A Phase II Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Uproleselan (GMI-1271) for GI Toxicity Prophylaxis During Melphalan-Conditioned Autologous Hematopoietic Cell Transplantation (auto-HCT) for Multiple Myeloma (MM)

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A Phase II Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Uproleselan (GMI-1271) for GI Toxicity Prophylaxis During Melphalan-Conditioned Autologous Hematopoietic Cell Transplantation (auto-HCT) for Multiple Myeloma (MM)

Protocol Revision History

Initial Approval Version	**01 March 2021**
Amendment #1 Version	**01 June 2021**
Amendment #2 Version	**22 March 2022**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BMT	Bone marrow transplant
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete
CRm	Morphologic complete remission
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network

NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PI	Principal investigator
PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee
RFS	Relapse free survival
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TSH	Thyroid stimulating hormone
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
WBC	White blood cell (count)

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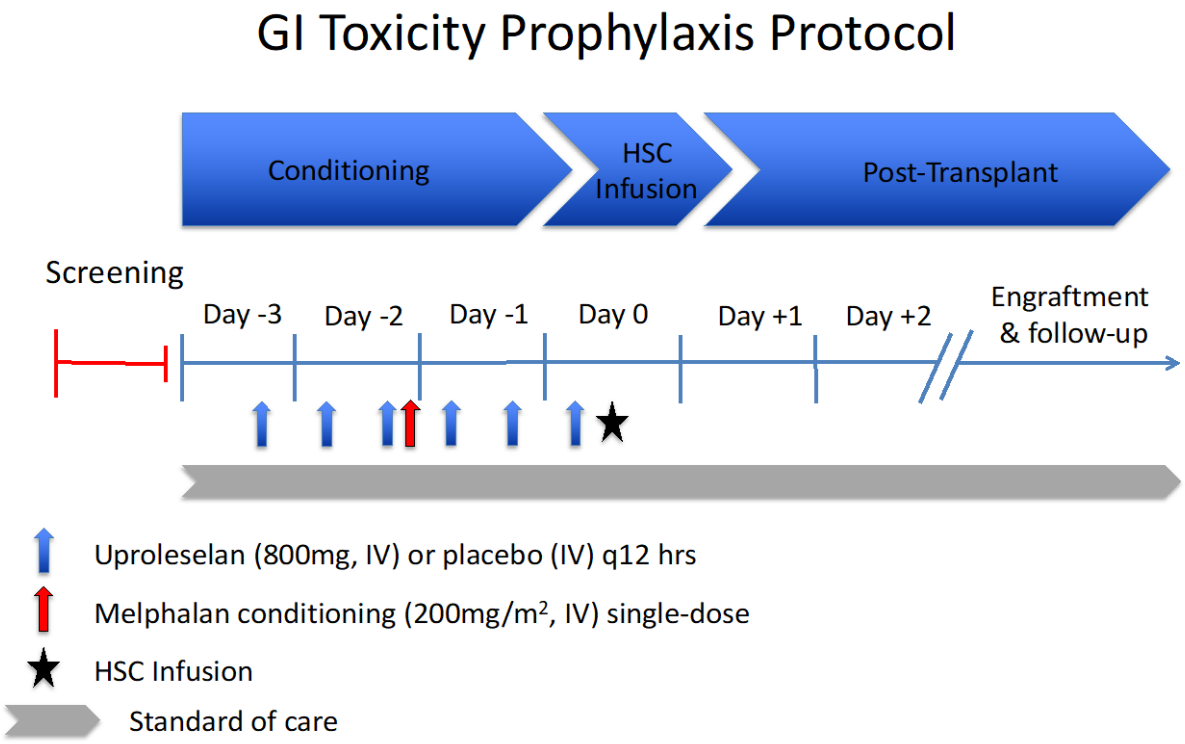
PROTOCOL SUMMARY

Title:	A Phase II Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Uproleselan (GMI-1271) for GI Toxicity Prophylaxis During Melphalan-Conditioned Autologous Hematopoietic Cell Transplantation (auto-HCT) for Multiple Myeloma (MM)
Study Description:	This is a Phase II, single-center, randomized, double-blind, placebo-controlled clinical trial. Eligible patients undergoing first auto-HCT with melphalan conditioning (200mg/m^2) for MM will be randomized in a 1:1 allocation to receive either prophylactic uproleselan + SOC or placebo + SOC. Randomization will be stratified by age ≥65 years and <65 years, due to increased frequency of GI toxicity in elderly populations.
Objectives:	<u>Primary Outcome:</u> To demonstrate the superiority of prophylactic uproleselan (GMI-1271) plus standard of care (SOC) compared to placebo plus SOC to reduce diarrhea severity in patients receiving high-dose melphalan conditioning in preparation for auto-HCT in MM. <u>Secondary Outcomes:</u> • To demonstrate the superiority of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC to: o Reduce oral mucositis severity o Reduce alternative GI toxicities (e.g. esophagitis, enterocolitis, etc.) • To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on: o Time to engraftment o hospital length of stay (LOS) o Use of anti-diarrheal and pain medications o Patient nutritional status pre-conditioning and post-HCT o Change in Bristol Stool Scale o Incidence of post-HCT infection prior to engraftment • To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on PRO and QoL related to GI toxicity, on D-3, D+8 and date of discharge or D+14 (whichever is sooner) <u>Exploratory Outcomes:</u> • To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on: o Minimal Residual Disease (MRD) at 100 days post-HCT o Soluble E-selectin levels at pre-dose (D-3) and post-conditioning (D-0) time points o Progression Free Survival (PFS) o Overall Survival (OS)

	• To descriptively assess biomarkers of GI permeability and GI epithelial injury, in collaboration with the Division of Gastroenterology
Endpoints:	<u>Primary Endpoint:</u> Change in diarrhea severity, assessed per CTCAE v5.0, in patients receiving high-dose melphalan conditioning in preparation for auto-HCT for MM who receive prophylactic uproleselan (GMI-1271) plus standard of care (SOC) compared to placebo plus SOC. <u>Secondary Endpoints:</u> • Change in mucositis severity, per CTCAE v5.0 Oral Mucositis criteria • Change in alternative GI toxicities (e.g. esophagitis, enterocolitis, etc; per CTCAE v5.0) • Time to neutrophil engraftment defined as ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days or $\geq 1.0 \times 10^9$/L for 1 day • Duration of hospital length of stay (LOS), from date of admission for auto-HCT to date of discharge • Quantitative use of anti-diarrheal medications (loperamide, diphenoxylate, etc.) and pain medications (e.g. opioids converted to morphine equivalents) • Patient nutritional status before conditioning and at D+14 or date of discharge (whichever is sooner), as assessed by total TPN days and change in standing weight comparing D-3, D+8 and date of discharge or D+14 (whichever is sooner) • Change in Bristol Stool Scale, assessed daily • Incidence of infection assessed by rates of bacteremia (with organism reported when available), time to first antibiotics and *c. diff* infections • PRO and QoL, per the CTCAE PRO Form v1.0 with items selected for relevance to GI toxicity and patient QoL (see Supplement 1), assessed on D-3, D+8 and date of discharge or D+14 (whichever is sooner) <u>Exploratory Endpoints:</u> • Post-HCT Minimal Residual Disease (MRD) testing at D+100 via ImmunoSeq B-cell receptor sequencing (Adaptive Biotechnologies) • Soluble E-selectin levels by ELISA assay at pre-dose (D-3) and post-conditioning (D-0) time points • Progression Free Survival (PFS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis) • Overall Survival (OS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis)

	• Fecal calprotectin and neutrophil gelatinase-associated lipocalin-2 (lipocalin-2) biomarkers (Tarr Lab) on D-3, D0, D+8 and date of discharge or D+14 (whichever is sooner)
Study Population:	Fifty patients with biopsy-proven diagnosis of multiple myeloma (MM) aged 18-75 years are eligible for this study. Must have ECOG PS 0-1, undergoing first auto-HCT for MM in first PR or better. Patients requiring renal replacement therapy, with a history of inflammatory bowel disease or alternative chronic diarrheal syndrome will be excluded.
Phase:	Phase II
Description of Study Intervention:	Patients enrolled on study will receive investigational product/placebo for 3 consecutive days totaling 6 doses. Follow-up for the key secondary endpoints of engraftment will include D+30, D+100, 6-month and 12-month assessments. The remaining follow-up will be conducted via phone-calls every 3-6 months to assess for PFS and OS for up to 2 years post-HCT.
Study Duration:	12 months (recruitment) + 24 months (intervention and follow-up) + 12 months (data analysis) = 48 months.
Participant Duration:	Approximately 1 week of active study intervention (participants will be in-patient during this period); 1 year of in-person follow-up; 1 year of phone and medical record follow-up.

