Phase who do not complete the DLT window for reasons other than toxicity may be replaced. Similarly, if a subject in the Safety Run-in Phase receives ≤ 50% of planned doses of RGI-2001 for reasons other than toxicity considered related to RGI-2001, this subject may be replaced. All subjects who receive at least one dose of RGI-2001 in the Expansion Phase will be considered evaluable.

Subjects who have cancelled alloHSCT will also be replaced.

8 STUDY DRUG

Refer also to the current sponsor approved study Pharmacy Manual for details.

8.1 Physical Description

8.2 Packaging and Labeling

RGI-2001 for Injection is supplied as a sterile liquid suspension filled into depyrogenated USP Type 1 5-mL glass vials with a 2.5 mL fill volume, using a closure system consisting of sterilized rubber stoppers (22 mm) with aluminum royal blue seals and flip-off caps. The dosing is based on the dose of the liposome-encapsulated ingredient, RGI7000. Each vial contains 5 mg/mL of RGI7000 and 50 mg/mL of lipid blend in a 10% sucrose solution containing 20 mM Histidine.

The product is for single-use only and does not contain a preservative.

8.3 Storage

RGI-2001 should be stored at 2°–8°C, protected from freezing and exposure to light.

8.4 Study Drug Accountability

The PI or designee is responsible for maintaining accurate records (including dates and quantities) of IP received, subjects to whom IP is dispensed (subject-by- subject dose specific accounting), and IP lost or accidentally or deliberately destroyed. The PI or designee must retain all unused or expired study supplies until a Sponsor-designated Clinical Research Associate (CRA) has confirmed the accountability data.

8.5 Return and Disposition of Study Drug

Unused study drug must be kept in a secure location for accountability and reconciliation by the Sponsor-designated CRA. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after Sponsor or its designee has granted approval for drug destruction. The Sponsor-designated CRA must account for all study drug in a formal reconciliation process prior to study drug destruction. All onsite study drug destruction must be documented. Documentation must be provided to the Sponsor or its designee and the original retained in the PI's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to Sponsor's designee upon request.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned, according to applicable state and federal regulations and study procedures.

8.6 Administration and Dosing Regimen

All subjects will receive 6 weekly doses of RGI-2001 100 μg/kg via IV administration over 30 minutes. Weight should be taken within one day of dosing and the dosage of RGI-2001 should be verified to be the same as the planned dose. The dosage of RGI-2001 will be diluted in 50 ml 0.9% normal saline and the first dose will administered intravenously at approximately 30 minutes and no later than 1 hour after completion of the allogeneic HSCT on Day 0 (study Day 1 if transplant occurs over 2 days). If cytokine release/infusion reaction is observed during or after HSCT, then RGI-2001 should be postponed until at least 30 minutes after the reaction has resolved. Subsequent RGI-2001 administrations should be administered on Days 7, 14, 21, 28, and 35 + /- 1 day. Pre-medications should not be administered prophylactically. However, if a grade 2 cytokine release is observed, pre-medication with an antihistamine (e.g., diphenhydramine), an anti-pyretic (e.g. acetaminophen) and corticosteroids (e.g., 4 mg dexamethasone or equivalent) should be administered. Consideration may be made to administer premedication for Grade 1 cytokine release, depending on the constellation of symptoms. In addition, the SRC may recommend pre-medications in all current and future subjects depending on safety reviews.

8.7 Randomization and Blinding

This is an open-label study and there is no randomization or blinding.

8.8 Prior and Concomitant Medications

Please see exclusion criteria for prohibited medications.

Concomitant medications are any prescription or over-the-counter preparations used from 2 days prior to the preparatory regimen before Day 0 through the end of the subject's study participation.

Standard myeloablative preparatory regimens, (i.e., reduced intensity conditioning, non myeloablative conditioning, experimental regimens or drugs are not allowed), HSCT and standard supportive care/ prophylactic treatments (including but not limited to colony stimulating factors, transfusions, antibiotics/anti-virals/anti-fungals) per institutional guidelines for optimal medical care shall be permitted during participation of this study. The dose of steroids that are required for reasons unrelated to the underlying malignancy or HSCT process or sequelae must not be higher than physiologic doses (the equivalent of 20 mg/day of prednisone). No anti-thymocyte globulin (ATG) is allowed in the conditioning regimen.

GvHD prophylaxis must consist of a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with MTX or MMF. Dosing, schedule and monitoring of the GvHD regimen should follow institutional guidelines. Please see respective prescribing information for safety information. Steroids, sirolimus, post-transplant cyclophosphamide, ATG, other GvHD

prophylactic agents (including investigational agents) or manipulation of the graft to reduce GvHD are not allowed.

Post transplant maintenance therapy that includes an investigational agent, or any treatments that can be used for GvHD are not allowed. Maintenance therapy for actionable targeted mutations (e.g., FLT3 inhibitors) or with FDA approved agents in any indication should not be initiated prior to Day 42 post alloHSCT.

Treatment of GvHD should follow institutional guidelines and may include steroid treatment at supra-physiologic doses. See Section 7.5.3 for development of GVHD prior to completion of RGI-001 dosing.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Medical Monitor must be notified of the use of any medications, except acetaminophen, immediately after use. Any concomitant medications added or discontinued during the study should be recorded on the electronic case report form (eCRF.)

8.9 Dietary or Other Protocol Restrictions

Dietary restrictions per institutional guidelines (e.g. neutropenic diet) may be imposed on study subjects. Alcohol and tobacco use should be limited as per institutional guidelines.

8.10 Dose Modification/Treatment Cessation

If a subject permanently discontinues treatment in the Safety Run-in or Expansion Phase as specified below, see Section 7.5.3 Discontinuation of Study Treatment and/or Withdrawal of Subjects Prior to Study Completion, for further details.

8.10.1 Safety Run-in Phase

RGI-2001 will be administered at a dose of 100 µg/kg IV weekly for 6 doses. There are no dose reductions or escalations in this portion of the study except as recommended by the SRC at the end of the run-in period. Each individual infusion is allowed to be delayed up to 2 weeks for ongoing grade 3+ AEs, regardless of causality. However, if a subject enrolled in the run-in period is not able to receive at least 50% of RGI-2001 doses during the DLT window for reasons other than toxicity, then that subject will be replaced. Subjects requiring delay of an infusion of > 2 weeks should be discontinued from treatment.

Subjects enrolled in the Run-in Phase beyond the DLT window who meet DLT criteria should be discontinued from study treatment. Supportive care should be administered as appropriate.

8.10.2 Expansion Phase

RGI-2001 will be administered at the dose and schedule agreed upon by the SRC at the completion of the Safety Run-In Phase. No dose escalations will be allowed.

If a subject has a treatment related Grade 3 adverse event (excluding any hematologic AE or CRS) that is not considered to be related to extraneous cause ((i.e. disease progression, preparatory regimen, HSCT infusion), subsequent doses will be held until the toxicity returns to ≤ Grade 2 or baseline. RGI-2001 may be restarted at a dose of 10 µg/kg IV infusion.

Subjects who meet DLT criteria (including Grade 3+ CRS) at any point in the study should be permanently discontinued from study treatment. Supportive care should be administered as appropriate.

If subject has a 2nd occurrence of Grade 3 adverse event, RGI-2001 will be held until the toxicity returns to ≤ Grade 2 or baseline. RGI-2001 will be restarted at a dose of 1 µg/kg IV infusion.

If a subject experiences a Grade 4 adverse event that is related or continues to have recurrence of Grade 3 adverse events beyond the 2nd instance, discontinue RGI-2001 permanently.

If a subject does not demonstrate evidence of myeloid engraftment by Day 28, discontinue RGI-2001 permanently.

8.11 Management of Cytokine Release Syndrome

Pre-medications for RGI-2001 will not be administered initially as no signs of cytokine release were observed in the Phase 1 study. If symptoms suggestive of cytokine release (fever, chills, etc.) are observed with administration of RGI-2001, subjects should be treated according to institutional guidelines. The SRC may provide additional recommendations for such situations (please refer to Section 6.4). For Grade 2 AEs, acetaminophen, diphenhydramine and/or steroids may be administered. Premedication for subsequent RGI-2001 infusions may consist of intravenous or oral dexamethasone (4 mg), acetaminophen and diphenhydramine prior to each administration of RGI-2001. Details should be discussed with the Medical Monitor prior to the next infusion. For subjects with Grade 3–4 infusion reaction/cytokine release symptoms should be discontinued from further RGI-2001 therapy regardless of whether prophylactic treatment was administered.

Table 1 Medical Guidelines for Cytokine Release Reactions

Grade 1	• Continue to monitor subject carefully. • No treatment is needed unless symptoms worsen • Consider pre-medications for subsequent infusions depending on the presentation.
Grade 2	• Hold infusion until symptoms resolve. • Supportive care as per institutional guidelines. May include but not limited to acetaminophen, diphenhydramine, H2 blockers, dexamethasone or equivalent, oxygen, demerol or equivalent, IV fluids, anti-emetics • For subsequent RGI-2001 infusions, premedicate with acetaminophen, diphenhydramine, dexamethasone 4mg or equivalent

Grade 3-4	• Discontinue RGI-2001 treatment • Supportive care as per institutional guidelines. May include but not limited to acetaminophen, diphenhydramine, H2 blockers, dexamethasone or equivalent, oxygen, demerol or equivalent, IV fluids, anti-emetics, vasopressors, mechanical ventilation.

9 STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Assessments in Section 3 describes the frequency and timing of the study assessments and procedures. The schedule of PK and PD sample collection is provided in Appendix 1. All enrolled subjects will undergo the same study procedures unless otherwise noted.

All screening evaluations must be completed and reviewed to confirm a potential subject meets all eligibility criteria prior to alloHSCT, including the preparatory regimen. Investigators are to maintain a screening log of all potential subjects.

Screening assessments must be performed within 14 days prior to initiation of any treatments related to the HSCT including the preparatory regimen unless otherwise specified. Informed consent, screening hepatitis, HIV tests, and tumor assessment (provided that no intervening therapy for their malignancy has been administered) may be obtained up to 42 days before the preparatory regimen. PFTs and ECHO may be obtained as per institutional standard of care criteria within 84 days prior to the preparatory regimen provided no intervening therapy for their malignancy has been administered. Pregnancy test must be conducted within 7 days before preparatory regimen. Standard of care tests/procedures, performed prior to the subject signing the informed consent form (ICF) can be used as part of the screening assessments as long as the tests/procedures are performed within the appropriate screening window. Screening assessments do not need to be repeated due to minor delays in procurement of donor HSC's.

9.1 General Study Procedures

9.1.1 Informed Consent

Except as noted in Section 9, informed consent must be obtained before conducting any study-specific activities/procedures and documented in the subject's source documents.

9.1.2 Demographics

Subject demographics (including date/year of birth, sex, race, ethnicity, and age at the time of consent) will be collected.

9.1.3 Medical/Cancer/Surgical History

A complete medical, cancer and surgical history starting prior to enrollment through the time of consent will be obtained from each subject at the Screening visit.

Prior cancer history includes: (i) date of diagnosis, (ii) prognostic score if applicable (iii) all previous therapies (i.e., chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (i.e., regimen, start and stop dates), (v) best response for each regimen

Data from SOC procedures will be part of the subject's medical history and may be used for study purposes.