SCHEMA


GI Toxicity Prophylaxis Protocol
Conditioning
HSC Infusion
Post-Transplant
Screening
Day -3
Day -2
Day -1
Day 0
Day +1
Day +2
Engraftment & follow-up
Uproleselan (800mg, IV) or placebo (IV) q12 hrs
Melphalan conditioning (200mg/m², IV) single-dose
HSC Infusion
Standard of care

SCHEDULE OF ACTIVITIES

Activity	Screening[1]	Day -3	Day -2	Day -1	Day 0	Day +1	Day +8	DOD or D +14[12]	Follow-Up[13]
Informed consent	X								
Eligibility check	X								
Physical exam	X								X
Medical history	X								
Laboratory evaluation	X[2]	daily labs as per BMT protocol							X
Pregnancy test[3]	X	X							
Randomization[4]	X								
Bone marrow evaluation	X[5]								X[5]
Soluble E-selectin levels (peripheral blood)		X			X				
Fecal calprotectin and lipocalin-2 biomarkers		X			X		X	X	
Uproleselan 800 mg (iv) or placebo (iv) q 12 hrs		X	X[6]	X	X				
Melphalan conditioning 200 mg/m^2			X[6]						
HSC infusion					X[7]				
Standing weight (unless unable to stand)	X	X					X	X	
NCI PRO CTCAE QoL assessment[8]		X					X	X	
Standard AE assessments[9]	X	X----------daily----------X							X
Study-specific CTCAE v5.0 AE assessments[10]	X	X----------daily----------X							
Bristol Stool Scale assessment[11]		X----------daily----------X							

1. Screening window to be D-90 through D-3
2. CBC with differential, CMP, PT/INR, PTT, HIV and acute hepatitis panel.
3. For women of childbearing potential, pregnancy test must be obtained at screening and on admission to the hospital prior to starting treatment on study.
4. Randomization will occur following consent, screening and confirmation of eligibility.
5. Screening and D+100 bone marrow assessment to include MRD testing of bone marrow aspirate on all patients. Otherwise, bone marrow assessments to be conducted per standard of care and institutional practice for disease response assessments.
6. 3 doses of uproleselan should be administered prior to administration of the melphalan conditioning regimen and 3 doses of uproleselan administered following administration of the melphalan conditioning regimen.
7. HSC infusion 4 hours (+/- 2 hours) following last dose of uproleselan.
8. See Supplement 1 for CTI PRO CTCAE assessment form.
9. Baseline AE assessment is intended to establish patient's current medical condition. No regulatory reporting of AEs at baseline is required unless occurring as a result of a study-related procedure. AEs are collected through D+30.
10. Baseline and D-3 through DOD study-specific AE assessments must include the study specific CTCAE v5.0 assessments for the primary and secondary endpoints (see Section 11.0).
11. See Appendix D.
12. DOD = date of discharge. Assessment on DOD or D+14, whichever is sooner.
13. Follow-up assessments will take place after transplant, at D+30, D+100, 6 months, and 12 months. Medical record data will be collected for up to 2 years post-HCT for survival.

1.0 INTRODUCTION

1.1 Background

1.1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignancy of plasma cells resulting in infiltration of the bone marrow, pancytopenia and lytic bone lesions. MM is the second most common hematologic malignancy[1-3] and accounts for approximately 15% of all hematologic malignancies[4]. The median age of patients at the time of diagnosis is approximately 65 years and impacts African Americans at rates 2-3x higher than rest of the population[5]. Common clinical features of MM are bone pain with pathologic fractures secondary to lytic lesions, renal failure, fatigue secondary to anemia and recurrent infections[5].

1.1.2 High-dose Chemotherapy and Stem-cell Rescue Therapy

Historically, with conventional chemotherapy, median overall survival for MM patients was 24-30 months. In the 1980s, high-dose chemotherapy and stem-cell rescue therapy via autologous hematopoietic cell transplantation (auto-HCT) was introduced. In subsequent randomized trials, auto-HCT for the treatment of MM has been shown to improve event free survival compared to conventional chemotherapy alone in patients with standard-risk MM, while lengthening the time patients are without symptoms, treatment and treatment toxicity[6-8]. Currently, a combined approach of auto-HCT with additional novel therapies has increased median overall survival to >80 months[9-13].

1.1.3 Chemotherapy-Related GI Toxicity

The conditioning regimens used for preparative chemotherapy prior to rescue auto-HCT are associated with high rates (70-80%) of both hematologic and non-hematologic AEs[14-15]. High-dose melphalan, which is one of the most commonly used regimens, carries particularly high rates of GI toxicity with diarrhea occurring in >90% of patients[15-16]. These toxicities adversely affect patients and frequently increase healthcare utilization by increasing hospital length of stay (LOS), increasing palliative medication usage, decreasing nutritional status, worsening patient quality of life (QoL) and having a detrimental impact on clinical outcomes[17-20]. Meanwhile, current management strategies focus primarily on palliation of the GI toxicity once it has occurred, rather than preventing its occurrence[21]. Improved, prophylactic strategies are needed.

1.1.4 Gastrointestinal Inflammation and Permeability

Although the underlying mechanism of chemotherapy-related GI toxicity is not completely understood, it is well-documented that cytotoxic chemotherapy disproportionately impacts cell populations with high turnover, including

malignant cells as well as highly proliferative normal tissues like the GI epithelium, likely contributing to high rates of GI toxicity (diarrhea, mucositis, etc.). However, a growing body of data suggest that this chemotherapy-initiated epithelial injury subsequently leads to inflammatory chemokine and cytokine signaling, as well as upregulated selectin and integrin expression on the vascular endothelium at sites of inflammation[22, 23]. For example, upregulated E-selectin expression has been shown to be as high as 10x the baseline levels on vascular endothelial cells at sites GI epithelial inflammation[23]. This leads to increased intravascular leukocyte rolling, adhesion, trans-endothelial migration and chemotaxis of proinflammatory cells to these sites of epithelial injury resulting in additional, pathologic immune-mediated inflammatory injury to the GI epithelium[22,23].

This concept of pathologic, inflammatory GI epithelial injury by inflammatory leukocytes has been well-described in alternative settings of GI injury, such as graft versus host disease (GHVD) and inflammatory bowel disease (IBD)[24-26]. Therefore, in addition to evaluating mechanisms of inflammation as a therapeutic target for intervention in inflammatory GI disorders, the development of diagnostic biomarkers of GI inflammation represents an active area of investigation. Some well-described inflammatory markers of intestinal inflammation in GVHD and IBD include fecal calprotectin[24-26], fecal lipocalin-2[27, 28] and fecal neopterin[29, 30], which have been shown to correlate with severity of GI inflammatory epithelial injury and have been investigated as measures of treatment response leading to decreased GI inflammation.

Therefore, presence of increased biomarkers of GI inflammation would represent strong supportive evidence of the proposed mechanism of chemotherapy-initiated epithelial injury leading to further inflammatory-mediated GI toxicity.

1.1.5 E-Selectin

E-selectin is a highly conserved adhesion molecule expressed on the surface of vascular endothelial cells which is upregulated at sites of inflammation, leading to increased intravascular cell rolling, trans-endothelial migration and trafficking of proinflammatory cells to these sites of inflammation[22]. Emerging pre-clinical data suggest that chemotherapy-induced mucositis and neutropenia may also be associated with E-selectin up-regulation on vascular endothelium at sites of acute chemotherapy-related inflammation along the GI epithelium, leading to additional cell-mediated inflammatory epithelial injury[23]. E-selectin is also constitutively expressed in vascular niches within the bone marrow, where it has been shown to co-localize and bind with malignant acute myeloid leukemia (AML) and multiple myeloma (MM) cells leading to cell adhesion-mediated chemotherapy resistance[31-33].

1.1.6 Investigational Intervention – Uproleselan (GMI-1271)

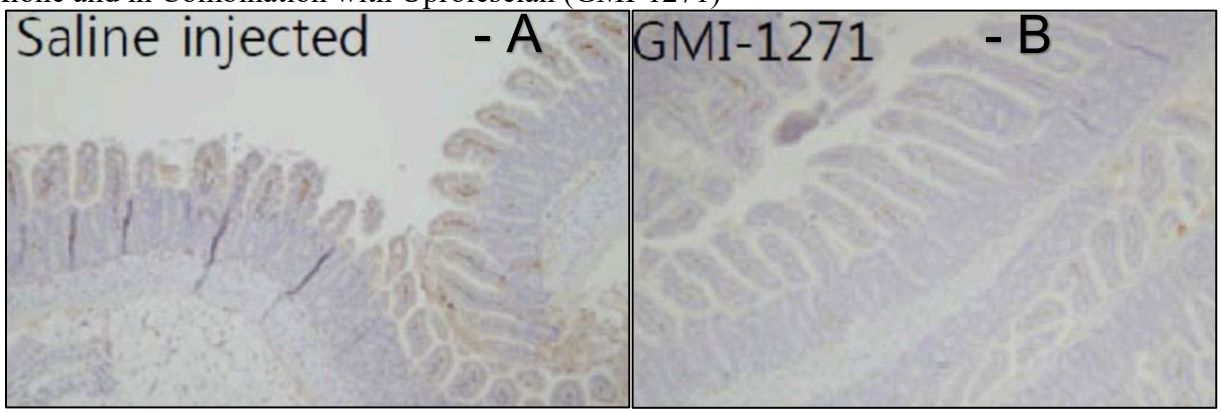
Uproleselan is a synthetic E-selectin antagonist which competitively inhibits E-

selectin, thereby interrupting E-selectin-mediated interactions and effects[34].

1.1.6.1 Pre-Clinical Data

Pre-clinical trials suggest that chemotherapy-induced mucositis and neutropenia may be associated with E-selectin up-regulation, while E-selectin inhibition with uproleselan as an adjunct to chemotherapy protected mice from weight loss and chemotherapy induced GI toxicity while also enhancing neutrophil recovery[23]. Importantly, the administration of uproleselan effectively blocked secondary migration of inflammatory F4/80+ Ly-6C+ macrophages to intestines of mice following chemotherapy as one mechanism of reduced GI toxicity (Figure 1)[23, 34].

Figure 1: Macrophage Staining of Murine Small Intestines after Administration of Chemotherapy Alone and in Combination with Uproleselan (GMI-1271)



A. Chemotherapy-treated with saline control injections, sustained epithelial injury, substantial macrophage infiltration, villous loss and epithelial erosions. B. Chemotherapy-treated, uproleselan-injected (GMI-1271), prevented macrophage infiltration, villous loss and epithelial injury.

E-selectin inhibition with uproleselan in various pre-clinical models has also been observed to disrupt adhesion and mobilize malignant cells into circulation, increasing sensitivity to cytotoxic chemotherapy[31, 35] Interestingly, treatment with uproleselan resulted in mobilization of MM cells to the peripheral blood beyond drug elimination in mouse xenograft models, suggesting a sustained effect following drug administration[35]. Additional *in vivo* studies using MM mouse models evaluating uproleselan plus melphalan demonstrated significantly improved survival and tumor growth inhibition when compared to melphalan alone[35].