9.2 Efficacy Assessments

Efficacy evaluations will be performed as described below. Refer to the SoA, Section 3 for the timing of all efficacy evaluations.

9.3 Evaluation of GvHD

The frequency of acute and chronic GvHD will be assessed in both parts of the study. Assessment for GvHD should be performed during every examination or per institutional guidelines from the time of engraftment to end of study. Documentation of the timing, severity treatment for GvHD and outcome including any biopsies should be obtained at regular intervals per the SoA.

The clinical activity of RGI-2001 will be evaluated by assessment of GvHD according to the MAGIC Criteria and Modified Keystone Criteria for grading acute GvHD (Appendix 2 and Appendix 3) NIH 2014 criteria will be used to assess chronic GvHD.

9.3.1 Tumor Assessment

Evaluation of status of hematologic malignancy should be conducted as per institutional guidelines but should include a bone marrow aspirate and biopsy with cytogenetics, molecular diagnostics and chimerism as appropriate based on disease histology.

[redacted]

9.4 Safety Assessments

Safety will be assessed by clinical laboratory studies, time to myeloid and platelet engraftment and by monitoring of AEs.

Potential safety issues associated with the route of administration or the pharmacology of RGI-2001 include hypersensitivity to RGI-2001, organomegaly, microgranuloma, and infections. Subjects will be monitored closely for hypersensitivity reactions to RGI-2001. Infections will be recorded throughout the study. Subjects will be followed for 30 days following end of treatment and monitored for the occurrence of adverse events by means of physical examination, and laboratory testing, including hematology, T-cell, immunophenotyping, other serum chemistry, urinalysis and liver function tests.

9.4.1 Marrow Engraftment and Graft Failure

Myeloid engraftment will be defined as the first of 3 consecutive days when the absolute neutrophil counts (ANC) exceeds 0.5 $x10^9$/L and platelet engraftment will be defined as the first of 3 consecutive days when the platelet count exceeds 20 x $x10^9$/L without transfusion support. Graft failure will be defined as the lack of myeloid engraftment in subjects surviving in remission for at least 28 days after transplantation.

9.4.2 Dose Limiting Toxicities

Subjects enrolled in the Safety Run-in Phase will be monitored for DLTs (Section 4.1).

9.4.3 Adverse Events

Information regarding AEs and SAEs will be collected as per Section 10.

9.4.4 Concomitant Medications

Concomitant medications will be documented for each subject at each scheduled visit. All concomitant medications including prescription or OTC preparations used from 2 days prior to the preparatory regimen before Day 0 through the end of the subject's study participation, including changes is medication, should be recorded.

9.4.5 Weight and Height

Weight (indoor clothing without shoes) in kilograms, should be taken within 1 day of dosing and the dosage of RGI-2001 should be verified to be the same as the planned dose. Height (without shoes) in centimeters, should be obtained prior to initiation of the preparatory regimen only.

9.4.6 Physical Examinations, Vital Signs and Karnofsky Performance Status

A complete physical examination will be performed by the investigator or designee at time points specified in the Schedule of Assessments Section 3. Examination at screening should include HEENT, dermatologic, cardiovascular, respiratory, GI (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems. Physical examinations at all other time points should be limited, symptom-directed physical examinations of an AE or SAE, including body systems as appropriate.

Please also refer to Efficacy Assessments Section 9.3 for description of MAGIC and Modified Keystone Criteria symptom assessments for GvHD.

Vital signs and KPS will be performed as indicated in the SoA. Vital signs including systolic and diastolic blood pressure (BP), body temperature, heart rate, and respiratory rate should be taken in supine or seated position. Vital signs should be obtained within 15 minutes prior to RGI-2001 infusion and should be repeated within 30 minutes after the infusion. Additional vital signs measurements should be obtained as clinically indicated.

KPS will be assessed as per Appendix 5.

9.4.7 Electrocardiogram

A single, 12-lead ECG will be performed at the time point specific in the SoA (Section 3).

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible.

The electrocardiogram should be performed in a standardized method, prior to blood draws or other invasive procedures. The ECG must include the following measurements: QRS, QT, QTc using Fredericia's formula, RR, and PR intervals. If the ECG is abnormal, including QTc >450 msec, perform in triplicate approximately 30 seconds apart, and record the average of the three readings.

The PI or designated site physician will review all ECGs. Standard ECG machines should be used for all study-related ECG requirements.

9.4.8 Clinical Laboratory Assessments

Blood samples for safety laboratory tests, which include clinical chemistry, hematology and coagulation, will be collected according to the SoA (Section 3). Additional laboratory assessments include pregnancy test, hepatitis B and C testing. All clinical laboratory analyses will be performed by the site local laboratory unless otherwise indicated. Reference ranges will

be supplied by the laboratory and used to assess the data for clinical significance and out-of-range values. Biomarker and pharmacokinetic samples will be shipped to a specialty laboratory.

Screening laboratory assessments used to determine subject eligibility may be repeated once (up to a total of 2 times during the 14 day screening period), if necessary.

Clinical laboratory tests will be performed as indicated in Table 2:

Table 2 Clinical Laboratory Tests

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Total bilirubin Direct bilirubin Alk phos LDH AST ALT GGT	PT/INR aPTT or PTT	Specific gravity pH Blood Protein Glucose Bilirubin Ketones Urobilirubin	RBC Hemoglobin Hematocrit Platelets WBC Differential Neutrophils Eosinophils Basophils Lymphocytes Monocytes Blasts	Hep B surface antigen Hep C antibody Hep B total core antibody Hep B viral load Hep C viral load Pregnancy test Bone marrow aspirate and biopsy Cytogenetics Molecular markers Chimerism [redacted] Immunophenotyping

Alk phos: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; PTT: partial thromboplastin time; PT: prothrombin time; aPTT: abbreviated partial prothromboplastin time; RBC: red blood cell; WBC: white blood cell

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed local guidance/regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further information around blood volumes can be found in the Laboratory Manual.

Any abnormal clinical laboratory test results that lead to a change in subject management (ie dose delay, clinical condition, need for additional medication or monitoring) are considered clinically significant. The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE eCRF. Any abnormal clinical laboratory test result determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until the cause of the

abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

9.4.8.1 Donor/Host Chimerism

Donor/host chimerism for the evaluation of engraftment status of the stem cell transplantation will be evaluated at the local laboratory.

9.4.8.2 Pregnancy Testing

A serum pregnancy test will be performed on each female subject of childbearing potential at the screening visit. A negative pregnancy test must be documented prior to administration of study drug.

10 ADVERSE EVENTS

10.1 Definitions

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition),
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

10.1.1 Serious Adverse Event

A serious adverse event is any adverse event that at any dose meets any of the following criteria:

- **Fatal** (i.e., the adverse event actually causes or leads to death)
- **Life threatening** (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- **Requires inpatient hospitalization** or prolongation of existing hospitalization
- **Results in persistent or significant disability/incapacity** (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- **Congenital anomaly/birth defect** in a neonate/infant born to a mother exposed to study drug
- **Significant medical event.** An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment by the Investigator or the Sponsor, it may jeopardize the patient and may require medical or surgical

intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include second primary malignancies developed months after the end of the study treatment, or convulsions that do not result in in-patient hospitalization.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria v. 5.0; see Section 10.2.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

10.2 Adverse Event Reporting

The reporting period for non-serious adverse events starts at the commencement of the infusion of RGI-2001 on Day 0 and continues for at least 30 days following the last dose of study drug. Medical conditions that start after the ICF is signed, but before the first dose of study drug should be recorded on the medical history eCRF.

If an AE remains unresolved 30 days following the last dose of study drug, the subject will be followed, at the investigator's discretion, until resolution of the event. Resolution is defined as return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the subject non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the subject, or through physical examination, laboratory tests, or other clinical assessments.

10.2.1 Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the Screening visit) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

Not every laboratory or ECG abnormality qualifies as an AE. A laboratory or ECG test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory abnormality. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory or ECG abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the AE eCRF.

If a clinically significant laboratory or ECG abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

10.2.2 Adverse Event Severity

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as a "serious" AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v.5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

If there is not a specific NCI CTCAE grading scale for an AE, the severity will be characterized as mild, moderate, severe, or life-threatening, according to the following definitions:

Grade	Description
1 (Mild)	Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated No limitation of usual daily activities
2 (Moderate)	Some limitation of usual daily activities Minimal, local or non invasive intervention indicated, limiting instrumental activities of daily activities

Grade	Description
3 (Severe)	Severe or Medically significant but not immediately life threatening, hospitalization or prolongation of hospitalization indicated, disabling. Intervention typically required.
4 (Life Threatening)	Events that are considered life-threatening, urgent intervention indicated
5 (fatal)	Death*

*Grade 5 events must be reported as SAEs (see Section 10.3.1 for reporting instructions), per the definition of an SAE in Section 10.1.

10.2.3 Adverse Event Causality

The Investigator should use their knowledge of the study subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug. The following guidance should be taken into consideration. Discuss with medical monitor if needed:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Relationship	Description
Not Related	Exposure to the investigational product has not occurred, or the occurrence of the AE is not reasonably related in time, or the event is readily and more likely explained by the subject's clinical state or by other modes of therapy administered to the subject. Note: per your institution standard, if relationship is determined to be unlikely, it should be classified as Not Related unless the investigator determines possibly related or probably related are more appropriate with the definitions below.
Possibly Related	The administration of the IP and the occurrence of the AE are reasonably related in time, and The AE could be explained equally well by factors or causes other than exposure to the IP. Follows a reasonable temporal sequence from study drug administration; but could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

Relationship	Description
Probably Related	The study treatment and the AE were reasonably related in time, and the AE is more likely explained by exposure to the study product than by other causes, or the investigational product was the most likely cause of the AE

10.3 Serious Adverse Events

SAEs that occur at any time between the signing of the ICF up to the first dose of study drug must be reported (in addition to SAEs that occur after the first dose of study drug).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. See definition of SAE in Section 10.1.

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate 24-hour urine collection) or other medical procedures are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission into the ward on the floor that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as an inpatient to the hospital (e.g., undesirable effects of any administered treatment) and must be documented as an SAE.

10.3.1 Serious Adverse Events Reporting

SAEs that occur at any time between the signing of the ICF until at least 30 days after the subject has stopped study drug must be reported regardless of the casual relationship to the study drug.

SAEs will be reported immediately (within 24 hours of learning of the event) to the Sponsor or its designee by email using the study-specific SAE Report Form and recorded in the eCRF. In addition to the outcome of the SAE, any medication or other therapeutic measures used to treat the event will be recorded on the appropriate eCRF page(s). Investigators should not wait to collect additional information that fully documents the event before notifying Sponsor or its designee of an SAE. Sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by Sponsor or its designee as soon as it becomes available.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements. Adequate documentation must be obtained by Sponsor or its designee showing that the IRB was properly and promptly notified as required.

The SAE form should be emailed to: sae.regimmune@clindatrix.com

The Investigator is encouraged to discuss with the medical monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is as follows:

[redacted]

Any SAE observed after the 30-day follow-up period should only be reported to the Sponsor if the Investigator suspects that the SAE has a causal relationship to the study drug. An SAE should be followed until its resolution or until it is judged to be stable. An assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome of the event.