1.1.6.1 Clinical Data

To date, E-selectin inhibition with uproleselan has been evaluated in a total of 6 early-phase clinical trials conducted in healthy volunteers (NCT02168595, NCT02271113, NCT02703051), AML (NCT02306291)

and MM with an acceptable safety, pharmacokinetic (PK), pharmacodynamic (PD) profile[34]. In a recently completed Phase I/II clinical trial (NCT02306291) evaluating uproleselan plus chemotherapy in patients with AML demonstrated promising overall response rates of 80% (newly Dx AML, 7+3 chemo) and 48% (relapsed/refractory, MEC chemo), leading to a Phase III trial (NCT03616470) which our group is currently participating in[34]. Interestingly, only 4/157 (2.5%) of AML patients treated with uproleselan plus chemotherapy in the Phase I/II trial experienced grade 3-4 mucositis, which is remarkably lower than expected based on historically observed rates of 10-30% for the chemotherapy agents administered (NCT02306291)[34]. Furthermore, this clinical observation is supported by the nonclinical pharmacology data for uproleselan in mucositis animal models[23]. Of note, in a Phase I open-label study evaluating uproleselan as a chemo-sensitizing agent added to proteasome-based chemotherapy regimens in multiple myeloma patients, E-selectin inhibition with uproleselan was found to be relatively safe and well-tolerated (NCT02811822)[34].

Therefore, considering the frequent prevalence of MM, the pivotal therapeutic role of high-dose chemotherapy with rescue auto-HCT and the high rates of AEs associated with this treatment approach, these data are sufficient to warrant further evaluation of uproleselan as a prophylactic supportive-care therapy to reduce conditioning regimen-associated GI toxicity and improve patient QoL, while potentially decreasing healthcare resource utilization and improving outcomes.

1.1.7 Hypothesis

We hypothesize that prophylactic E-selectin inhibition via administration of uproleselan during melphalan conditioning will reduce the GI toxicity in MM patients undergoing auto-transplant, as assessed via diarrhea severity scoring per CTCAE v5.0, while potentially increasing chemosensitivity of malignant MM cells to high-dose melphalan.

1.1.8 Correlative Studies Background

Testing of MRD status on routine bone marrow assessments following auto-HCT) has become standard of care. We propose assessment of MRD status at screening pre-HCT and D+100 post-transplant in all patients, as post-HCT MRD negativity has been correlated with improved survival in multiple studies[36-37]. We will also monitor for PFS and OS to confirm if these are associated with MRD status in this cohort. Soluble E-selectin levels will be measured in order to confirm on-target effect of the drug, as previously described[34]. Based on the mechanism of action of uproleselan, we are also interested in an interdisciplinary collaboration assessing biomarkers of GI epithelial injury including fecal calprotectin, fecal lipocalin-2 and potentially additional biomarkers such as neopterin. Calprotectin, a neutrophil-

derived S100A8-S100A9 dimer is extensively used as a treatment target in IBD[24]. People with GI GVHD have elevated fecal calprotectin concentrations[25, 26]. Lipocalin-2 (Lcn-2) is neutrophil gelatinase-associated lipocalin, a pleotropic mediator of intestinal and systemic innate immunity[27]. The function of lipocalin is complex, and includes antibacterial and anti-inflammatory effects in the gut, and pro-inflammatory effects on extra-intestinal organs such as the liver. Circulating lipocalin concentrations correlate with acute and chronic GVHD, and mortality[28]. Neopterin (from macrophages and T-cells) similarly correlates with disease activity in IBD[29, 30]. Lastly, given the importance of assessing patient reported outcomes in clinical trials and in particular supportive care trials, we will assess the effect of uproleselan on patient reported quality of life.

1.2 Study Design

1.2.1 Overall Design

This is a Phase II, single-center, randomized, double-blind, placebo-controlled clinical trial. Eligible patients undergoing 1st auto-HCT with melphalan conditioning for MM will be randomized in a 1:1 allocation to receive either prophylactic uproleselan + SOC or placebo + SOC. Randomization will be stratified by age ≥65 years and <65 years, due to the known increased frequency of GI toxicity in elderly populations.

1.2.2 Scientific Rationale for Study Design

Considering the frequent prevalence of MM, the pivotal therapeutic role of high-dose chemotherapy with rescue auto-HCT and the high rates of AEs associated with this treatment approach, further evaluation of uproleselan as a prophylactic therapy to reduce conditioning regimen-associated GI toxicity, improve patient QoL, decrease healthcare resource utilization and improve outcomes is warranted. Phase I data are available to guide safety and dosing. Therefore, this trial is designed as a Phase II study to evaluate the RP2D dose for efficacy, safety and tolerability. All patients will receive SOC prophylaxis with cryotherapy per institutional protocol. Given the lack of additional, highly effective prophylactic strategies, randomization to placebo versus investigational treatment is a rational approach. Furthermore, given the inherent challenges associated with assessments of diarrhea severity along with the potential for multiple confounding variables, randomization, double-blinding and placebo-control are necessary design elements.

1.2.3 Justification for Dose

Based on the initial Phase I pharmacokinetic and safety data showing clearance of uproleselan is not based on body size and in keeping with the dosing approach in the Phase II AML study, we propose using a fixed dose of uproleselan (GMI-1271) 800mg, administered as an initial intravenous (IV) dose in the PM of D-3, followed

by 800mg IV every 12 hours through the conditioning chemotherapy period (total of 6 doses, last dose AM of D-0, 4 hours prior to HSC infusion).

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

Uproleselan (GMI-1271)
Human safety information regarding uproleselan is available from Phase 1 clinical trials in healthy volunteers and subjects with MM, and a Phase 1/2 clinical trial in subjects with AML. Currently, clinical trials for AML, in which uproleselan is used as an adjunct to standard chemotherapy are ongoing, including administration alone, with cytarabine-based chemotherapy regimens for AML. To date, no specific toxicities, or target organs for toxicity, have been identified thus far in nonclinical studies or in clinical trials for uproleselan. Non-specific toxicities considered treatment-emergent adverse events (TEAEs) ≥Grade 3 were observed in 34/102 (33.3%) patients across the aforementioned studies. Hematologic AEs (neutropenia, anemia and thrombocytopenia) were most commonly observed, accounting for 25/102 of the ≥Grade 3 TEAEs and typically occurring with co-administration of chemotherapy regimens also associated with myelosuppression. Please see IB Table 7-1 for full table listing all observed TEAEs, along with IB Section 7.9 for overlap with expected AEs associated with concurrent chemotherapy regimens administered[34].

High-dose Melphalan and Rescue Auto-HCT
Melphalan is a commonly used chemotherapy, administered in high-doses as a conditioning regimen prior to rescue auto-HCT in the treatment of MM. Commonly observed toxicities with melphalan are detailed in Table 1. Auto-HCT in MM is associated with a one-year non-relapse related mortality of 2%. All appropriate standard of care interventions will be undertaken to manage these associated risks and toxicities.

1.3.2 Table 1 Non-Hematologic Adverse Reactions in ≥25% of Patients with Multiple Myeloma Who Received Melphalan Conditioning for Auto-HCT

Adverse Reactions	Number (%) of Patients (N=61)	
	All Grades	Grade 3or 4
All Adverse Reactions	61	61
Diarrhea	57 (93%)	2 (3%)
Nausea	55 (90%)	1 (2%)
Fatigue	47 (77%)	1 (2%)
Hypokalemia	45 (74%)	17 (28%)
Vomiting	39 (64%)	0 (0%)
Hypophosphatemia	30 (49%)	29 (48%)
Decreased Appetite	30 (49%)	0 (0%)
Pyrexia	29 (48%)	2 (3%)
Constipation	29 (48%)	0 (0%)
Febrile Neutropenia	25 (41%)	17 (28%)
Mucosal Inflammation	23 (38%)	6 (10%)
Dizziness	23 (38%)	0 (0%)
Edema Peripheral	20 (33%)	0 (0%)
Stomatitis	17 (28%)	3 (5%)
Abdominal Pain	17 (28%)	0 (0%)
Dysgeusia	17 (28%)	0 (0%)
Dyspepsia	16 (26%)	0 (0%)

1.3.3 Known Potential Benefits

Uproleselan (GMI-1271)

The efficacy of uproleselan as prophylaxis for GI-toxicity or as a chemo-sensitizing agent has not been established. However, pre-clinical trials suggest that chemotherapy-induced mucositis and neutropenia may be associated with E-selectin up-regulation, while E-selectin inhibition with uproleselan as an adjunct to chemotherapy protected mice from weight loss and chemotherapy induced GI toxicity while also enhancing neutrophil recovery[23]. Importantly, the administration of uproleselan effectively blocked secondary migration of inflammatory F4/80+ Ly-6C+ macrophages to intestines of mice following chemotherapy as one mechanism of reduced GI toxicity. To date, uproleselan has been evaluated in clinical trials for acute myeloid leukemia (AML) and MM as a potential chemo-sensitizing agent with an acceptable safety, pharmacokinetic (PK), pharmacodynamic (PD) profile. Additionally, data from these trials demonstrated a low incidence and severity of mucositis in patients administered uproleselan[34]. Therefore, the potential benefits of uproleselan may include reduced trafficking of inflammatory cells to the GI epithelium leading to reduced conditioning regimen-associated GI toxicity and improved patient QoL. Meanwhile, uproleselan may also increase MM cell chemosensitivity, leading to improved treatment response to high-dose melphalan and improved long-term outcomes.

High-dose Melphalan and Rescue Auto-HCT

In the 1980s, high-dose chemotherapy and stem-cell rescue therapy via autologous hematopoietic cell transplantation (auto-HCT) was introduced. High-dose melphalan is the standard conditioning regimen prior to rescue auto-HCT in the treatment of MM. Randomized trials evaluating melphalan conditioning followed by auto-HCT for the treatment of MM have been shown to improve event free survival compared to conventional chemotherapy alone in patients with standard-risk MM, while lengthening the time patients are without symptoms, treatment and long-term treatment toxicity[6-8].

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the superiority of prophylactic uproleselan (GMI-1271) plus standard of care (SOC) compared to placebo plus SOC to reduce diarrhea severity in patients receiving high-dose melphalan conditioning in preparation for auto-HCT in MM.	Change in diarrhea severity, assessed per CTCAE v5.0, in patients receiving high-dose melphalan conditioning in preparation for auto-HCT for MM who receive prophylactic uproleselan (GMI-1271) plus standard of care (SOC) compared to placebo plus SOC.
Secondary	
• To demonstrate the superiority of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC to: o Reduce mucositis severity o Reduce alternative GI toxicities (e.g. esophagitis, enterocolitis, etc.) • To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on: o Time to engraftment o hospital length of stay (LOS) o Use of anti-diarrheal and pain medications o Patient nutritional status pre-conditioning and post-HCT o Change in Bristol Stool Scale o Incidence of post-HCT infection prior to engraftment	• Change in mucositis severity, per CTCAE v5.0 Oral Mucositis criteria • Change in alternative GI toxicities (e.g. esophagitis, enterocolitis, etc; per CTCAE v5.0) • Time to neutrophil engraftment defined as ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days or $\geq 1.0 \times 10^9$/L for 1 day • Duration of hospital length of stay (LOS), from date of admission for auto-HCT to date of discharge • Quantitative use of anti-diarrheal medications (loperamide, diphenoxylate, etc.) and pain medications (e.g. opioids converted to morphine equivalents) • Patient nutritional status before conditioning and at D+14 or date of discharge (whichever is sooner), as assessed by total TPN days and change in standing weight comparing D-3, D+8 and date of discharge or D+14 (whichever is sooner) • Change in Bristol Stool Scale, assessed daily (see Appendix D)

• To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on PRO and QoL related to GI toxicity, on D-3, D+8 and date of discharge or D+14 (whichever is sooner)	• Incidence of infection assessed by rates of bacteremia (with organism reported when available), time to first antibiotics and *c. diff* infections • PRO and QoL, per the CTCAE PRO Form v1.0 with items selected for relevance to GI toxicity and patient QoL (see Supplement 1), assessed on D-3, D+8 and date of discharge or D+14 (whichever is sooner)
Exploratory	
• To descriptively assess the effects of prophylactic uproleselan (GMI-1271) plus SOC compared to placebo plus SOC on: o Minimal Residual Disease (MRD) at 100 days post-HCT o Soluble E-selectin levels at pre-dose (D-3) and post-conditioning (D-0) time points o Progression Free Survival (PFS) o Overall Survival (OS) • To descriptively assess biomarkers of GI inflammation and GI epithelial injury, in collaboration with the Division of Gastroenterology	• Post-HCT Minimal Residual Disease (MRD) testing at D+100 via ImmunoSeq B-cell receptor sequencing (Adaptive Biotechnologies) • Soluble E-selectin levels by ELISA assay at pre-dose (D-3) and post-conditioning (D-0) time points • Progression Free Survival (PFS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis) • Overall Survival (OS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis) • Fecal calprotectin and neutrophil gelatinase-associated lipocalin-2 (lipocalin-2) biomarkers (Tarr Lab) on D-3, D0, D+8 and date of discharge or D+14 (whichever is sooner)

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Biopsy-confirmed multiple myeloma (MM) (per IMWG criteria).

2. Undergoing first auto-HCT for MM in first partial response (PR) or better (see Section 11.0).

3. Conditioning regimen to be single agent melphalan (200 mg/m^2)

4. Adults 18 to 75 years of age, inclusive

5. ECOG performance status ≤ 2 (see Appendix A)

6. Mobilized ≥ 5.0 x 10^6 CD34+ cells/kg (i.e. sufficient CD34+ HSCs for one auto-HCT, with at least one back-up graft in reserve)

7. Adequate bone marrow and organ function prior to stem cell mobilization, as defined below:
   a. Leukocytes, absolute neutrophil count, and platelets all within institutional standard limits for high-dose melphalan autologous stem cell transplant
   b. Total bilirubin ≤ 1.5 x ULN (unless the patient has a history of Gilbert's Syndrome, in which case, total bilirubin must be ≤ 2.5 times the ULN)
   c. AST(SGOT)/ALT(SGPT) ≤ 3.0 x ULN
   d. Creatinine clearance ≥ 30 mL/min by Cockcroft-Gault
   e. Baseline pulmonary function test (PFT) with carbon monoxide diffusion capacity in the lung (DLCO) ≥ 50% and forced expiratory volume in 1 second (FEV1) both within institutional standard limits for high-dose melphalan autologous stem cell transplant

8. The effects of uproleselan (GMI-1271) on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, prior sterilization procedure, abstinence, etc.) prior to study entry, for the duration of study participation and for 12 weeks after the completion of the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Should a man who is participating in the study become aware that he has impregnated a partner, he must inform his treating physician immediately.

9. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. A history of other malignancy with the exception of malignancies for which all treatment was completed at least 2 years before registration and the patient has no evidence of disease.

2. Active signs or symptoms of CNS involvement by malignancy (lumbar puncture not required). Prior history of CNS involvement is acceptable, if patient has completed treatment for CNS involvement with documented treatment response.

3. Prior exposure to uproleselan (GMI-1271)

4. Currently receiving any other investigational agents

5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to uproleselan or melphalan

6. Known active infection with hepatitis A, B (e.g., HBsAg positive), or C (e.g., anti-HCV positive), or human immunodeficiency virus

7. Uncontrolled acute life-threatening bacterial, viral, or fungal infection

8. Myocardial infarction within 6 months of uproleselan/placebo dosing, or subject has current significant cardiovascular disease, such as uncontrolled or symptomatic arrhythmias, congestive heart failure, hemodynamic instability, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification

9. Any medical, psychiatric, or other condition which, in the opinion of the investigator, unfavorably alters the risk-benefit of subject participation, is likely to interfere with trial completion, assessments, or interpretation of trial results, or otherwise would make the subject an inappropriate subject for this trial.

10. Pregnant and/or breastfeeding.

11. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the trial and for 12 weeks following the last dose of uproleselan/placebo. Women who are postmenopausal with amenorrhea for at least 1 year prior to trial entry and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status (>28U/L) will be considered NOT of childbearing potential. Highly effective contraception includes:
    a. Total abstinence with a male partner.
    b. Female sterilization (has had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before uproleselan/placebo. In case of oophorectomy alone, the subject would be eligible only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    c. Male sterilization (at least 6 months prior to Screening). For female subjects on the trial, the vasectomized male partner should be the sole partner for that subject.
    d. BOTH of the following forms of contraception consistently used together:
        i. Injected, transdermal, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%) with the exception of intrauterine devices, which are excluded due to the risk of infection and bleeding.
        ii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with or without spermicidal foam/gel/film/cream/vaginal suppository.
        iii. Men who are sexually active and **not** willing to use condoms during the trial and for 12 weeks following the last dose of uproleselan/placebo, unless they have undergone vasectomy for sterilization (at least 6 months prior to Screening), are excluded from trial participation.

12. Men who are sexually active and **not** willing to use condoms during the trial and for 12 weeks following the last dose of uproleselan/placebo, unless they have undergone vasectomy for sterilization (at least 6 months prior to Screening), are excluded from trial participation.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Measures to Minimize Bias: Randomization and Blinding

4.5.1 Randomization

Fifty patients with MM will be randomized in a 1:1 allocation to receive either uproleselan plus SOC or placebo plus SOC as GI-toxicity prophylaxis during melphalan conditioning prior to auto-HCT. Randomization will be stratified by age ≥65 years and <65 years, due to increased frequency of GI toxicity in elderly populations. The randomization table will be generated using the SAS program PROC PLAN. To better ensure the balance of patient characteristics across two arms, treatment assignment will be implemented in small blocks of 4 or 6 patients. Enrollment will continue until 50 evaluable patients are enrolled. Randomization will occur following registration and implemented with the OnCore system.

After the Screening evaluations have been performed and a patient is confirmed to be eligible for study, they will be to a treatment group.

The Interactive Web Response System (IWRS) will provide the designated unblinded investigational pharmacist the subject's treatment assignment. Dose preparation procedures will be performed by the pharmacist utilizing uproleselan or placebo provided by GlycoMimetics.

Treatment assignment received at randomization will be maintained throughout the conditioning period.

4.5.2 Blinding

This trial will be double-blinded and placebo-controlled. All healthcare providers, ancillary support staff, research support staff and patients participating in the trial will remain blinded to treatment, including personnel at GlycoMimetics. The investigational pharmacists participating in the study will be unblinded to treatment assignments. Investigational drug or placebo will be IV saline solution, provided by the investigational pharmacy in a blinded manner to the non-pharmacy study personnel for administration to trial patients, based on the patients' treatment assignment at randomization.

The blind will be maintained for treatment assignment for randomized subjects until 30 days after the last patient has completed HCT and has been fully assessed for the primary endpoint of the study.

The blind will be maintained in the following manner:

- The investigational pharmacist (or authorized designee) will be unblinded and will prepare uproleselan and placebo in a blinded manner in order to maintain the blind for all other trial personnel.

- Unblinding may only be performed in emergencies where knowledge of the subject's treatment assignment is essential for immediate management of the subject's medical care. It is anticipated that such situations will be extremely rare. If the treatment of the AE/safety issue is the same regardless of the treatment assignment, the blind should not be broken. Unblinding a subject's treatment assignment by the investigator under any other circumstances will be considered a protocol violation.
- Subjects whose treatment assignment is unblinded will continue all trial treatment and assessments per protocol.
- Any intentional or unintentional unblinding events must be reported to the Principal Investigator (PI) immediately and also documented in the medical record, including: date, time, and reason for breaking the blind.
- Treatment randomization information, and any analytical results will be kept confidential and will not be released to the investigator or blinded personnel until the conclusion of the trial.

4.6 Replacement of Patients

Patients who are screened, found to be eligible, and randomized to a treatment arm but who subsequently do not undergo auto-HCT or are removed from the study prior to receiving study-related treatments are not evaluable for the primary endpoint and therefore will be replaced in order to achieve the target enrollment of 50 evaluable patients.