Recurrent episodes, complications, or progression of the initial SAE must be reported, as follow-up to the original episode, within 24 hours of the Investigator receiving the follow-up information.

10.4 Reporting of Disease Progression

Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period. Any sudden or unexplained death should be reported as an SAE. However, the underlying disease or condition, which led to the fatal outcome, should be used as an SAE term. Death as an SAE term should be avoided, with the exception of rare situations when the cause of death is unknown. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

10.5 Reporting of GvHD

The event of GvHD disease is a criterion for assessment of clinical activity and is therefore not considered to be an AE. GvHD should be reported within the eCRF. AEs and SAEs that occur in relation to GvHD that are not consistent with the nature and natural progression of the subject's disease should be recorded as AE/SAE. Death due to GvHD that is consistent with the nature and natural progression of the subject's disease is not recorded as an AE/SAE.

10.6 Medication Errors

Any dose or route of administration of RGI-2001 that was not administered as prescribed in the protocol should be reported as an AE in the eCRF regardless of whether or not there is an associated AE. Medication errors that meet the definition of an SAE will be reported per the SAE reporting guidelines.

10.7 Pregnancy

Although pregnancy is not considered an AE or SAE, all pregnancies occurring in subjects enrolled in this study or in a female partner of a male subject in this study must be reported to the Sponsor within 24 hours of becoming aware, and followed to outcome, even after the end of the study. If a female subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study. Any pregnancies that occur within 150 days for females or 90 days for males following the last dose of study treatment must be reported to the Sponsor.

Refer to Appendix 6 for complete information regarding pregnancies including highly effective contraceptive methods and recording and reporting guidelines in the event of a pregnancy.

11 REGISTRATION OF CIBMTR SUBJECTS FOR THE CONTROL GROUP

This clinical trial will compare certain outcome parameters from subjects enrolled in the RGI-2001 treatment study to a contemporaneous control group obtained from the CIBMTR. (refer to Section 12)

11.1 Selection of Control Arm Transplant Centers

The CIBMTR will be contracted with the Sponsor to provide transplant subject data for the control group. Only CIBMTR research centers participating in the treatment protocol with experience in submitting comprehensive report forms to the CIBMTR will be eligible to participate in the study. Additionally, participating centers will need to agree to participate in this study and submit all CIBMTR report forms required for this study according to the CIBMTR pre-specified time schedule.

11.2 Enrollment Procedure for the Transplant Subjects in the Control Arm via the CIBMTR

Data reported on pre-transplant Transplant Essential Data (TED) forms to the CIBMTR by participating centers will be monitored to screen subjects who fulfill the eligibility criteria (Section 7). Control subjects who fulfill eligibility criteria and who have a signed ICF to allow their data to be used for research will be assigned to the CIBMTR comprehensive data reporting track (CRF-track) and centers will be notified. Forms due requirements for the case report form (CRF) track will be implemented.

It is anticipated that a minimum of 250 transplant subjects will be enrolled to ensure sufficient subjects are comparable to the RGI-2001 treatment population.

12 STATISTICS

The primary objective of this study is to assess the potential efficacy of RGI-2001. The primary endpoint for these purposes is grades II-IV acute GvHD, and the study subjects will be compared to a control group of subjects supplied by the CIBMTR. Control subjects will be chosen so as to meet all eligibility requirements for the clinical trial, have received a transplant in the same time window as the study subjects, and have been transplanted in a center that participates in this study.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
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Based on these estimates, it is anticipated that a total of 50 subjects who receive at least one dose of RGI-2001 will be enrolled, this including subjects from the run-in stage treated at the dose moved forward to the Expansion Phase. It is anticipated that a minimum of 250 subjects will be included in the control group.

12.2 Demographics and Baseline Characteristics

Categorical factors will be summarized with proportions, and continuous variables will be summarized using means and medians.

12.3 Analysis Population, Handling of Dropouts, and Missing Data

All subjects who receive at least one dose of RGI-2001 will be used for comparison to the CIBMTR subjects.

12.3.1 Analysis of Efficacy Data

The primary endpoint grades II-IV acute GvHD by Day 100 according to the MAGIC criteria will be compared between the study group and CIBMTR controls using logistic regression. The factors that will be considered for adjustment in this model include subject age, gender, donor age, type of donor (MRD, 8/8 URD 7/8 URD), source of allograft, diagnosis (AML, ALL, MDS, MPD including CMML), preparative regimen, GvHD prophylaxis regimen.

Secondary endpoints that will be modeled as binary outcomes will similarly be compared using logistic regression. Secondary endpoints that will be modeled as time-to-event outcomes will be compared using Cox regression.

Potential interactions of RGI-2001 and various factors will be examined by including appropriate factors into regression models.

Given that this is not a randomized study and that the intention is only to assess outcomes for a potential signal, no adjustments will be made for multiple comparisons. As such, a Type II error (or a false negative) is prioritized over a Type I error (or a false positive).

Binary exploratory outcomes will be summarized with proportions, continuous outcomes with means and medians, and time-to-event outcomes with Kaplan-Meier estimates or cumulative incidence estimates for endpoints with competing risks.