5.0 TREATMENT PLAN

5.1 Study Intervention Description

Following consent, patients will undergo all screening procedures, and those meeting eligibility requirements will be randomized as described in Section 4.5.1 to either uproleselan + SOC or placebo + SOC. All patients will be admitted to the hospital 3 days (Day -3) prior to the scheduled date of HSC infusion (Day 0).

- On the evening of Day -3, patients will receive dose #1 of uproleselan or placebo (suggested dosing time is 8:00pm).
- On the following morning of Day -2 (12 +/- 2 hours from prior dose), patients will receive dose #2 of uproleselan or placebo.
- On the evening of Day -2 (12 +/- 2 hours from prior dose), patients will receive dose #3 of uproleselan or placebo.
- On Day -2 following completion of dose #3 of uproleselan or placebo, the patient will be administered the conditioning dose of melphalan (200mg/m^2) as per institutional practice.
- On the following morning of Day -1 (12 +/- 2 hours from prior dose), patients will receive dose #4 of uproleselan or placebo.
- On the evening of Day -1 (12 +/- 2 hours from prior dose), patients will receive dose #5 of uproleselan or placebo.

- On the following morning of Day 0 (12 +/- 2 hours from prior dose) patients will receive dose #6 (final dose) of uproleselan or placebo.
- On Day 0, 4 hours (+/- 2 hours) after the final dose of uproleselan or placebo, the patient will be infused with the HSC product. The patient will remain inpatient until engraftment and will follow-up for study assessments per the full schedule of assessments.

5.1.1 Uproleselan (GMI-1271) and Placebo Preparation and Dosing

Uproleselan injection, 50 mg/mL is supplied in single-dose vials at a concentration of 50 mg/mL. Uproleselan injection 50 mg/mL is stored per the specified conditions on the label, frozen (10 °C to -25 °C) prior to administration. The frozen product can appear as a homogenous solid, a striated solid, or as a super-cooled liquid. When using frozen supply, vials should be brought to room temperature before dose preparation. Upon thawing, the product should be gently inverted 4 to 5 times to ensure homogeneity of the solution. The thawed solution is clear, colorless to slightly yellow, and free from visible particulates.

Uproleselan should be administered IV into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes (+/-2 minutes) using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration is highly recommended. Dilution of uproleselan may be performed with normal saline (0.9% Sodium Chloride).

Compatibility with other therapeutic agents has not been determined; therefore, uproleselan injection should be administered via a separate IV line and should not be administered concurrently with anything other than saline. If a flush is used, saline flush is preferred.

When prepared in syringes or intravenous (IV) bags without an administration set attached, uproleselan may be stored refrigerated up to 72 hours prior to administration or up to 24 hours at controlled room temperature prior to administration. Administration sets manufactured from materials of construction other than polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP) can be primed up to 72 hours before dosing if stored refrigerated or up to 24 hours before dosing if stored at controlled room temperature. Intravenous lines consisting of PVC with DEHP should be avoided when possible. If PVC with DEHP administration sets must be used they should be primed with uproleselan solution no more than 2 hours before dosing. It is highly recommended that uproleselan prepared prior to administration be refrigerated until 1 hour prior to dosing.

Uproleselan (GMI-1271) will be given as a single dose at 800 mg, administered as an initial intravenous (IV) dose in the evening of Day -3, followed by 800 mg IV every 12 hours through the conditioning chemotherapy period (total of 6 doses, last dose AM of Day 0 prior to HSC infusion). Three doses of uproleselan should be

administered prior to administration of the melphalan conditioning regimen, with 3 doses administered following administration of the melphalan conditioning regimen.

As placebo, commercially available saline (0.9% Sodium Chloride Injection) will be prepared by the site's pharmacist in IV administration components (syringe, bag, tubing, etc.) matching those used for active treatment to maintain the blind. The dosing schedule and procedure for placebo will be identical to that for uproleselan. It is recommended that placebo prepared prior to administration be refrigerated until one hour prior to dosing, to match pharmacy procedures for uproleselan. Preparation of placebo in advance of administration should be in accordance with institutional pharmacy standards and commercial label for the placebo control.

5.1.2 Melphalan Dosing

Melphalan will be administered as a single, IV dose at 200 mg/m^2 infused over 20 minutes on HCT Day -2, with the following guidance:

- Dosing instructions:
  - If actual Body Weight (BW) is less than ideal BW, use actual BW
  - If actual BW is greater than ideal BW, but less than 120% of ideal BW, use ideal BW
  - If actual BW is greater than or equal to 120% of ideal BW, use corrected BW
    - Corrected BW = ([actual BW – ideal BW] x 0.2) + ideal BW
- Dose rounding:
  - Dosing will be rounded to the nearest 50mg provided that the dose is within 5% of the calculated dose, as above
- Dose administration:
  - Melphalan will be administered as per instructional practice and guidelines, which is typically at 9PM.

5.2 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients who receive at least one dose of uproleselan or placebo and undergo auto-HCT are evaluable for disease response unless they are removed from the study prior to undergoing any study-related disease response assessment. Patients who do not undergo auto-HCT or are removed from the study prior to receive study-related treatments will be replaced.

5.3 Concomitant Therapy and Supportive Care Guidelines

At Trial Start: Prior G-CSF, granulocyte macrophage-colony stimulating factor (GM-CSF) or plerixafor is prohibited within 3 days prior to uproleselan/placebo dosing.

GI Toxicity Prophylaxis: SOC cryotherapy will be provided to all patients for GI-toxicity prophylaxis, per institutional practice.

Post-auto-HCT: G-CSF may not be initiated until 72 hours after the last dose of uproleselan/placebo in each cycle. The use of erythropoiesis-stimulating agents such as epoetin and darbepoetin is not allowed.

Supportive Care: All additional and medically indicated supportive cares, including pain medications, anti-diarrheal medications, antimicrobials and any other indicated palliative therapy will be available and provided to the patients, per institutional practice and best standards of care.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum/urine pregnancy test at screening and again on Day -3 prior to the first dose of uproleselan/placebo. Women who are postmenopausal with amenorrhea for at least 1 year prior to trial entry and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status (>28U/L) will be considered NOT of childbearing potential.

Female and male patients (along with their female partners) are required to use highly effective contraception during participation in the study and for at least 12 weeks following the last dose of uproleselan/placebo. Highly effective contraception includes:

a. Total abstinence with a male partner.
b. Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before uproleselan/placebo
c. Male sterilization (at least 6 months prior to Screening). For female subjects on the trial, the vasectomized male partner should be the sole partner for that subject.
d. BOTH of the following forms of contraception consistently used together:
    i. Injected, transdermal, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%) with the exception of intrauterine devices, which are excluded due to the risk of infection and bleeding.
    ii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with or without spermicidal foam/gel/film/cream/vaginal suppository.

If a patient is suspected to be pregnant, uproleselan/placebo should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 12 weeks after the last dose of uproleselan/placebo, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 6 doses of uproleselan or placebo or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed at D+30, D+100, 6 months, and 12 months with SOC assessments per institutional practice. Of note, the D+100 bone marrow assessment will include a bone marrow sample sent for MRD testing. Following that, patients will be contacted by phone every 3-6 months to assess for PFS and OS for an additional year (ending at 2 years post-HCT). Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 6 weeks following a scheduled visit and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 6 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

No dose modifications are recommended for uproleselan/placebo, nor should dose modifications be made without direct consultation with the PI. Dose delays should only occur in the event of a medical emergency, and the PI should be made aware of any anticipated deviations from the dosing protocol given the importance of timely administration of uproleselan concurrent with melphalan (3 doses of uproleselan prior to melphalan administration and 3 doses following melphalan), as well as the completion of the sixth and final dose of uproleselan/placebo 4 hours (+/- 2 hours) prior to the HSC infusion.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through D+30 post auto-HCT. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- AEs related to the initial induction chemotherapy and mobilization

AEs related to the conditioning regimen (melphalan) and auto-HCT should be recorded in the CRF, given the primary outcome being reduction in chemotherapy-related GI toxicities.

Refer to the data submission schedule in Section 10 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to GlycoMimetics, Inc.

According to the timelines referenced in Appendix C, the Sponsor shall use commercially reasonable efforts to forward assessed case information regarding SAEs and other safety information that it receives from a patient receiving the investigational product or placebo.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix B for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix B) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix B) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Uproleselan (GMI-1271)

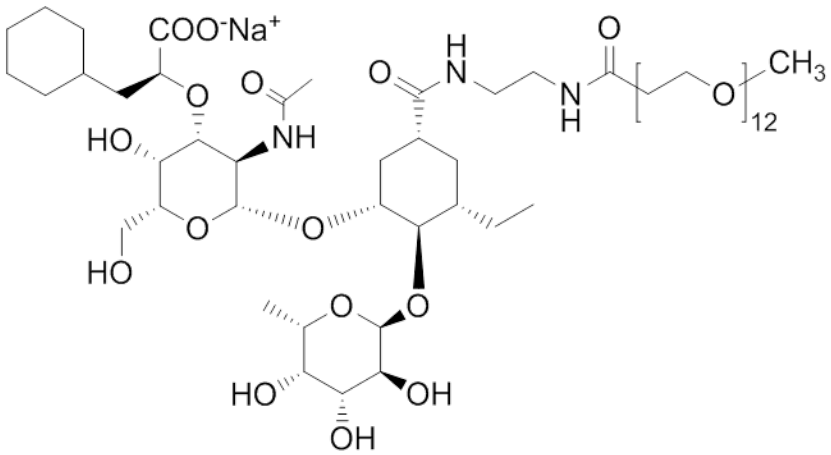
8.1.1 Uproleselan (GMI-1271) Description

Chemical Name: Sodium (1*R*, 3*R*, 4*R*, 5*S*)-3-({2-N-acetylamino-2-deoxy-3-O-[(1*S*)-1-carboxylato-2-cyclohexylethyl]-β-D-galactopyranosyl}oxy)-4-({6-deoxy-α-L-galactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29, 32,35-dodecaoxa-39-azahentetracontan-41-yl) carboxamide

Chemical Formula: C60H108N3NaO27

Molecular Weight: 1326.5

Figure 4-1. Uproleselan Chemical Structure



8.1.2 Clinical Pharmacology

PK evaluations in healthy volunteers showed a dose-linear relationship in mean PK parameters after IV infusion of uproleselan 2 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg and 40 mg/kg. Uproleselan is characterized by a half-life of 1.4-2.5 hours and does not accumulate after doses up to 20 mg/kg BID. Population PK analysis in healthy volunteers and patients with AML demonstrate similar PK profiles, PK parameters, and dose-proportionality. Clearance was found to depend on renal function and have a similar magnitude in both healthy volunteers and in patients with AML. Clearance is not dependent on body size which allows for flat-fixed dosing. The PK of uproleselan does not appear to be affected when co-administered with chemotherapy.