12.4 Suspension Rules Based on Safety (RRT, Graft Failure, and NRM)

Careful monitoring of safety will take place beyond the Safety Run-in Phase, with safety encompassing the outcomes grade 4-5 regimen-rated toxicity (RRT), graft failure, and NRM. The study will be suspended pending SRC review if there is sufficient evidence to suggest that the true failure rate for any of these outcomes is excessive. A true graft failure (as defined in Section 9.4.1) rate of 5% or higher is considered excessive (Olsson et al), a true Day-100 NRM rate of 10 or higher is considered excessive (Styczyński et al), and a true Day 30 grade 4-5 RRT rate of 50% or higher is considered excessive (defined as any non-hematologic toxicity that occurs as a result of the transplant process including the preparatory regimen or RGI-2001 infusions). This rate is extrapolated from published results of D30 NRM (Styczyński et al) and increased further to encompass grade 4 events in the allogeneic myeloablative setting based on site experience. Sufficient evidence will be taken to be a lower limit to the one-sided 80% confidence interval associated with an estimated failure rate that exceeds the appropriate level listed above. Table 3 below shows observed outcomes that would trigger suspension, and Table 4 below summarizes the operating characteristics of the listed suspension rule separately for each safety endpoint (e.g., separately for Day 30 grade 4-5 RRT, graft failure, Day-100 NRM).

Table 3 Suspension Rules for Grade 4-5 RRT, Graft Failure, and Day-100 NRM

Safety outcome	Occurrences that would trigger suspension rule and SRC review
Day 30 grade 4-5 RRT	3 RRT of first 3 pts, 4 RRT of first 5 or fewer pts, 5/6, 6/7-8, 7/9-10, 8/11-12, 9/13, 10/14-15, 11/16-17, 12/18-19, 13/20-21, 14/22, 15/23-24, 16/25-26, 17/27-28, 18/29-30, 19/31-32, 20/33-34, 21/35, 22/36-37, 23/38-39, 24/40-41, 25/42-43, 26/44-45, 27/46-47, 28/48-49, 29/50
Graft Failure	2 failures of first 16 pts or fewer, 3/17-30, 4/31-46, 5/47-50
Day-100 NRM	2 failures of first 8 pts or fewer, 3/9-15, 4/16-23, 5/24-31, 6/32-39, 7/40-47, 8/48-50

Table 4 Operating Characteristics of Suspension Rules

Safety outcome	**True probability of failure**	**Number of patients**	**Probability of suspension rule being triggered after listed number of patients**
Grade 4-5 RRT	.30	10 25 45	.05 .05 .10
Grade 4-5 RRT	.70	10 25 45	.72 .94 .99
Graft Failure	.02	10 25 45	.02 .04 .05
Graft Failure	.12	10 25 45	.36 .68 .88
Day-100 NRM	.05	10 25 45	.06 .08 .08
Day-100 NRM	.20	10 25 45	.51 .78 .91

13 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

13.1 Ethics

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigator abide by Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines. The study will also be carried out in keeping with applicable local laws and regulations.

13.2 Compliance Statement

This study will be conducted in accordance with the protocol and with GCP and ICH guidelines, as well as all applicable regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate Institutional Review Board (IRB) prior to the enrollment of any study subjects.

13.3 Institutional Review Board

The investigator will submit this protocol, the informed consent, investigator's brochure (IB), and any other relevant supporting information to the appropriate IRB and the local regulatory agency for review and approval prior to study initiation. A letter confirming IRB approval of the protocol and informed consent, a statement that the IRB is organized and operates according to GCP and the applicable laws and regulations, and financial disclosures must be forwarded to the Sponsor prior to screening subjects for the study.

Amendments to the protocol must also be approved by the IRB and the local regulatory agency, as appropriate, prior to the implementation of changes in this study. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment, should be submitted to the IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

13.4 Informed Consent and Human Subject Protection

13.4.1 Direct Access to Source Data/Source Documents

The study will be carried out in keeping with applicable local laws and regulations. This may include an inspection by Sponsor representatives/designees, and/or regulatory authority representatives at any time. The investigator/institution must agree to the inspection of study-related records by the regulatory authority/Sponsor representatives/designees, and must allow direct access to source documents to the regulatory authority/Sponsor representatives/ designees/IRB. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/Sponsor representatives.

13.4.2 Data Quality Control and Quality Assurance: Data Handling and Recordkeeping

Data collection will involve the use of the electronic data capture (EDC) system, to which only authorized personnel will have access. Entries made on the electronic case report form (eCRF) must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring and data reviewing process) and the originator of the data change (if applicable), as well as the PI's approval of all changes performed on his/her subjects' data, will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation, according to FDA and ICH requirements. The study file and all source data should be retained until written notification is given by the sponsor or designee for destruction.

13.4.3 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number and initials will be recorded on the case report form (eCRF). If the subject name appears on any other document (e.g., pathologist report) or study materials (e.g., biopsy tissue slides), then that information must be deleted before a copy of the document is supplied to the sponsor. Study data stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

14 FINAL STUDY REPORT AND PUBLICATION POLICY

A study report will be prepared by the Sponsor. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff will comply with the terms of the clinical Trial Agreement between the Sponsor, and the investigational site and/or investigator.

The Sponsor will comply with applicable laws regarding the requirements for publication of study results.