Absolute CD34+ counts did not increase in peripheral blood after administration of uproleselan.

8.1.3 Pharmacokinetics and Drug Metabolism

A population PK analysis was conducted using data from trial GMI-1271-201 to understand the PK of uproleselan when administered with cytotoxic chemotherapy in patients with AML. This analysis revealed a similar PK profile in these patients and healthy volunteers. It was found that clearance of uproleselan varies with renal function and does not vary with body size or any other covariate evaluated. Minimal accumulation of uproleselan at any dose level was observed, as expected from the short half-life.

Following from the population PK finding that clearance does not depend on body size, conversion to a flat-fixed dose for subsequent trials is appropriate. Exposure-response analyses further demonstrated that safety and efficacy responses are not dependent on exposure. In the GMI-1271-201 trial, the majority of patients with R/R AML were administered a dose of 10 mg/kg at a median body weight of 82.6 kg. The corresponding flat-fixed dose is 800 mg. Therefore, a flat-fixed dose of 800 mg will be used in this trial.

8.1.4 Supplier

Uproleselan will be supplied by GlycoMimetics, Inc.

8.1.5 Dosage Form and Preparation

Uproleselan will be supplied in sterile single-dose vials at a concentration of 50 mg/mL. The drug product should be stored frozen (-10°C to -25°C) or refrigerated (2°C to 8°C) per the label directions until time of use. The frozen product can appear as a homogenous solid, a striated solid, or as a super-cooled liquid. Frozen drug product should be brought to room temperature before dose preparation. Upon thawing, the product should be gently inverted 4 to 5 times to ensure homogeneity of the solution. The thawed or refrigerated solution is clear, colorless to slightly yellow, and free from visible particulates.

8.1.6 Storage and Stability

Uproleselan injection 50 mg/mL is stored per the specified conditions on the label, either frozen (-10°C to -25°C) or refrigerated (2°C to 8°C), prior to administration. The frozen product can appear as a homogenous solid, a striated solid, or as a super-cooled liquid. Frozen vials should be brought to room temperature before dose preparation. Upon thawing, the product should be gently inverted 4 to 5 times to ensure homogeneity of the solution. The thawed or refrigerated solution is clear, colorless to slightly yellow, and free from visible particulates. Reconstitution and dilution are not necessary. Dilution up to 5X may be performed with normal saline.

When prepared in syringes or intravenous (IV) bags without an administration set attached, uproleselan may be stored refrigerated up to 72 hours prior to administration or up to 24 hours at controlled room temperature prior to administration. Administration sets manufactured from materials of construction other than polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP) can be primed up to 72 hours before dosing if stored refrigerated or up to 24 hours before dosing if stored at controlled room temperature. Intravenous lines consisting of PVC with DEHP should be avoided when possible. If PVC with DEHP administration sets must be used they should be primed with uproleselan solution no more than 2 hours before dosing. It is highly recommended that uproleselan prepared prior to administration be refrigerated until 1 hour prior to dosing.

The investigational product is to be in a locked and secured storage facility, accessible only to those individuals authorized by the PI.

8.1.7 Administration

Uproleselan injection is a sterile solution for IV administration, supplied in single-dose vials at a concentration of 50 mg/mL.

Uproleselan injection should be administered IV into a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration is highly recommended.

Compatibility with other therapeutic agents has not been determined; therefore, uproleselan injection should be administered via a separate IV line, and should not be administered concurrently with anything other than saline. If a flush is used, saline flush is preferred.

8.2 Placebo

As placebo, commercially available saline (0.9% Sodium Chloride Injection) will be prepared by the site's pharmacist in IV administration components (syringe, bag, tubing, etc.) matching those used for active treatment to maintain the blind. The dosing schedule

and procedure for placebo will be identical to that for uproleselan. It is recommended that placebo prepared prior to administration be refrigerated until one hour prior to dosing, to match pharmacy procedures for uproleselan. Preparation of placebo in advance of administration should be in accordance with institutional pharmacy standards and commercial label for the placebo control.

9.0 CORRELATIVE STUDIES

9.1 Minimal Residual Disease (MRD) Status Following HCT

Post-HCT MRD testing will be performed on the D+100 bone marrow biopsy sample for all patients, with pre-HCT MRD testing during screening as baseline. The MRD testing will be performed per SOC and institutional practice as a send-out test via ImmunoSeq B-cell receptor sequencing (Adaptive Biotechnologies). Standard handling, processing, preserving, and shipping will proceed as per the current institutional practices.

9.1.1 Collection of Specimen(s)

Collect 2 mL of bone marrow aspirate (BMA) in an EDTA tube.

9.1.2 Handling of Specimen(s)

- No onsite processing of the specimen is required.
- The fresh BMA specimen collection and submission kits will include the following:
  - One (1) 3 mL EDTA tube for BMA collection
  - One (1) ambient pack
  - One (1) FedEx clinical pack pre-labeled with a FedEx shipping label
- Store specimen in ambient pack for same day shipment for next day 10 AM PT delivery
- If same day shipment is not an option, store specimen refrigerated until shipment for next day 10 AM PT delivery. Fresh specimens should be received at Adaptive within 5 days of collection.

9.1.3 Shipping of Specimen(s)

Specimens must be packaged and shipped according to the instructions provided with the specimen kit.

Batch shipping is not allowed.

Specimens must be transported on the same day as collected via express courier (FedEx is recommended) using standard next day delivery service to arrive on Monday through Saturday

For Saturday delivery, be sure to check the Saturday delivery box on the express courier form. If not checked, the courier will deliver on Monday, and the sample will be too old to process.

The specimen will be shipped to Adaptive Biotechnologies:
Phone: 888-552-8988
E-mail: clinicalservices@adaptivebiotech.com

9.2 E-selectin Levels

Soluble E-selectin levels will be assessed on Day -3 prior to administration of uproleselan and on D0 following completion of the conditioning regimen and uproleselan dosing, but prior to HSC infusion via ELISA assay.

9.2.1 Collection of Specimen(s)

Collect 3 mL of peripheral blood in a Na Citrate (light blue top) tube.

9.2.2 Handling of Specimen(s)

Samples will be taken to the Washington University Tissue Procurement Core and processed per standard operating procedure. Blood will be drawn into sodium citrate tubes, inverted 3-4 times and stored in an ice bath until centrifugation. Samples will be centrifuged at 1,300 g at room temperature for 5 minutes. Ideally, samples should be immediately centrifuged following collection. If institutional staffing and/or logistics do not allow for this, samples may be stored (via an ice bath or at approximately 4°C) for 48-72 hours before centrifugation.

After centrifugation, pipette half of plasma into an appropriately labeled cryovial (primary aliquot). Pipette the remaining plasma into an additional appropriately labeled cryovials (back-up aliquot). Labels should include date and time of collection and subject ID/UPN.

The aliquots will be placed into a freezer at -80°C for temporary storage and then transferred to storage in liquid nitrogen vapor until shipped for analysis.

9.2.3 Shipping of Specimen(s)

Samples will be batch-shipped at the completion of the study. The primary and back-up aliquots will be shipped on separate days to mitigate loss (Monday - Wednesday only), via overnight carrier with the appropriate amount of dry ice.

QPS, LLC
ATTN Sample Coordinator
1 Innovation Way, Suite 200
Newark, Delaware 19711

Contact: Susan ZONDLO
E-mail: susan.zondlo@qps.com and tlmsmt@qps.com
Tel.: + 1 302 453 5911

Upon shipment of the samples, an e-mail will be sent containing a sample manifest, the name of the courier, the airway bill number, and a confirmation of the number of samples in the shipment.

9.3 GI Epithelial Inflammation and Permeability Biomarkers

Based on the mechanism of action of uproleselan, we are also interested in an interdisciplinary collaboration assessing biomarkers of GI epithelial injury and GI permeability, including fecal calprotectin and fecal lipocalin-2, as well as other potential exploratory biomarkers such as neopterin. Fecal samples for banking will be collected on Day -3 (or first available stool), Day 0 (or Day 1 if not available Day 0), Day +8 (or Day 9 if not available Day 0), and Day +14 or date of discharge (+/-1 day, whichever is sooner).

9.3.1 Fecal calprotectin, lipocalin-2 & Stool Biomarker Banking

Collect 15 mL (minimum 5 mL) of feces/stool in a stool container to be banked as a fecal specimen for later assessment of calprotectin, lipocalin-2 and other stool biomarkers of inflammation via ELISA assay (or other assay as indicated).

Collect a fresh random fecal specimen, no preservative.

Banked fecal specimens will be sent to the Tissue Procurement Core for frozen banking. The total specimen will be divided into 5 aliquots of equal volume. The 5 aliquots will be placed into a freezer at -80°C for temporary storage and then transferred to storage in liquid nitrogen vapor until shipped for analysis.

At the time of specimen analysis, the fecal specimens will be sent out (frozen) to Mayo Lab, per standard processing.