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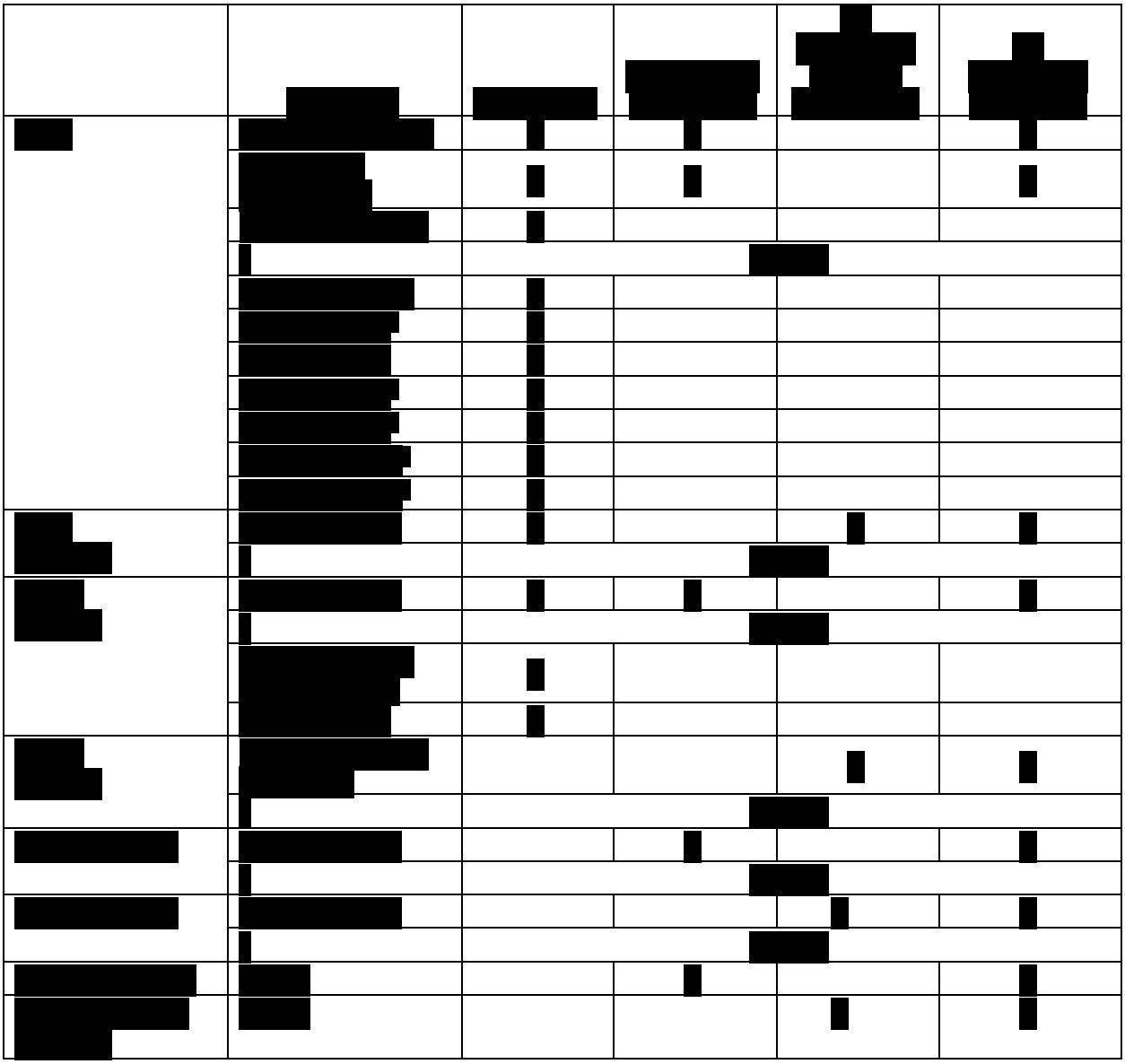
15 APPENDICES

[redacted]



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APPENDIX 2 MAGIC GVHD ASSESSMENT CRITERIA

GvHD Target Organ Staging				
Stage	**Skin[a]**	**Liver (bilirubin)**	**Upper GI**	**Lower GI (stool output/day)**
0	No active (erythematous) GvHD rash	Total serum bilirubin < 34 umol/L (< 2 mg/dL)	No or intermittent[b] anorexia, nausea or vomiting	Diarrhea <500mL per day or <3 episodes/day for adults [c]
1	Maculopapular rash < 25% of BSA	Total serum bilirubin 34-50 umol/L (2 to 3 mg/dL)	Persistent anorexia or nausea or vomiting	Diarrhea 500 -999 mL per day or 3-4 episodes per day for adults [c]
2	Maculopapular rash 25 to 50% of BSA	Total serum bilirubin 51-102umol/L (3.1 to 6 mg/dL)		Diarrhea 1000–1500 mL per day or 5–7 episodes for adults[c]
3	Maculopapular rash > 50% of BSA	Total serum bilirubin 103-255 umol/L (6.1 to 15 mg/dL)		Diarrhea > 1500 mL per day or > 7 episodes for adults [b]
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% of BSA	Total Serum bilirubin > 255umol/L (> 15 mg/dL)		Severe abdominal pain with or without ileus or grossly bloody stools (regardless of stool volume) [c]

BSA: body surface area, GI: gastro-intestinal tract, GvHD: Graft versus Host Disease MAGIC: Mount Sinai Acute GvHD International Consortium

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

[a] Use the "rule of nines" or burn chart to determine extent of rash

[b] To be suggestive for GvHD: anorexia should be accompanied by weight loss, nausea should last at least 3 days, or be accompanied by at least 2 vomiting episodes per day for at least 2 days

[c] One episode of diarrhea is considered to be about 200 ml for an adult and 3 ml/kg for a child (< 50 kg)

Confidence Level Criteria				
Confidence Level	**Pathologic Evidence**	**Clinician Assessment**	**Treatment for Acute GvHD**	**Comments**
Confirmed	Unequivocal pathologic evidence of GvHD	GvHD is the etiology for symptoms	Not applicable	GVHD is clearly present even if other etiologies may coexist simultaneously.
Probable	Not required	GvHD most likely etiology for symptoms (as evidenced by treatment being provided)	Yes	GVHD is most likely present, but other etiologies may also explain the symptoms, and there is insufficient evidence to make a confirmed diagnosis.
Possible	Not required	GvHD in differential diagnosis (but no treatment is being provided)	No	GVHD may be present, but other etiologies are favored to the degree that GVHD treatment is not initiated.
Negative	Unequivocal evidence of a diagnosis other than GvHD (e.g. drug rash	GvHD is no considered as an explanation for the symptoms	No and the symptoms resolve without GvHD treatment	GVHD may be present, but other etiologies are favored to the degree that GVHD treatment is not initiated.

Biopsy Results and Confidence Levels			
Pathology Results	**Target Organ Confidence Level**		
	Treated as GvHD	**Not treated but GvHD in Differential Diagnosis**	**Not Treated and GvHD Not in Differential Diagnosis**
Positive	Confirmed	Confirmed	Confirmed
Equivocal	Probable	Possible	Possible
Nondiagnostic	Probable	Possible	Negative
Non-GvHD etiology	Probable	Negative	Negative

Source: Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 2016;22:4-10

APPENDIX 3 MODIFIED KEYSTONE CRITERIA FOR ACUTE GVHD

GvHD Assessment			
Stage	**Skin[a]**	**Liver[b,c]**	**Gut[c]**
0	No GvHD rash	Bilirubin < 2 mg/dL	Diarrhea ≤ 500mL per day No anorexia or persistent nausea or anorexia[d]
1	Rash < 25% of skin	Bilirubin 2 to 3 mg/dL	Diarrhea > 500 mL per day or persistent nausea or nausea[d]
2	Rash 25 to 50% of skin	Bilirubin 3.1 to 6 mg/dL	Diarrhea ≥ 1000 mL per day
3	Rash > 50% of skin	Bilirubin 6.1 to 15 mg/dL	Diarrhea ≥ 1500 mL per day
4	Generalized erythroderma with bullous formation	Bilirubin > 15 mg/dL	Severe abdominal pain with or without ileus

Overall Grade[e]			
I	Stage 1 to 2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	–	Stage 2 to 3 or	Stage 2 to 4
IV[f]	Stage 4 or	Stage 4	–

[a] The Rules of Nines or burn chart was used to determine the extent of rash. The percent of body surface area involved with rash: head and neck (9%), right arm (9%), left arm (9%), anterior trunk (18%), posterior trunk (18%), right leg (18%), left leg (18%), groin and perineum (1%).

[b] Range given as total bilirubin.

[c] For liver or gut, downgrade 1 stage if additional cause of elevated bilirubin or diarrhea had been documented.

[d] Persistent nausea or anorexia, with histologic evidence of GvHD in the stomach or duodenum.

[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[f] Grade IV could have also included lesser organ involvement but with extreme decrease in performance

Source: Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995 Jun;15(6):825-8.

APPENDIX 4 NIH DEFINED DIAGNOSTIC OR DISTINCTIVE FEATURES OF CHRONIC GVHD 2014

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation Papulosquaous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair, Scaling	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia Females Males	Lichen planus-like features Lichen sclerosus-like features Vaginal scarring or clitoral/labial agglutination Phimosis or urethral/meatus scarring or stenosis	Erosions Fissures Ulcers		

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[a] (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[b]	Common[c] (Seen with Both Acute and Chronic GVHD)
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase > 2 ULN ALT or AST > 2 ULN
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS[d]	Air trapping and bronchiolitis obliterans on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease[e]	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis[f]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

GVHD indicates graft-versus-host disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

[a] In all cases, infection, drug effects, malignancy, or other causes must be excluded.

[b] Can be acknowledged as part of the chronic GvHD manifestations if diagnosis is confirmed.

[c] Common refers to shared features by both acute and chronic GVHD

[d] BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ

[e] Pulmonary entities under investigation or unclassified.

[f] Diagnosis of chronic GVHD requires biopsy.

Source: Jagasia, Madan H. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biology of Blood and Marrow Transplantation, 2015 March; 21 (3):389–401

NIH Global Severity of Chronic GvHD

Mild chronic GvHD	1 or 2 organs involved with no more than score 1 *plus* Lung score 0
Moderate chronic GvHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe chronic GvHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3
Key points:	In skin: higher of the two scores are to be used for calculating global severity. In lung: FEV1 is used instead of clinical score for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity. In the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Source: Jagasia, Madan H. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biology of Blood and Marrow Transplantation, 2015 March; 21 (3):389–401

APPENDIX 5 KARNOFSKY PERFORMANCE STATUS SCORES

Score (%)	Karnofsky Performance Status
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Source: Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. Page 196.

APPENDIX 6 CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Woman of Childbearing Potential (WCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods:

Male patients

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method as described under highly effective contraceptive methods when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male patients must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study treatment.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from the start of study treatment until 90 days after study treatment.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception throughout the study and for 90 days after the end of study treatment.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Pregnancy Testing:

- WCBP must have a negative serum pregnancy test prior to initiation of study drug.

Pregnancy Reporting Guidelines:

Although pregnancy is not considered an AE or SAE, all pregnancies occurring in subjects enrolled in this study or in a female partner of a male subject in this study must be reported to the Sponsor on an expedited basis and followed to outcome, even after the end of the study.

If a female subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study. Any pregnancies that occur within 150 days for females or 90 days for males following the last dose of study treatment must be reported to the Sponsor.

The investigator should report all pregnancies in clinical trial to the Sponsor within 24 hours of becoming aware. A Pregnancy Report Form must be completed and submitted to the Medical Monitor. If the pregnancy has occurred in the female partner of a male subject, the investigator should attempt to collect pregnancy information after obtaining the necessary signed ICF from the pregnant female partner directly.

The outcome of the pregnancy should be reported on a separate Pregnancy Outcome Report Form.

Some complications of the pregnancy may constitute an SAE. Those include spontaneous and elective abortion, premature delivery, congenital anomaly or birth defect in an offspring, death of a newborn within 28 days of birth. In these cases, a separate SAE Report Form should be filled in and submitted on an offspring, along with the Pregnancy Outcome Report Form on the mother.