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Completion of treatment

Toxicity Form	Continuous (start of treatment through Day +30)
Follow Up Form	Day 30, Day 60, Day 100, Month 6, Month 12, Month 15, Month 18, Month 21, Month 24
MRD Form	Day 100
E-selectin Form	Day -3
GI Biomarkers Form QOL Form	Day -3, Day 0 (GI Biomarkers Form only), Day 8, Day 14/DOD
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

10.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

11.0 MEASUREMENT OF EFFECT

11.1 GI Toxicity Adverse Events

Primary and Secondary Endpoints related to GI toxicity Adverse Events, as they pertain to the Primary and Secondary Endpoints of the study will be measured via the NIH National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, as detailed below.

11.1.1 Diarrhea Severity (Primary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					

11.1.2 Oral Mucositis (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					

11.1.3 Esophagitis (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall. **Navigational Note:** -					

11.1.4 Esophageal Pain (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region. **Navigational Note:** -					

11.1.5 Gastritis (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach. **Navigational Note:** -					

11.1.6 Abdominal Pain (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region. **Navigational Note:** -					

11.1.7 Nausea (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit. **Navigational Note:** -					

11.1.8 Vomiting (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. **Navigational Note:** -					

11.1.9 Enterocolitis (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines. **Navigational Note:** If reporting a known abnormality of the colon, use Gastrointestinal disorders: Colitis. If reporting a documented infection, use Infections and infestations: Enterocolitis infectious.					

11.1.10 Proctitis (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum. **Navigational Note:** -					

11.1.11 Hemorrhoids (Secondary Endpoint)

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area. **Navigational Note:** -					

11.2 Response Criteria

Response assessment based on IMWG Response Criteria[39] to be determined relative to the labs at time of diagnosis prior to induction chemotherapy, as enumerated below.

11.2.1 MRD negative Complete Response

MRD negative complete response requires all of the following:

- CR as defined below
- Normal free light chain ratio
- Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence

- Absence of clonal plasma cells by NGS on bone marrow aspirate using ImmunoSeq B-cell receptor sequencing (Adaptive Biotechnologies)

11.2.2 Stringent Complete Response

Stringent complete response (sCR) requires all of the following:

- CR as defined below
- Normal free light chain ratio
- Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence

11.2.3 Complete Response

Complete response (CR) requires all of the following:

- Disappearance monoclonal protein by both protein electrophoresis and immunofixation studies* from the blood and urine
- <5% plasma cells in the bone marrow
- Disappearance of soft tissue plasmacytomas

  * The monoclonal protein at time of diagnosis, prior to induction chemotherapy, will be used for determination

11.2.4 Very Good Partial Response

Very good partial response (VGPR) requires all of the following:

- Serum and urine monoclonal protein detectable by immunofixation* but not on electrophoresis

  OR

  $\geq$ 90% reduction in serum monoclonal protein with urine monoclonal protein < 100 mg per 24 hours

  * The monoclonal protein at time of diagnosis, prior to induction chemotherapy, will be used for determination

- If present, $\geq$ 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations)

11.2.5 Partial Response

Partial response (PR) requires all of the following:

- $\geq$ 50% reduction in the level of the serum monoclonal protein
- Reduction in urine monoclonal protein by either $\geq$ 90% or to $\leq$ 200 mg

- If present, ≥ 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations)
- If serum and urine monoclonal protein are unmeasurable, a ≥50% decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must be ≥ 10 mg/dl)
- If serum and urine monoclonal protein are unmeasurable and serum free light chain is unmeasurable, a ≥ 50% reduction in plasma cells is required in place of monoclonal protein provided that baseline bone marrow plasma cell percentage was ≥ 30%

11.2.6 Minimal Response

Minimal response (MR) requires all of the following:

- ≥ 25% to < 49% reduction in the level of serum monoclonal protein
- If present, a 50 to 89% reduction in 24-hour urine monoclonal protein which still exceeds 200 mg/24hr
- 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examinations)
- No increase in size or number of lytic bone lesions (development of compression fracture dose not exclude response)

Note: MR includes participants in whom some but not all criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR.

11.2.7 Stable Disease

Stable disease (SD) is defined as not meeting criteria for any other response as defined in this section.

11.2.8 Progressive Disease

Progressive disease (PD) with be defined from T_0 and requires one or more of the following:

- ≥ 25% increase in the level of serum monoclonal protein, which must also be an absolute increase of at least 0.5 g/dL
- ≥ 25% increase in 24-hour urine monoclonal protein, which must also be an absolute increase of at least 200 mg/24hr
- ≥ 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%
- ≥ 25% increase in the difference between involved and uninvolved free light chain levels (The absolute increase must be ≥10 mg/dl)
- Definite increase in the size of existing lytic bone lesions or soft tissue

plasmacytomas. A definite increase is defined as at least 50% (and at least 1 cm) increase as measured serially as the sum of the products of the cross-diameters of the lesions.
- Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture)
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any cause other than progressive multiple myeloma)

Note: A response of progressive disease nullifies any other concurrent response. For example, at a given time point a participant meets criteria for VGPR but has development of new bone lesions the response is PD not VGPR.

11.2.9 Clinical Relapse

Clinical relapse (i.e. progressive disease requiring alternate myeloma treatment) requires one or more of the following:

- Decrease in hemoglobin $\geq$ 2 g/dl not attributable to any cause other than progressive multiple myeloma
- Increase in creatinine by $\geq$ 2 mg/dl not attributable to any cause other than progressive multiple myeloma
- Other worsening laboratory result, or clinical condition that the treating physician determines is not attributable to any cause other than progressive multiple myeloma

11.2.10 Relapse from Complete Response

Relapse from a complete response requires a prior CR or sCR as described above and subsequently developing one or more of the following:

- Reappearance of serum or urinary paraprotein on immunofixation* or routine electrophoresis excluding oligoclonal immune reconstitution for at least two determinations.
- $\geq$ 5% plasma cells in the bone marrow aspirate or biopsy.

  * The monoclonal protein at time of CR or better will be used for determination.

11.3 Progression-Free Survival

Progression-free survival (PFS) will be defined as time from D0 of auto-HCT to progressive disease (biochemical and/or clinical) or death. Patients who are alive and progression-free or were lost to follow-up at the time of data analyses will be censored on the last known alive date.

11.4 Overall Survival

Overall survival (OS) will be defined as time from D0 of auto-HCT to death due to any causes. Patients who are alive or were lost to follow-up at the time of data analyses will be censored on the last known alive date.

11.5 Overall Response Rate

Overall response rate (ORR) will be defined as the proportion of patients meeting the criteria for PR, VGPR, CR, sCR or MRD-negative CR.

11.6 Complete Response Rate

Complete response rate (CRR) will be defined as the proportion of patients meeting the criteria CR, sCR or MRD-negative CR.

12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members, including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after study activation at Washington University, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician.
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study.
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason.
- Study-wide target accrual and study-wide actual accrual.

- Protocol activation date.
- Average rate of accrual observed in year 1, year 2, and subsequent years.
- Expected accrual end date, and accrual by group.
- Objectives of protocol with supporting data and list the number of participants who have met each objective.
- Measures of efficacy.
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules.
- Summary of toxicities.
- Abstract submissions/publications.
- Summary of any recent literature that may affect the safety or ethics of the study.

Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

13.0 STATISTICAL CONSIDERATIONS

13.1 Statistical Hypotheses

Prophylactic administration of uproleselan (GMI-1271) throughout melphalan conditioning in preparation for auto-HCT will reduce the rate of diarrhea, as assessed by a validated chemotherapy-related diarrhea severity scoring system (CTCAE v5.0 Diarrhea).

13.2 Sample Size Determination

We expect an event rate of diarrhea of any grade of 90% with a distribution of Grade 1: 20%, Grade 2: 30%, Grade 3: 40%, Grade 4: 0% and Grade 5: 0%. We estimate a sample size of 50 patients (25 per arm) evaluable for the primary endpoint would provide 80% power (alpha 0.20) to detect an odds ratio (OR) of 0.42 for reduction in the grade of diarrhea severity, using a one-sided proportional odds model for ordinal categorical data. We anticipate that more power could be achieved in the actual analysis because of richer information (daily during hospitalization) available for GI toxicity evaluation. Note that one purpose of a randomized phase II trial design is to detect signals of efficacy in an experimental regimen for further evaluation rather than to have a definitive conclusion regarding the efficacy of an experimental regimen. Therefore, a relatively larger type I error (alpha or false positive error) is acceptable in a randomized phase II setting and the

level of type I error can be relaxed to alpha=0.2, according to Korn et al[40] and Rubinstein et al[41].

13.3 Population for Analyses

All randomized patients evaluable for the primary and secondary endpoints will be analyzed on an intention-to-treat basis. Additionally, the same patient population will also be analyzed on a per-protocol basis for the same endpoints.

13.4 Statistical Analyses

13.4.1 General Approach

In general, categorical variables will be expressed as percentages of the total number of patients meeting that endpoint. Continuous data will typically be expressed as a median value.

13.4.2 Analysis of the Primary Endpoint

The primary endpoint will be the change in diarrhea severity (CTCAE v5.0, Figure 2) in patients receiving high-dose melphalan conditioning in preparation for auto-HCT for MM who receive prophylactic uproleselan (GMI-1271) plus standard of care (SOC) compared to placebo plus SOC. All randomized patients meeting eligibility criteria who receive at least one dose of uproleselan or placebo and who undergo a melphalan-conditioned auto-HCT will be evaluable for the primary endpoint analysis based on an intent-to-treat principle. Patients will also be evaluated for the primary endpoint based on a per-protocol analysis. The outcome will be reported as a median score with high/low ranges for the duration of the hospitalization, comparing the treatment and placebo cohorts. The primary endpoint is anticipated to follow a non-normal distribution and the overall difference between arms will be compared using generalized estimation equation (GEE) which is less sensitive to parametric distributions.

Figure 2: CTCAE v5.0 Diarrhea Score:

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					

13.4.3 Analysis of the Secondary Endpoints

All secondary endpoints will be analyzed using the appropriate, descriptive statistics on an intent-to-treat and per-protocol basis, comparing the treatment and

placebo cohorts. However, the study will not be powered to detect significant differences in these outcomes.

- Change in mucositis severity (per CTCAE v5.0 Oral Mucositis criteria) and change in alternative GI toxicities (e.g. esophagitis, enterocolitis, etc.; per CTCAE v5.0) will be reported as median scores with high/low ranges for the duration of the hospitalization.

- Time to neutrophil engraftment defined as ANC $\geq$0.5 x 10^9/L for 3 consecutive days or $\geq$1.0 x 10^9/L for 1 day will be reported as a median time engraftment.

- Duration of hospital LOS will be reported in median number of days, from date of admission for auto-HCT to date of discharge.

- Quantitative use of anti-diarrheal medications will be reported as the median number of daily doses administered (loperamide, diphenoxylate, etc.) and pain medications will be reported as the median number of daily morphine equivalents, minus the baseline level of morphine equivalents the patient may have been taking prior to admission as an outpatient medication.

- Nutritional status before conditioning and at D+14 or date of discharge (whichever is sooner), will be reported as the median number of TPN days and in change in standing weight comparing D-3, D+8 and date of discharge or D+14 (whichever is sooner).
- Change in Bristol Stool Scale, assessed daily (see Appendix D), will be reported as the median stool type with high/low ranges.

- Incidence of infection will be reported as a percentage of patients who develop of bacteremia during the hospitalization for HCT (with organism reported when available), median time to first antibiotics and percentage of patients who develop a *c. diff* infection.

- The differences between treatment arms will be described using GEE (for longitudinal endpoints such as mucositis severity, Bristol Stool Scale, nutritional status, etc.), Kaplan-Meier product limit methods and log-rank test (for time-to-event endpoints such as time to neutrophil engraftment, length of hospital stay, etc.), and Fisher's exact test (for incidence of infection) as appropriate.

13.4.4 Analysis of the Exploratory Endpoints

Correlative Endpoints:

- Minimal Residual Disease (MRD) testing via ImmunoSeq B-cell receptor sequencing (Adaptive Biotechnologies) at D+100, expressed as percentage

of patients being MRD negative, comparing the treatment and placebo cohorts.

- Soluble E-selectin levels by ELISA assay at pre-dose (D-3) and post-conditioning (D-0) time points, comparing the treatment and placebo cohorts.

- Fecal calprotectin, lipocalin-2 and any additional fecal biomarkers on D-3, D0, D+8 and date of discharge or D+14 (whichever is sooner), comparing the treatment and placebo cohorts

- Progression Free Survival (PFS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis), comparing the treatment and placebo cohorts

- Overall Survival (OS) with up to 2-year follow up assessed by time-to event (Kaplan-Meier analysis), comparing the treatment and placebo cohorts

- The differences between treatment arms will be described using Wilcoxon-Mann-Whitney or GEE (soluble E-selectin levels, fecal biomarkers, etc.), Kaplan-Meier product limit methods and log-rank test (PFS, OS), and Fisher's exact test (minimal residual disease at Day 100), as appropriate.

13.4.5 Analysis of the PRO/QoL Endpoint

PRO and QoL scores assessed via the CTCAE PRO Form v1.0 with items selected for relevance to GI toxicity and patient quality of life (see Supplement 1) will be reported as median scores on D-3, D+8 and date of discharge or D+14 (whichever is sooner), comparing the treatment and placebo cohorts.

13.4.6 Baseline Descriptive Statistics

Baseline characteristics, including demographics, laboratory measurements, induction treatment regimens and disease response status at the time of HCT will be reported, using descriptive statistics.

13.4.7 Safety Analyses

An independent data monitor will assess for treatment-related death and/or non-engraftment, with enrollment suspended for review whenever there is any case of treatment-related death or non-engraftment.

Non-engraftment will be defined as failure to achieve neutrophil engraftment (ANC $\geq 0.5 \times 10^9$/L for 3 consecutive days or $\geq 1.0 \times 10^9$/L for 1 day) by post-HCT D+21. Additionally, all patients participating in the study must have mobilized sufficient CD34+ HSCs for initial auto-HCT and a mandatory back-up graft (total cells

collected: ≥5.0 x 10^6 CD34+ cells/kg; and cells per HCT: ≥2.5 x 10^6 CD34+ cells/kg).

A Bayesian safety monitoring rule will also be implemented for each arm separately once the first 5 evaluable subjects are available in the given arm. The stopping rule is defined as $Pr(\theta_T > 0.2 \mid data) > 0.7$, where θ_T denotes the incidence of Grade 3 or higher non-hematologic, uproleselan-related toxicities, with the exception of toxicities reported in >25% of patients receiving high-dose melphalan conditioning, as detailed in Section 1.3.2. That is, enrollment will be stopped early whenever, given the accumulated observed data, there is a high probability (>70%) that the incidence of targeted toxicities is above 20%. The stopping boundaries are obtained using the online study design tools from M.D. Anderson Cancer Center (https://www.trialdesign.org/one-page-shell.html#BTOX). Specifically, we assume that θ_T follows a beta distribution, beta ($\alpha + x$, $\beta + n - x$), where x and n-x represent the observed numbers of toxicity and non-toxicity cases, while α and β are parameters for prior distribution. We set the prior as beta (0.5, 0.5), i.e., with a non-informative prior. A treatment arm will be recommended to stop for excessive toxicities if we observe 2 events out of the first 5 subjects, 3 events out of 10 subjects, 4 events out of 15 subjects, 5 events out of 20 subjects, or 6^{th} event observed before the last subject enrolled. A simulation study (with 1000 simulated trials) is also performed to assess the operating characteristics of the above monitoring rule. With a true toxicity rate of 10%, there will be only 14% chance of early termination. Conversely, there will be 88% chance of claiming excessive toxicity when the true toxicity rate is 30%.

13.4.8 Interim Analyses for Futility

An interim analysis will be scheduled to protect patients from receiving inferior treatment. An interim analysis will be performed after the first 50% patients are randomized. The summary statistics for primary endpoint (diarrhea severity during hospital stay) will be calculated. An early termination due to futility will be recommended if the statistics of the primary endpoint are in favor of the control arm[42].

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

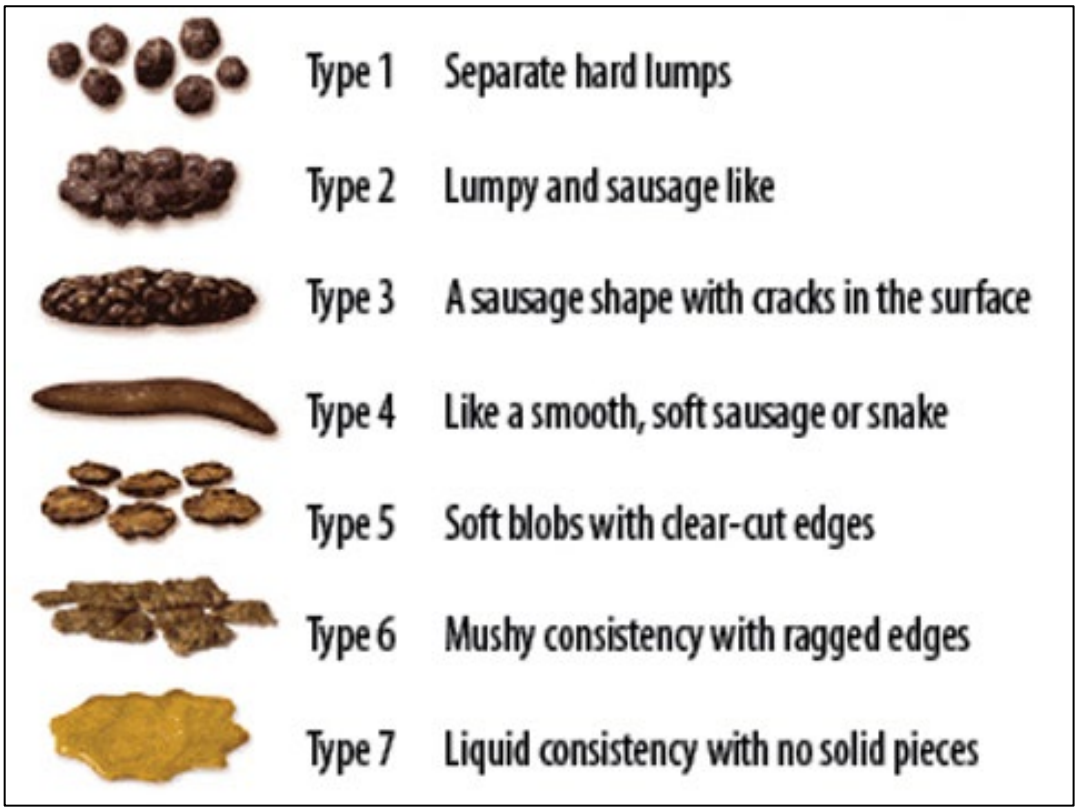
Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Glycomimetics, Inc.**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Completed Regulatory Form (MedWatch / CIOMS I) for initial and follow-up in parallel with submission to the FDA for patients exposed to GMI product.
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Completed Regulatory Form (MedWatch / CIOMS I) for initial and follow-up in parallel with submission to the FDA for patients exposed to GMI product.
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		In parallel with the submission to the HRPO.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	In parallel with submission to the FDA.

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Glycomimetics, Inc.**
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Glycomimetics, Inc.**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	All SAEs and follow-up 15 days post-Sponsor awareness date for patients exposed to GMI product.
Overdose, pregnancy, and lactation cases not associated with an SAE where a subject was exposed to GlycoMimetics compound				Completed Regulatory Form (MedWatch / CIOMS I) for initial and follow-up in parallel on a monthly cycle.
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR			

	noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

APPENDIX D: Bristol Stool Scale



SUPPLEMENT 1: GI-Specific NCI CTCAE PRO v1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
4.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
6.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
7.	In the last 7 days, did you have any INCREASED PASSING OF GAS (FLATULENCE)?				
	○ Yes		○ No		
8.	In the last 7 days, how OFTEN did you have BLOATING OF THE ABDOMEN (BELLY)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your BLOATING OF THE ABDOMEN (BELLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
9.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
10.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe