Official Title: A Phase Ib, Open-Label, Randomized, Dose-Finding, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of GDC-8264 in Combination with Standard of Care in the Treatment of Acute Graft-Versus-Host Disease in Patients who have Undergone Allogeneic Hematopoietic Stem Cell Transplantation

NCT Number: NCT05673876

Document Date: Protocol Version 4: 20-Jul-2023

PROTOCOL

TITLE:	**A PHASE Ib, OPEN-LABEL, RANDOMIZED, DOSE-FINDING, MULTICENTER STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF GDC-8264 IN COMBINATION WITH STANDARD OF CARE IN THE TREATMENT OF ACUTE GRAFT-VERSUS-HOST DISEASE IN PATIENTS WHO HAVE UNDERGONE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION**
PROTOCOL NUMBER:	GA43861
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	161860
TEST PRODUCT:	GDC-8264 (RO7288817)
SPONSOR NAME and ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
APPROVAL:	See electronic signature and date stamp on the final page of this document

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic signature and date stamp on the final page of this document
3	26 August 2022
2	22 July 2022
1	2 February 2022

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GA43861 has been amended primarily to update how adverse events are recorded, the eligibility criteria, and changes from Protocol Clarification Letters. Changes to the protocol, along with a rationale for each change, are summarized below.

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.
- A reference to a recently published scientific article has been added to provide additional evidence supporting the role of receptor-interacting protein 1 (RIP1) inhibition in a nonclinical graft-versus-host disease (GVHD) model (Section 1.2.1).
- The name of the independent Data Safety Monitoring Committee (DSMC) has been corrected to Data and Safety Monitoring Board (DSMB) (Sections 1.3, 3.1.1, 3.1.2, 3.1.3, 4.2.1, 4.6.1, 4.6.3, 5.1, 5.1.1.2, 5.3.5.7, and 9.4).
- The term "objective response rate" has been changed to "overall response rate" to align with the standard terminology used with acute graft-versus-host disease (aGVHD) and bone marrow transplants (Sections 2.0, 4.5.5, and 6.6.1).
- Canada has been added to the list of countries participating in the trial. Clinical trial sites within both the United States and Canada are able to enroll participants. In addition, the number of sites has increased from approximately 10 to 20 (Sections 3.1.1 and 9.4).
- Administrative updates have been made to allow, in exceptional cases, an extended window of [redacted], rather than [redacted], from initiation of systemic corticosteroids to first dose of GDC-8264, when there are administrative delays or other logistical reasons (Sections 3.1.1, 4.1.1, 4.3.2.2, and 4.5.2; Appendix 1).
- Receipt of solid organ transplants that are target organs for aGVHD (e.g., liver transplant) has been added as an exclusion criterion because presentations of liver aGVHD and liver rejection may be difficult to differentiate (e.g., similar elevation of liver enzymes, bilirubin, and findings on biopsy) and because this population has an elevated rate of solid organ transplant failure within the same time frame after allogeneic transplant that aGVHD typically develops and a lower overall survival (Basak et al. 2015) (Section 4.1.2).
- A clarification has been added to the exclusion criterion "Higher risk of seizures" to explicitly exclude patients with mass lesion on brain imaging with evidence of vasogenic edema (Section 4.1.2).
- Dosing instruction has been updated to clarify that there is a [redacted] window for dosing and reinforce that the time of dosing should be recorded (Section 4.3.2.1 and Appendix 1).

- Instructions have been added to clarify how to report significant non-serious events and conditions that occur after informed consent but prior to initiation of GDC-8264 (Sections 4.5.2 and 5.4.2.1).
- Electrocardiogram procedures have been updated to align with guidance on ECG measurements of the QT interval corrected through use of Fridericia's formula (Sections 4.5.10 and 5.1.2.3).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.13.6).
- A criterion has been added for study drug discontinuation for newly discovered brain lesion associated with a higher risk of seizure (e.g., new mass lesion with surrounding vasogenic edema) (Section 4.6.1).
- Since patients with Minnesota High Risk aGVHD are acutely ill with a life-threatening condition, accurate documentation of adverse events prior to and after study treatment is critical. The reporting of adverse events prior to initiation of GDC-8264 has been updated to all serious adverse events (Sections 5.3.1 and 5.4.2.1; Appendix 1).
- Text has been removed describing the use of a single Institutional Review Board (IRB) by all sites for centralizing review efforts. This change acknowledges that more than a single IRB/Ethics Committee may be used by the sites within their respective countries (Section 9.4).
- Text has been modified to clarify that summaries of clinical study results may be available for public access in health authority databases (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. New changes appear in italics. This amendment represents cumulative changes to the original protocol.

Reference

Basak GW, Wiktor-Jedrzejczak W, Labopin M, et al. Allogeneic hematopoietic stem cell transplantation in solid organ transplant recipients: a retrospective, multicenter study of the EBMT. Am J Transplant 2015;15:705–14.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib, OPEN-LABEL, RANDOMIZED, DOSE-FINDING, MULTICENTER STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF GDC-8264 IN COMBINATION WITH STANDARD OF CARE IN THE TREATMENT OF ACUTE GRAFT-VERSUS-HOST DISEASE IN PATIENTS WHO HAVE UNDERGONE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION**
PROTOCOL NUMBER:	GA43861
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	161860
TEST PRODUCT:	GDC-8264 (RO7288817)
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your assigned study monitor or CRO staff.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib, OPEN-LABEL, RANDOMIZED, DOSE-FINDING, MULTICENTER STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF GDC-8264 IN COMBINATION WITH STANDARD OF CARE IN THE TREATMENT OF ACUTE GRAFT-VERSUS-HOST DISEASE IN PATIENTS WHO HAVE UNDERGONE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION**
PROTOCOL NUMBER:	GA43861
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	161860
TEST PRODUCT:	GDC-8264 (RO7288817)
PHASE:	Phase Ib
INDICATION:	Graft-versus-host disease
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of GDC-8264 given in combination with standard-of-care corticosteroid treatment in patients with high-risk acute graft-versus-host disease (aGVHD). The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, pharmacokinetic (PK), and efficacy data. Specific objectives and corresponding endpoints for the study are outlined below.

Co-Primary Objectives	Corresponding Endpoint
• To evaluate the safety of GDC-8264	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale
• To characterize the pharmacokinetics of GDC-8264	• Plasma concentration of GDC-8264 at specified timepoints, and relevant PK parameters

aGVHD = acute graft-versus-host disease; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; DOR = duration of response; FFS = failure-free survival; MAP = Mount Sinai Acute GVHD International Consortium [MAGIC] algorithm probability; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NRM = non-relapse mortality; ORR = *overall* response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; VGPR = very good partial response.

[a] Responses are determined by the investigator.

[b] Baseline defined as last value prior to initiation of GDC-8264.

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of GDC-8264	• ORR, defined as the proportion of patients with a CR, VGPR, or PR on Day 29 with no intervening additional line of aGVHD therapy, as determined by the investigator [a] • DOR, defined as the time from response (CR, VGPR or PR) on Day 29 to aGVHD progression from nadir in any organ, new systemic therapy for aGVHD, or death from any cause (whichever occurs first), as determined by the investigator [a] • Cumulative incidence of aGVHD flares by Day 56 • Cumulative incidence of NRM by Day 180
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of GDC-8264	• Time from initiation of GDC-8264 to first response (i.e., CR, VGPR, or PR) • [redacted] • FFS rate at [redacted] • Cumulative incidence of chronic GVHD by [redacted] • Cumulative incidence of relapse of underlying malignancy by [redacted] • OS rate at [redacted] defined as the proportion of patients who have not experienced death from any cause at [redacted] • Proportion of patients with maximum Grade III or IV aGVHD by [redacted] • Cumulative corticosteroid dose at [redacted]
• To evaluate the safety of GDC-8264 with respect to infection adverse events	• Incidence and severity of infection adverse events, with severity determined according to the BMT CTN infection severity grading scale
• To evaluate potential relationships between drug exposure and the efficacy and safety of GDC-8264	• Relationship between plasma concentration or PK parameters for GDC-8264 and efficacy endpoints • Relationship between plasma concentration or PK parameters for GDC-8264 and safety endpoints

aGVHD = acute graft-versus-host disease; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; DOR = duration of response; FFS = failure-free survival; MAP = Mount Sinai Acute GVHD International Consortium [MAGIC] algorithm probability; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NRM = non-relapse mortality; ORR = *overall* response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; VGPR = very good partial response.

[a] Responses are determined by the investigator.

[b] Baseline defined as last value prior to initiation of GDC-8264.

Exploratory Objectives (cont.)	Corresponding Endpoints
• To identify and/or evaluate biomarkers [b] that are predictive of response to GDC-8264 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to GDC-8264, can provide evidence of GDC-8264 activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology or pharmacokinetics	• Relationship between levels of circulating biomarkers and efficacy endpoints • Relationship between biomarkers in tissue (pending availability) and efficacy endpoints • Relationship between levels of biomarkers and plasma concentration or PK parameters • Change from baseline [b] in MAP at [redacted]

aGVHD = acute graft-versus-host disease; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; DOR = duration of response; FFS = failure-free survival; MAP = Mount Sinai Acute GVHD International Consortium [MAGIC] algorithm probability; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NRM = non-relapse mortality; ORR = *overall* response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; VGPR = very good partial response.

[a] Responses are determined by the investigator.

[b] Baseline defined as last value prior to initiation of GDC-8264.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase Ib, open-label, randomized, dose-finding, multicenter study designed to evaluate the safety, pharmacokinetics, and efficacy of GDC-8264 given in combination with standard-of-care corticosteroid treatment in patients with high-risk aGVHD who have undergone one allogeneic hematopoietic stem cell transplantation (HSCT). The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, PK, and efficacy data. The study will enroll approximately 40 patients, who will be randomized in a 1:1 ratio to one of two GDC-8264 dose cohorts (35 mg once a day [QD] and 75 mg QD) at approximately *20 sites* in the United States *and Canada*. If necessary, additional patients may be enrolled to ensure that at least 12 patients per cohort have received at least 10 doses of GDC-8264 within the [redacted] of the treatment period.

The study consists of a screening period of up to [redacted] following initial diagnosis of aGVHD, a treatment period of 28 days, an optional treatment extension period of 28 days, a post-treatment safety follow-up period for [redacted] and a long-term follow-up period through approximately [redacted] days after initiation of GDC-8264.

Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will maintain a record of reasons for screen failure.

Blood samples will be obtained from all patients for PK and biomarker assessments. Residual samples from biopsies of involved aGVHD target organs (e.g., skin, gastrointestinal [GI] tract) obtained as part of standard of care up to 2 weeks prior to enrollment or during the study will be provided to the Sponsor for exploratory biomarker research after the samples are no longer needed for patient clinical care. Biopsy of involved aGVHD target organs consistent with institutional guidelines is encouraged but is not required for this study, and enrollment should not be delayed for biopsy and pathology results.

Patient safety will be monitored on a regular basis by the Mount Sinai Acute GVHD International Consortium (MAGIC) Principal Investigator, the Sponsor, and the *Data and Safety Monitoring Board* (*DSMB*) through assessment of the nature, frequency, and severity of adverse events, available PK data, and other relevant clinical data.

Patients will be assessed for organ-specific aGVHD stage, aGVHD flare, treatment response and duration of response, primary disease relapse and progression, and survival during the study and for approximately one year after initiation of GDC-8264. For patients who meet the criteria for corticosteroid-refractory aGVHD after enrollment, initiation of any second-line therapy will require discontinuation of GDC-8264.

NUMBER OF PATIENTS

Approximately 40 patients will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form from the patient or legal representative
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of post–allogeneic HSCT aGVHD at screening, with the following aspects of HSCT permissible:
  - Any malignant or non-malignant indication leading to HSCT
  - Any HSCT donor type (e.g., related, unrelated) or stem cell source (i.e., bone marrow, peripheral blood, cord blood)
  - Any GVHD prophylaxis regimen
  - Any conditioning regimen (i.e., myeloablative, reduced intensity, and non-myeloablative)
- Evidence of engraftment post-transplant, as indicated by the following values: ANC ≥ 500/μL (0.5×10^9/L) and platelet count ≥ 10,000/μL (100×10^9/L)

  ANC and platelet counts may be repeated once during screening.

  Use of growth-factor supplementation to maintain neutrophil count is allowed.

  If platelet-transfusion refractoriness is suspected, platelet count will be measured approximately 1 hour after transfusion.

- Diagnosis of high-risk aGVHD, defined as meeting any one criterion from either of the following sets of refined Minnesota high-risk aGVHD criteria during screening, with staging determined through use of MAGIC aGVHD Target Organ Staging:
  - Single-organ involvement
    - Stage 4 skin
    - Stage 3–4 lower GI
    - Stage 1–4 liver
  - Multiple-organ involvement
    - Stage 1–2 lower GI plus any liver
    - Stage 2 lower GI plus any skin
    - Stage 3–4 lower GI plus any liver or skin
    - Any three-organ involvement
- Initiation of treatment with systemic corticosteroids for aGVHD at a dose of prednisone ≥2 mg/kg/day by mouth (PO) or methylprednisolone ≥2 mg/kg/day intravenously (or equivalent) in divided doses at diagnosis and up to 3 days prior to or on the same day as initiation of GDC-8264 (Day 1), with no taper planned prior to Day 3

  As clinically indicated, corticosteroid treatment may be initiated at a lower dose and increased on Day 1 to the doses specified above.

  In exceptional cases of administrative delays or other logistical reasons (i.e., due to the potential participant's health insurance provider[s] issues, screening of a patient during weekends, or extended holidays), a participant who has received systemic corticosteroids up to [redacted] *prior to initiation of GDC-8264 (Day 1), may be enrolled, provided that the participant is not experiencing worsening of aGVHD. The MAGIC Principal Investigator and Medical Monitor are available to advise as needed. The investigator will maintain a record of reasons for the delay in enrollment.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for [redacted] after the final dose of GDC-8264.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for [redacted] after the final dose of GDC-8264 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of relapsed, progressing, or persistent malignancy, or treatment for relapse after transplant, or requirement for rapid immune suppression withdrawal as preemergent treatment of early malignancy relapse
- Prior receipt of more than one allogeneic HSCT
- *Prior receipt of solid organ transplantation that are target organs for aGVHD (e.g., liver transplant)*
- Prior systemic treatment for aGVHD, except for the standard-of-care corticosteroid treatment initiated as part of this trial

  Topical skin corticosteroid treatment and non-absorbable oral corticosteroid treatment for GI aGVHD are permissible.
- Diagnosis of chronic GVHD or overlap syndrome
- Uncontrolled active infection (i.e., progressive symptoms related to infection despite treatment, or persistently positive blood cultures despite treatment, or any other evidence of severe sepsis)

  Persistent fever without signs or symptoms will not be interpreted as an uncontrolled active infection.

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
- Severe organ dysfunction (e.g., acute liver failure, renal failure requiring dialysis, ventilator support, or vasopressor therapy)
- Direct bilirubin >2 mg/dL within 3 days prior to initiation of GDC-8264 unless the elevation is due to Gilbert syndrome or aGVHD
- ALT/SGPT and AST/SGOT $>5\times$ the upper limit of normal (ULN) within [redacted] prior to initiation of GDC-8264, unless due to aGVHD
- Creatinine clearance or estimated glomerular filtration rate <30 mL/min as calculated by institutional practice (e.g., Cockcroft-Gault equation, CKD-EPI equation)
- Treatment with an investigational small molecule therapy within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264

  An investigational therapy is defined as a drug that has not been approved or authorized by the U.S. Food and Drug Administration for any use.
- Treatment with an investigational biologic therapy (e.g., monoclonal antibody) within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264, unless the investigator determines, after consultation with the MAGIC Principal Investigator and the Medical Monitor, that the treatment would not interfere with patient safety or achievement of study objectives
- Initiation or planned use of a marketed small molecule (excluding corticosteroids) or biologic therapy as treatment for aGVHD from the start of screening through the treatment period
- History of seizure or convulsions, except history of childhood febrile seizures

- Higher risk of seizure, as determined by the investigator (including, but not limited to, history of stroke; known Alzheimer's disease or non-Alzheimer's dementia; structural brain disease including arteriovenous malformations or other mass lesions; clinical diagnosis of traumatic brain injury or concussion within previous 6 months)

  Patients with mass lesion on brain imaging with evidence of vasogenic edema are excluded.

  Patients on concomitant medications known to increase the risk of seizure may continue taking those medications, provided they have not previously experienced a seizure at or below the dose level being administered prior to initiation of GDC-8264.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within [redacted] after the final dose of GDC-8264

  Women of childbearing potential must have a negative serum pregnancy test result within [redacted] prior to initiation of GDC-8264. A negative urine pregnancy test result may be substituted if obtaining results from a serum pregnancy test would delay enrollment.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- QT interval corrected through use of Fridericia's formula (QTcF) > 500 ms demonstrated by at least two ECGs > 30 minutes apart

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis (i.e., [redacted] overall survival) or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately [redacted] after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

Patients will receive an oral dose of GDC-8264 once a day for approximately 28 days. Patients with PR, VGPR, or CR (as defined in Section 3.1.4 of the protocol) on Day 29 may receive an additional 28 days of treatment with GDC-8264 at the same dose level (for a total of 56 days) at the discretion of the investigator. *If necessary, a planned dose may be delayed for up to* [redacted] *per the investigator's clinical judgment.*

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Standard-of-care therapies with systemic corticosteroids are considered non-investigational medicinal products (NIMPs) for this study. Patients will receive standard-of-care high-dose corticosteroid treatment of prednisone ≥ 2 mg/kg/day PO or methylprednisolone ≥2 mg/kg/day intravenously (or equivalent) in divided doses initiated after aGVHD diagnosis and up to 3 days prior to Day 1. The dose of corticosteroids may not be tapered prior to study Day 3; thereafter, the corticosteroid tapering protocol (based on BMT CTN GVHD therapy studies) as outlined in the study protocol should be followed.

STATISTICAL METHODS

PRIMARY ANALYSIS

The co-primary objectives of this study are to evaluate the safety and pharmacokinetics of GDC-8264. The safety analysis population will consist of all patients who received at least one dose of GDC-8264, with patients grouped according to treatment received. The PK analysis population will consist of patients who have received at least one dose of GDC-8264 and have at least one evaluable postdose PK concentration.

DETERMINATION OF SAMPLE SIZE

This study is exploratory in nature. The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, PK, and efficacy data. A sample size of approximately 20 patients per dose cohort is believed to be clinically appropriate to assess the preliminary safety, pharmacokinetics, and efficacy in this initial study in patients with aGVHD and to inform future development of GDC-8264. The sample size calculation is not based on a statistical power consideration.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aGVHD	acute graft-versus-host disease
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
$AUC_{0-24\ hr}$	AUC from 0 to 24 hours
$AUC_{0-24\ hr,ss}$	AUC from 0 to 24 hours at steady state
AUC_{0-last}	AUC from Time 0 to last measurable concentration
AUC_{inf}	AUC from Time 0 to infinity
BMT	bone-marrow transplant
BMT CTN	Blood and Marrow Transplant Clinical Trial Network
CBR1	carbonyl reductase 1
C_{max}	maximum plasma concentration observed
$C_{max,ss}$	C_{max} at steady state
C_{min}	minimum plasma concentration under steady-state conditions within a dosing interval
$C_{min,ss}$	C_{min} at steady state
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CV	coefficient of variation
DAP	Data Analysis Plan
DCC	Data Coordinating Center
DOR	duration of response
DSMB	*Data and Safety Monitoring Board*
EC	Ethics Committee
EC_{90}	90% effective concentration level
eCRF	electronic Case Report Form
EDC	electronic data capture
ESMO	European Society for Medical Oncology
FDA	(U.S.) Food and Drug Administration
FFS	failure-free survival
GI	gastrointestinal
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
H antigen	histocompatibility antigen
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen

Abbreviation	Definition
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
KD	kinase dead
KLH	keyhole limpet hemocyanin
LPLV	last patient, last visit
MAD	multiple ascending dose
MAGIC	Mount Sinai Acute GVHD International Consortium
MAP	MAGIC algorithm probability
MDZ	midazolam
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer (cell)
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NR	no response
NRM	non-relapse mortality
ORR	*overall* response rate
OS	overall survival
PD	pharmacodynamic
PK	pharmacokinetic
PO	orally, by mouth
pop-PK	population-pharmacokinetic
PR	partial response
pRIP1	autophosphorylated receptor-interacting protein 1
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
REG3α	regenerating islet-derived 3-alpha
RIP1	receptor-interacting protein 1
SAD	single ascending dose
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
ST2	suppressor of tumorigenesis 2
$t_{1/2}$	elimination half-life

Abbreviation	Definition
t_{max}	time to maximum concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
USPI	U.S. Prescribing Information
VGPR	very good partial response
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON ACUTE GRAFT-VERSUS-HOST DISEASE

Acute graft-versus-host disease (aGVHD) is a common and life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT). aGVHD occurs in nearly 60% of patients receiving allogeneic HSCT (Jagasia et al. 2012) and aGVHD remains the second leading cause of death after disease relapse (Aziz et al. 2020).

Current understanding of aGVHD pathophysiology is based primarily on murine models (Naymagon et al. 2017; Zeiser and Blazar 2017). aGVHD occurs as a result of host (recipient) tissue damage caused by the underlying hematologic disease and associated treatments, infection, and the conditioning regimen (Ghimire et al. 2017). Damaged host tissues release signals, including proinflammatory cytokines, which activate host antigen-presenting cells (APCs). Conditioning regimen–mediated damage to the gastrointestinal (GI) tract allows translocation of microbes and microbial products that amplifies host APC activation and causes infection. Host APCs activate donor T cells that destroy healthy host tissue, resulting in aGVHD (Naymagon et al. 2017). Risk factors for developing aGVHD include degree of human leukocyte antigen (HLA) mismatch, relatedness of the donor, intensity of conditioning regimen, source of graft, and aGVHD prophylactic regimen (Zeiser and Blazar 2017).

The most common organs affected by aGVHD are the skin, liver, and GI tract (Zeiser and Blazar 2017). Lower GI aGVHD is the most difficult form of aGVHD to treat and is the greatest cause of GVHD-related morbidity and mortality (Naymagon et al. 2017). Signs and symptoms associated with aGVHD include rash, dermatitis, hepatitis, jaundice, abdominal pain, and diarrhea. Diagnosis of aGVHD depends on the clinical, laboratory, and pathologic assessment of target organs. The Mount Sinai Acute GVHD International Consortium (MAGIC) (Harris et al. 2016) provides a standardized approach to aGVHD clinical staging criteria and grading based on the Glucksberg scale (Glucksberg et al. 1974). Severity is categorized as Grade I–IV, depending on the degree of skin, GI and/or liver involvement, with Grade IV representing the most severe disease.

aGVHD treatment is tailored to address the severity of the presentation and management of symptoms. Initial treatment ranges from simple observation or topical corticosteroids for Grade I aGVHD presenting with skin symptoms or aGVHD limited to the upper GI tract (a subset of Grade II aGVHD), to systemic corticosteroid treatment for Grade II–IV aGVHD (Nassereddine et al, 2017; NCCN 2021). Corticosteroid treatment is continued for several weeks in responders and then gradually tapered over a period of months. Corticosteroid treatment, especially at higher doses and with prolonged duration of treatment, has many well-documented side effects, some of which may increase the risk of complications after HSCT and negatively impact non-relapse mortality (NRM) (Matsumura-Kimoto et al, 2016; Fuji et al. 2021; RAYOS U.S. Prescribing Information [USPI]; SOLU-MEDROL® USPI). Side effects include

osteoporosis, hypertension, adrenal suppression, cataracts, hyperglycemia and diabetes mellitus, avascular necrosis, and myopathy, and impaired neutrophil function and lymphocytopenia contributing to increased susceptibility to serious infection (Dignass et al. 2010, Matsumura-Kimoto et al. 2016; Fuji et al. 2021). Balancing immunosuppression to control aGVHD while maintaining a degree of immunocompetence against infection is critical (Hooker et al. 2021). In one Phase III study, after initiation of high-dose corticosteroids (prednisone 2 mg/kg/day or methylprednisolone 1.6 mg/kg/day) at the time of aGVHD diagnosis, 64.7% of patients experienced at least one infection through Day 56, and the cumulative incidence of a severe, life-threatening, or fatal infection at 12 months was 42.9% (95% CI: 33.9 to 52.0; p=0.83) (Bolaños-Meade et al. 2014). In a retrospective study in patients with Grade III–IV aGVHD, the cumulative dose of corticosteroids during the first 4 weeks of aGVHD treatment was associated with an increased risk of fungal disease (hazard ratio [HR]: 3.65; 95% CI: 1.17 to 11.4; p=0.03) and non-cytomegalovirus viral diseases (HR: 4.14; 95% CI: 1.25 to 13.7, p=0.02) (Matsumura-Kimoto et al. 2016). First-line treatments administered in addition to corticosteroids have been studied, including etanercept, mycophenolate, denileukin, and pentostatin (Alousi et al. 2009), infliximab (Couriel et al. 2009), and natalizumab (Kekre et al. 2021), but no treatment has established a significant benefit compared with standard first-line corticosteroid treatment alone.

Despite recent advances in aGVHD prevention that permit the use of highly HLA-mismatched donors, data from almost 4000 patients enrolled in the MAGIC Natural History Study (a database and biorepository that contains detailed longitudinal biomarker and clinical data prospectively obtained according to an Institutional Review Board–approved protocol at each MAGIC participating center) reveal that the percentage of patients requiring high-dose corticosteroids has not changed since 2015. Moreover, the incidence of severe (Grade III–IV) aGVHD remains high (13% in 2020), despite the dramatic increase in post-transplant cyclophosphamide prophylaxis from 9% to 22%. As a result, the incidence of NRM driven by aGVHD of the GI tract remains unacceptably high at 15% (Aziz et al. 2020).

A major barrier to improving aGVHD treatment is that aGVHD symptom severity (i.e., grade) at presentation does not reliably predict treatment response or long-term outcomes (Levine et al. 2015). Maximum aGVHD grade, which can be determined only retrospectively after response to treatment is known, does correlate with NRM (Przepiorka et al. 1995; Rowlings 1997). Thus, patients who present with mild to moderate (Grade I–II) clinical symptoms at time of diagnosis and have higher risk for severe disease are under-treated.

1.1.1 Background on Minnesota Risk Score

The Minnesota group has defined an aGVHD risk score based on the number of involved organs and severity of aGVHD at the time of initiation of corticosteroid therapy

(MacMillan et al. 2015; Macmillan et al. 2020), with staging determined through use of the MAGIC aGVHD Target Organ Staging criteria (see Appendix 4). The refined definition of high-risk aGVHD includes either single-organ involvement with Stage 4 skin, Stage 3–4 lower GI, or Stage 1–4 liver; or multiple-organ involvement with Stage 1–2 lower GI plus any liver, Stage 2 lower GI plus any skin, Stage 3–4 lower GI plus any liver or skin, or any three-organ involvement. Standard-risk aGVHD includes single-organ involvement (either Stage 1–3 skin or stage 1–2 GI) or two-organ involvement (either Stage 1 GI plus Stage 1–3 skin; or Stage 1–3 skin plus Stage 1–4 liver). In a large cohort of patients from multiple centers ($n = 1723$) from 1990 to 2007, overall response (complete response and partial response) rate 28 days after initiation of corticosteroid therapy for aGVHD was lower for the high-risk aGVHD population (44% [95% CI: 38% to 50%; $p < 0.001$]) compared with the standard-risk aGVHD population (68% [95% CI: 66% to 70%; $p < 0.001$]) (MacMillan et al. 2015). Patients with high-risk aGVHD were less likely to respond at Day 28 (odds ratio 0.3, 95% CI:0.2 to 0.4; $p < 0.001$) and had higher risks of mortality (relative risk 2.1, 95% CI: 1.7 to 2.6; $p < 0.001$) and transplant-related mortality (relative risk 2.5, 95% CI: 2.0% to 3.2%; $p < 0.001$) compared with patients with standard-risk aGVHD (MacMillan et al. 2015). The Minnesota risk score was validated in a more contemporary cohort from 2007 to 2016, confirming that patients with high-risk aGVHD, the proposed population for this study, were less likely to respond at Day 28 and had higher risk of 2-year transplant–related mortality and overall mortality than patients with standard-risk aGVHD (MacMillan et al. 2020). The Minnesota risk score represents a valuable tool to identify patients at high risk with standard care who stand to benefit from novel treatment approaches.

1.1.2 Background on MAGIC Algorithm Probability

MAGIC has recently introduced a major innovation in aGVHD treatment by validating a biomarker–based risk stratification system, referred to as the MAGIC algorithm probability (MAP) (Hartwell et al. 2017; Major-Monfried et al. 2018; Srinagesh et al. 2019; Aziz et al. 2020). MAP combines the concentrations of two serum biomarkers to separate patients into three distinct risk strata, referred to as Ann Arbor scores 1, 2, and 3, with each representing a single probability of 6-month NRM (Hartwell et al. 2017; Aziz et al. 2018, Zhao et al. 2018; Srinagesh et al. 2019) (see Appendix 3). The two serum biomarkers (together known as MAGIC biomarkers) are interleukin (IL)-33 receptor suppressor of tumorigenesis 2 (ST2) and regenerating islet-derived 3-alpha (REG3α). Lethal aGVHD almost always results from extensive damage to the GI crypt, which is the primary source of ST2 and REG3α, and the presence of GI crypt damage portends a worse outcome, even when GI symptoms are minimal or absent (Levine et al. 2013; Levine et al. 2015; Hartwell et al. 2017). Hence, serum concentrations of ST2 and REG3α measured after transplant can predict outcomes through use of MAP and the resulting Ann Arbor score (Ferrara et al. 2011; Zhang 2015; Ferrara and Chaudhry 2018).

1.2 BACKGROUND ON GDC-8264 AND RIP1

GDC-8264 is a small molecule reversible inhibitor of receptor-interacting protein 1 (RIP1; also known as RIP1 kinase and RIPK1). RIP1 is a broadly expressed serine-threonine kinase that has a crucial role in regulating cell death in several tissues, and as such, may play an important role in multiple diseases including GVHD. Importantly, RIP1 can bind to the intracellular domain of tumor necrosis factor (TNF) and may contribute to TNF signaling in some contexts (Newton 2020). Inhibition of RIP1 activity reduces inflammation and tissue damage across multiple disease models, including models in which TNF signaling may be implicated (Newton et al. 2016; Patel et al. 2020).

Nonclinical data indicate that inhibition of RIP1 provides protection from GVHD and confers a survival benefit as well as protection of intestinal crypts and stem cells (see Section 1.2.1). The RIP1 pathway has also been implicated in studies of the autophagy gene *ATG16L1,* which functions to prevent necroptosis in the intestinal epithelium (Matsuzawa-Ishimoto et al. 2017). Mice with *ATG16L1* deficiency in the intestinal epithelial cells have increased GVHD severity and mortality. Administration of a RIP1 inhibitor reduces GVHD severity and increases intestinal Paneth-cell and epithelial-cell survival in this model (Matsuzawa-Ishimoto et al. 2020).

Thus, interrupting RIP1 activity in humans to protect tissue at risk could be therapeutic in several disease settings, particularly those in which TNF-mediated cell death may play a role (Newton et al. 2016; Degterev at al. 2019; Newton 2020; Patel et al. 2020).

A non-immunosuppressive treatment for GVHD is desirable to preserve the graft-versus-tumor response and to limit the risk of life-threatening infections, which are a major cause of morbidity and mortality in patients who have undergone allogeneic HSCT. Importantly, RIP1 kinase dead (KD) knock-in mice and rats do not exhibit any immunosuppressive phenotype and die at a similar age to their wild type (WT) littermates (Newton et al. 2014; Webster et al. 2020; Stark et al. 2021), indicating that RIP1 inhibition may represent a non-immunosuppressive therapy (see Section 5.1.1.1).

Refer to the GDC-8264 Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Background

Inhibition of RIP1 activity reduces inflammation and tissue damage across multiple disease models, including GVHD. The role of RIP1 inhibition in nonclinical GVHD mouse models was investigated using a potent mouse-RIP1 inhibitor GNE684 (Patel et al. 2020) in two standard bone-marrow transplant (BMT) models of GVHD (major–histocompatibility [H]-antigen mismatch and minor–H-antigen mismatch, respectively) (Zhao et al. 2018). Daily administration of GNE684 75 mg/kg following BMT provided significant protection from GVHD both to major H antigens (~70% survival benefit) and minor H antigens (100% survival). In dose-response experiments in the minor–H-antigen model, lower doses of GNE684 (25 mg/kg and 5 mg/kg) afforded significant benefit and survival of 94% and 69% respectively for treated mice, relative to 35% survival for vehicle-dosed mice. Administration of GNE684 75 mg/kg also significantly improved survival when treatment of established GVHD began one week after BMT in a minor–H-antigen model.

Similarly, RIP1 inhibition through the selective and potent RIP1 inhibitor, Zharp1-211, has been shown to arrest GVHD and reduce inflammation in the GI tract without compromising the graft-versus-leukemia effect in GVHD mouse models. Mice undergoing allogeneic hematopoietic cell transplantation treated with daily Zharp1-211 (5 mg/kg) for 7 days showed higher survival compared to vehicle-dosed mice (Yu X et al. 2023).

A blinded, retrospective analysis was conducted of a collection of GI biopsy specimens. Specimens were from patients who had undergone HSCT and had a range of clinical outcomes as well as Lerner scores (a histologic index of severity of GVHD in the GI tract). Immunohistochemical staining utilized a phospho-S166 RIP1 antibody that recognizes autophosphorylated RIP1 (pRIP1), an indicator of RIP1 activation. The pRIP1 labeling was seen predominantly in the lamina propria, which is associated with immune cell infiltrates. The extent of RIP1 phosphorylation correlated with the histologic GVHD severity and predicted six-month NRM (62% vs. 12% NRM in patients with high (immunohistochemistry [IHC] score of 2 or 3) vs. low (IHC score of 0 or 1) pRIP1 staining, respectively, $p = 0.027$).

Overall, these studies demonstrate significant benefit of RIP1 inhibition in animal GVHD models and prominent RIP1 activation in tissue samples from patients with GVHD. Additional nonclinical pharmacology studies of GDC-8264 have provided supporting data that this compound blocks necroptotic cell death, inflammation, and tissue damage in vivo.

The relationship between efficacy (% survival) and exposure for GNE684 in the nonclinical dose-ranging study conducted in mouse GVHD models described earlier was extrapolated to GDC-8264. [redacted]

A comprehensive battery of nonclinical toxicology studies in rats and cynomolgus monkeys was completed to evaluate the potential single- and repeat-dose oral toxicity, genetic toxicity, phototoxicity, and safety pharmacology of GDC-8264.

[redacted]

[redacted]

GDC-8264 was not mutagenic or clastogenic in vitro and in vivo and is not considered to pose a genotoxic risk. GDC-8264 poorly absorbs ultraviolet and visible light and thus poses little phototoxicity risk.

Treatment with GDC-8264 up to the highest doses tested did not lead to significant alterations in T-, B-, or NK-cell populations in the 13-week GLP repeat-dose toxicology study in cynomolgus monkeys. Other RIP1 inhibitors with comparable potency against RIP1 did not affect T-, B-, or NK-cell viability or stimulation in vitro. In addition, GDC-8264 did not alter the IgG or IgM responses to keyhole limpet hemocyanin (KLH) challenge in monkeys and similarly, no alterations to KLH responses were noted in RIP1 KD mice (Webster et al. 2020). Host resistance models revealed no altered susceptibility of RIP1 KD mice to murine gamma herpes virus MHV68 or to vaccinia

virus (Western Reserve strain) (Webster et al. 2020). Taken together, data from multiple nonclinical studies clearly indicate the absence of immunosuppressive activity of GDC-8264 and other RIP1 inhibitors.

Refer to the GDC-8264 Investigator's Brochure for additional detail on nonclinical studies.

1.2.2 Clinical Background

The experience with GDC-8264 in humans consists of one Phase I study in healthy subjects (GP41678) and one Phase 1 study in subjects with kidney failure requiring dialysis and matched healthy controls (GP42995).

Study GP41678 is a first-in-human, single-center, randomized, double-blinded, placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics of oral GDC-8264 in healthy subjects. The single ascending dose (SAD) stage evaluated doses from 5 mg to 225 mg; the multiple ascending dose (MAD) stage evaluated 50 mg once a day (QD) and 100 mg QD for 14 days. The study also explored the effect of food on the pharmacokinetics of GDC-8264 and the CYP3A induction effect of GDC-8264.

GDC-8264 was well tolerated at all dose levels evaluated in Study GP41678. No individual or group stopping criteria were met; there were no deaths, no serious or severe adverse events, and no clinically significant laboratory, ECG, or vital sign findings related to GDC-8264. Treatment-related adverse events were generally of mild severity.

Pharmacokinetic (PK) analyses from the SAD portion of Study GP41678 indicate that GDC-8264 peak concentrations (C_{max}) were observed at 1.29–4.00 hours (median t_{max}) after the administration of GDC-8264 as single doses over the dose range from 5 mg to 225 mg. The geometric mean elimination half-life ($t_{1/2}$) after single-dose administration ranged from 10.4 to 13.3 hours over this dose range, indicating that once-daily dosing is appropriate and that the $t_{1/2}$ is independent of dose and formulation. Exposure parameters C_{max}, $AUC_{0\text{-}24\ hr}$, and AUC from Time 0 to infinity [AUC_{inf}]) for the tablet formulation at single doses of 75 mg, 150 mg, and 225 mg increased proportionally with dose. Inter-individual exposure variability is low to moderate and ranges from 6.70% to 52.9%. Under fed conditions, C_{max} is approximately 21% higher and median t_{max} increases from 3 to 4 hours, compared with fasted administration, but overall exposure ($AUC_{0\text{-}24\ hr}$ and AUC_{inf}) is comparable under fasted and fed conditions. Hence, GDC-8264 can be given without regard to food. Low renal excretion of unchanged GDC-8264 was observed at all doses (mean % of GDC-8264 dose excreted in urine of 0.16%–0.22%). Geometric mean renal clearance was similar for all doses and ranged from 0.00901 L/h after 5 mg of GDC-8264 to 0.0119 L/h after 75 mg of GDC-8264 (fed).

Estimated accumulation ratios in the MAD stage after multiple daily dosing of GDC-8264 at 100 mg and 50 mg were 1.41 and 1.37, respectively, based on C_{max} and 1.31 and 1.39, respectively, based on $AUC_{0\text{-}24\ hr}$, consistent with the estimated half-life. The

geometric mean (% coefficient of variation [CV]) terminal $t_{1/2}$ after the last 50 mg QD dose was 11.2 (12.2%) hours and after the last 100 mg QD dose was 11.4 (18.6%) hours, similar to the estimated geometric mean (% CV) terminal $t_{1/2}$ after single doses of 5 mg to 225 mg (11.2 hours [27.5%]–13.3 hours [18.0%]), indicating time-independent pharmacokinetics.

The CYP3A induction potential of GDC-8264 (at 100 mg QD) was evaluated by administration of a single dose of midazolam (MDZ) 5 mg, a sensitive CYP3A substrate, alone (on Day 1) and then co-administered (single dose of MDZ 5 mg on Day 10) with GDC-8264 after 8 days administration of GDC-8264 100 mg QD. Geometric mean AUC values for MDZ were approximately 20% lower after co-administration of MDZ with GDC-8264 than after MDZ administered alone. The geometric mean ratios (90% CIs) for AUC from Time 0 to last measurable concentration and AUC_{inf} of MDZ co-administered with GDC-8264 versus MDZ alone were 0.7957 (90%CI: 0.7278 to 0.8700) and 0.7920 (90%CI:0.7257 to 0.8645), respectively, indicating weak induction of CYP3A by GDC-8264 at a dose of 100 mg QD (a weak inducer being a drug that decreases the AUC of sensitive index substrates of a given metabolic pathway by $\geq$20% to $<$50%).

Study GP42995 is an ongoing open-label, single-dose, parallel-group study to determine the pharmacokinetics and safety of GDC-8264 administered at [redacted] in 8 male and female adult subjects with kidney failure on hemodialysis, compared with 8 adult subjects with normal renal function. Available safety data from this study show that GDC-8264 has been well tolerated, with no severe or serious adverse events reported and no clinically significant changes related to GDC-8264 in safety laboratory tests, ECGs, or vital signs.

Refer to the GDC-8264 Investigator's Brochure for additional detail on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study will evaluate treatment with GDC-8264, an oral inhibitor of RIP1 in combination with standard-of-care high-dose corticosteroid treatment in patients with high–risk aGVHD. GDC-8264 is a novel, non-immunosuppressive therapeutic agent that has the potential to improve clinical outcomes in patients with aGVHD, based on its mechanism of action and results from nonclinical studies. RIP1 inhibition may be particularly well suited for patients with aGVHD involving lower GI damage, as this patient population has a high treatment-failure rate and stands to benefit from novel treatment approaches. The primary aim of the study is evaluation of the relationship between GDC-8264 dose and safety, PK, and efficacy endpoints. Integrated analysis of those data will inform selection of the optimal dose for use in future efficacy studies. Exploratory biomarker data will also be considered (e.g., change in MAP).

Currently there are no identified adverse drug reactions associated with GDC-8264, and all doses evaluated in Study GP41678 have been well tolerated. Potential risks of

GDC-8264 based on nonclinical findings are increased risk of serious infections and seizures (see Section 5.1.1). Risk-mitigation measures in this study include the following: exclusion of patients with uncontrolled active infections and patients who may be at higher risk for seizures (see Section 4.1.2); regular monitoring of adverse events, clinical and laboratory assessments; [redacted], including seizures and NRM (see Section 3.1.2); and postdose neurologic examinations at selected visits (see Appendix 1). Patients who experience a seizure will be discontinued from GDC-8264 (see Section 4.6.1). Management guidelines for the investigator have been provided for specified adverse events or abnormal safety laboratory findings (see Section 5.1.2.3). In addition, an independent *Data and Safety Monitoring Board (DSMB)* will review safety and available PK data periodically for early identification of potential new safety signals and to determine if continued patient enrollment is permitted (Section 3.1.3).

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with significant comorbidities, including those with aGVHD, are vulnerable and susceptible to the disease. Patients with aGVHD are immunocompromised and are usually receiving several immunosuppressant drugs including corticosteroids, tacrolimus, and potentially other immunocompromising drugs. An assessment has been conducted to determine the potential impact of the COVID-19 pandemic on the benefit-risk assessment of this study, taking into account the patient population under study and study treatment being evaluated. The safety monitoring, adverse event management guidelines, eligibility criteria, and risk-mitigation measures provided in the study are considered adequate to conduct the study during the COVID-19 pandemic. Investigators should manage severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the same way as infections caused by any other pathogen as per local guidelines.

Taking into consideration the results from nonclinical safety and efficacy studies, the safety profile of GDC-8264 in the first-in-human study, the risk-mitigation measures provided for this study, and the unmet need of this proposed patient population, the benefit-risk profile of GDC-8264 is considered favorable and supports further clinical development.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and efficacy of GDC-8264 given in combination with standard-of-care corticosteroid treatment in patients with high-risk aGVHD. The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, PK, and efficacy data. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study drug" refers to GDC-8264; "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., GDC-8264 and corticosteroids).

Table 1 Objectives and Corresponding Endpoints

Co-Primary Objectives	Corresponding Endpoint
• To evaluate the safety of GDC-8264	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale
• To characterize the pharmacokinetics of GDC-8264	• Plasma concentration of GDC-8264 at specified timepoints, and relevant PK parameters
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of GDC-8264	• ORR, defined as the proportion of patients with a CR, VGPR, or PR on Day 29 with no intervening additional line of aGVHD therapy, as determined by the investigator [a] • DOR, defined as the time from response (CR, VGPR or PR) on Day 29 to aGVHD progression from nadir in any organ, new systemic therapy for aGVHD, or death from any cause (whichever occurs first), as determined by the investigator [a] • Cumulative incidence of aGVHD flares by Day 56 • Cumulative incidence of NRM by Day 180

aGVHD = acute graft-versus-host disease; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; DOR = duration of response; FFS = failure-free survival; MAP = Mount Sinai Acute GVHD International Consortium [MAGIC] algorithm probability; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NRM = non-relapse mortality; ORR = *overall* response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; VGPR = very good partial response.

[a] Responses are determined by the investigator. See Section 3.1.4 for key definitions and details on response criteria.

[b] Baseline defined as last value prior to initiation of GDC-8264.

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the efficacy of GDC-8264	• Time from initiation of GDC-8264 to first response (i.e., CR, VGPR, or PR) • [redacted] • FFS rate at [redacted] • Cumulative incidence of chronic GVHD by [redacted] • Cumulative incidence of relapse of underlying malignancy by [redacted] • OS rate at [redacted] defined as the proportion of patients who have not experienced death from any cause at [redacted] • Proportion of patients with maximum Grade III or IV aGVHD by [redacted] • Cumulative corticosteroid dose at [redacted]
• To evaluate the safety of GDC-8264 with respect to infection adverse events	• Incidence and severity of infection adverse events, with severity determined according to the BMT CTN infection severity grading scale
• To evaluate potential relationships between drug exposure and the efficacy and safety of GDC-8264	• Relationship between plasma concentration or PK parameters for GDC-8264 and efficacy endpoints • Relationship between plasma concentration or PK parameters for GDC-8264 and safety endpoints
• To identify and/or evaluate biomarkers that are predictive of response to GDC-8264 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to GDC-8264, can provide evidence of GDC-8264 activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology or pharmacokinetics	• Relationship between levels of circulating biomarkers and efficacy endpoints • Relationship between biomarkers in tissue (pending availability) and efficacy endpoints • Relationship between levels of biomarkers and plasma concentration or PK parameters • Change from baseline [b] in MAP at [redacted]

aGVHD = acute graft-versus-host disease; BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; DOR = duration of response; FFS = failure-free survival; MAP = Mount Sinai Acute GVHD International Consortium [MAGIC] algorithm probability; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NRM = non-relapse mortality; ORR = *overall* response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; VGPR = very good partial response.

[a] Responses are determined by the investigator. See Section 3.1.4 for key definitions and details on response criteria.

[b] Baseline defined as last value prior to initiation of GDC-8264.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase Ib, open-label, randomized, dose-finding, multicenter study designed to evaluate the safety, pharmacokinetics, and efficacy of GDC-8264 given in combination with standard-of-care corticosteroid treatment in patients with high-risk aGVHD who have undergone one allogeneic HSCT. The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, PK, and efficacy data. The study will enroll approximately 40 patients, who will be randomized in a 1:1 ratio to one of two GDC-8264 dose cohorts (35 mg QD and 75 mg QD) at approximately *20 sites* in the United States *and Canada*. If necessary, additional patients may be enrolled to ensure that at least 12 patients per cohort have received at least 10 doses of GDC-8264 within the [redacted] of the treatment period.

The study consists of a screening period of up to [redacted] following initial diagnosis of aGVHD, a treatment period of 28 days, an optional treatment extension period of 28 days, a post-treatment safety follow-up period for [redacted] and a long-term follow-up period through approximately [redacted] days after initiation of GDC-8264 (see Figure 1).

Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will maintain a record of reasons for screen failure (see Section 4.5.1).

Patients will receive standard-of-care high-dose corticosteroid treatment as outlined below:

- Prednisone ≥2 mg/kg/day by mouth (PO) or methylprednisolone ≥2 mg/kg/day intravenously (or equivalent) in divided doses initiated after aGVHD diagnosis and up to 3 days prior to Day 1. *See Section 4.5.1 for additional details.*

  Patients who demonstrate a significant improvement in aGVHD severity between screening and the Day 1 severity assessment may be discontinued from the study (prior to initiation of GDC-8264 treatment) at the discretion of the investigator and replaced.

  In exceptional cases of administrative delays or other logistical reasons (i.e., due to the potential participant's health insurance provider[s] issues, screening of a patient during weekends, or extended holidays), a patient who has received systemic corticosteroids up to [redacted] prior to initiation of GDC-8264 (Day 1), may be enrolled, provided that the patient is not experiencing worsening of aGVHD. The MAGIC Principal Investigator and Medical Monitor are available to advise as needed. The investigator will maintain a record of reasons for the delay in enrollment.

Patients will also receive oral treatment with GDC-8264, randomly assigned at a dose of either 35 mg QD or 75 mg QD and administered on Days 1–28. At the investigator's discretion, patients with PR, very good partial response (VGPR), or CR (as defined in Section 3.1.4) on Day 29 may receive an additional 28 days of treatment with GDC-8264 at the same dose level and administered QD on Days 29–56. Patients who receive fewer than 10 doses of GDC-8264 within the [redacted] of the treatment period due to noncompliance, voluntary withdrawal, or reasons other than safety or (lack of) efficacy will be discontinued from GDC-8264 and the study. These patients will be replaced (see Section 4.6.2).

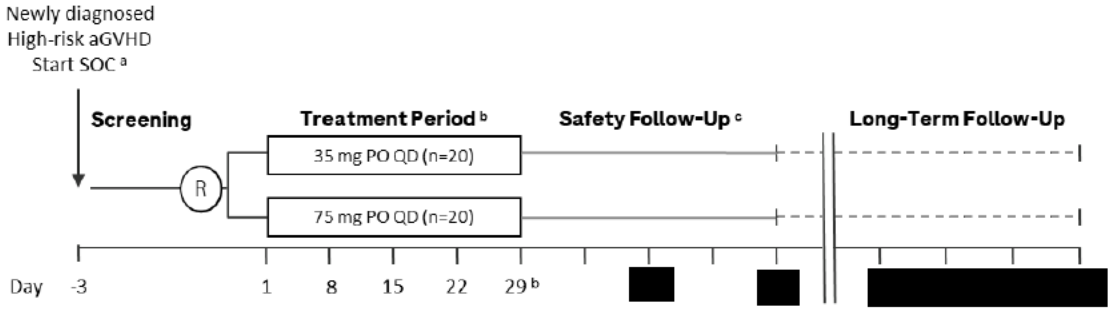
Blood samples will be obtained from all patients for PK and biomarker assessments as specified in Appendix 2. Residual samples from biopsies of involved aGVHD target organs (e.g., skin, GI tract) obtained as part of standard of care up to 2 weeks prior to enrollment or during the study will be provided to the Sponsor for exploratory biomarker research after the samples are no longer needed for patient clinical care. Biopsy of involved aGVHD target organs consistent with institutional guidelines is encouraged but is not required for this study, and enrollment should not be delayed for biopsy and pathology results.

Patient safety will be monitored on a regular basis by the MAGIC Principal Investigator, the Sponsor, and the $DSMB$ (see Section 3.1.3) through assessment of the nature, frequency, and severity of adverse events, available PK data, and other relevant clinical data.

Patients will be assessed for organ-specific aGVHD stage, aGVHD flare, treatment response and duration of response, primary disease relapse and progression, and survival during the study and for approximately one year after initiation of GDC-8264. For patients who meet the criteria for corticosteroid-refractory aGVHD (see Section 3.1.4.5) after enrollment, initiation of any second-line therapy will require discontinuation of GDC-8264.

Figure 1 presents an overview of the study schedule. A detailed schedule of activities is provided in Appendix 1. The schedule for PK and exploratory biomarker sample collection is provided in Appendix 2.

Figure 1 Study Schema



aGVHD = acute graft-versus-host disease; CR = complete response; PO = by mouth; PR = partial response; QD = once a day; R = randomization; SOC = standard of care; VGPR = very good partial response.

[a] SOC treatment defined as high-dose corticosteroid treatment (see Section 4.3.1.2).

[b] At the investigator's discretion, patients with PR, VGPR, or CR (as defined in Section 3.1.4) on Day 29 may receive an additional 28 days of treatment with GDC-8264 at the same dose level and administered QD on Days 29–56.

[c] For patients who undergo optional treatment extension, safety follow-up visits will occur at [redacted]

[redacted]

[redacted]

[redacted]

3.1.3 *Data and Safety Monitoring Board*

The *DSMB* for this study will consist of members of the Tisch Cancer Institute Data and Safety Monitoring Committee. The *DSMB* is external to the study and will be responsible for assessing the safety of GDC-8264 and monitoring the progress and overall conduct of the study.

The *DSMB* will review study conduct, all available PK data, and all available safety data from patients during the adverse event reporting period (as defined in Section 5.3.1). The first *DSMB* review will occur after the first 6 patients (total) enrolled in the study have completed the [redacted] assessments or [redacted] after the first patient is enrolled, whichever is earlier, and thereafter approximately [redacted]

Details on the *DSMB* will be provided in the *DSMB* Charter.

3.1.4 Key Definitions in the Study

Unless otherwise specified, patient fulfillment of the following response criteria is determined by the investigator.

3.1.4.1 Complete Response

Complete response (CR) is defined as all target organs (skin, liver, upper GI tract, and lower GI tract) evaluated as MAGIC aGVHD Stage 0 (see Section 4.5.6). For a response to be evaluated as CR, the patient must be in CR on the study day that response is evaluated and have had no intervening additional line of aGVHD therapy (as defined in Section 3.1.4.10).

3.1.4.2 Very Good Partial Response

Very good partial response (VGPR) is defined as resolution of signs and symptoms of aGVHD, as indicated by meeting all of the following criteria:

- Skin: no rash, or residual erythematous rash involving <25% of the body surface, without bullae (residual faint erythema and hyperpigmentation are excluded)
- Liver: total serum bilirubin concentration <2 mg/dL or <25% of baseline at screening
- GI tract (all of the following): a) toleration of food or enteral feeding; b) predominantly formed stools; c) no overt gastrointestinal bleeding or abdominal cramping; d) no more than occasional nausea or vomiting

For a response to be evaluated as VGPR, the patient must be in VGPR on the study day that response is evaluated and have had no intervening additional line of aGVHD therapy (as defined in Section 3.1.4.10).

3.1.4.3 Partial Response

Partial response (PR) is defined as improvement in one or more target organs (skin, liver, upper GI tract, and lower GI tract) involved with aGVHD symptoms without worsening in others. For a response to be scored as PR, the patient must be in PR on the study day that response is evaluated and have had no intervening additional line of aGVHD therapy (as defined in Section 3.1.4.10).

3.1.4.4 No Response

No response (NR) includes all responses that are not CR, VGPR or PR. Patients who receive any aGVHD therapy other than corticosteroid treatment, GDC-8264, non-absorbable oral corticosteroid therapy, or topical corticosteroids will be scored as NR on [redacted], regardless of organ staging.

3.1.4.5 Corticosteroid-Refractory Acute Graft-versus-Host Disease

Corticosteroid-refractory aGVHD is defined as meeting any of the following criteria:

- No response within [redacted] of initiation of corticosteroid treatment
- Initiation of additional lines of aGVHD therapy beyond corticosteroids
- Increase in aGVHD symptoms during a corticosteroid taper requiring initiation of additional line of therapy

3.1.4.6 Acute Graft-versus-Host Disease Flare

aGVHD flare is defined as an increase in aGVHD target organ stage by at least one stage for at least 3 days that requires either addition of a new line of systemic treatment or increase in corticosteroid dose >0.25 mg/kg/day.

3.1.4.7 Primary Disease Relapse or Progression

Primary disease relapse is defined as evidence of recurrent acute leukemia, myelodysplastic syndrome, or lymphoma per standard clinical, hematopathologic, and/or radiologic assessments (as indicated for primary disease). Primary disease progression applies to patients with lymphoproliferative diseases (lymphoma or chronic lymphocytic leukemia) not in remission prior to transplantation. The event is defined as increase in size of prior sites of disease or evidence of new sites of disease, documented or not by biopsy. See Appendix 6 for additional information.

3.1.4.8 Non-Relapse Mortality

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

3.1.4.9 Chronic Graft-versus-Host Disease

Chronic GVHD is defined through use of the National Institutes of Health consensus criteria regarding systemic treatment (see Section 4.5.7 and Appendix 5).

3.1.4.10 Line of Graft-versus-Host Disease Therapy

Any new systemic aGVHD therapy will be considered a line of therapy. New systemic therapy is considered to be new systemic treatment for aGVHD or an increase in the dose of corticosteroids to methylprednisolone ≥ 2 mg/kg/day (or equivalent).

Resumption or changes in GVHD prophylaxis, including substitutions of prophylaxis agents due to toxicities, are not considered new lines of therapy.

3.1.4.11 Duration of Response

Duration of response is defined as the time from response (CR, VGPR, or PR) on Day 29 to aGVHD progression from nadir in any organ, new systemic therapy for aGVHD, or death from any cause (whichever occurs first).

3.1.4.12 Failure-Free Survival Rate

Failure-free survival is defined as proportion of patients who are still alive, have not relapsed, have not required additional lines of therapy for aGVHD, and have not demonstrated signs or symptoms of chronic GHVD.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis (i.e., [redacted] OS) or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately [redacted] after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for GDC-8264 Dose and Schedule

The proposed study design includes administration of once-daily doses of GDC-8264 35 mg or 75 mg on Days 1–28. As detailed below, these doses are predicted to be safe and potentially efficacious in patients with aGVHD, provide robust target engagement ex vivo, and are sufficiently distinct in predicted PK exposures. The 28-day treatment period was selected on the basis of the observation that ORR at 4 weeks is similar to response at Day 56 and predicts 2-year transplant-related mortality (MacMillan et al. 2010).

3.3.1.1 Safety Margins

A preliminary population PK (pop-PK) model was used to simulate steady-state PK exposures for the proposed dosing regimens of 35 mg QD and 75 mg QD (see discussion below on pharmacokinetics and Table 5). The safety margins of these exposures to the NOAEL and the NOEL are presented in Table 4. Given the low inter-individual PK variability seen thus far, the acceptable safety profile demonstrated in healthy subjects and subjects with kidney failure on dialysis, and the benefit-risk assessment for patients with high-risk aGVHD, these margins are considered acceptable.

Table 4 Predicted Safety Margins for Planned Doses

Dose and Frequency	Exposure Safety Margins based on NOAEL [a]		Exposure Safety Margins based on NOEL [b]	
	$C_{max,ss}$ Ratio [c]	$AUC_{0–24\ hr,ss}$ Ratio [d]	$C_{max,ss}$ Ratio [c]	$AUC_{0–24\ hr,ss}$ Ratio [d]
35 mg QD	[redacted]			
75 mg QD				

[redacted]

As outlined in Section 1.2.2, in both Studies GP41678 and GP42995, no dose-limiting toxicities or individual stopping criteria were met, and no drug-related risks were identified.

No maximum tolerable dose was identified in Study GP41678, and significantly higher doses of GDC-8264 than those proposed for this study (both a single dose of 225 mg and daily doses of 100 mg for 14 days) were found to be safe and well-tolerated. At the highest tested single dose of 225 mg, the cohort mean C_{max} was 1830 ng/mL and $AUC_{0–24\ hr}$ was 31,600 ng • hr/mL. Following multiple doses of 100 mg QD (highest tested dose in the 14-day MAD stage), the cohort mean $C_{max,ss}$ was 1670 ng/mL and $AUC_{0–24\ hr,ss}$ was 21,200 ng • hr/mL. [redacted]

3.3.1.2 Pharmacokinetics

A preliminary two compartment pop-PK model with first-order absorption and first-order elimination was developed using the PK data from the SAD and MAD cohorts from Study GP41678 and adequately describes the available PK data (n=40; observed concentrations=873). The model was used to simulate the steady-state PK profiles after administration of GDC-8264 35 mg and 75 mg. As shown by the simulated PK parameters presented in Table 5, the predicted exposures are reasonably well separated.

Table 5 Simulated Arithmetic Mean (%CV) Steady-State PK Parameters for the Planned Doses

Dose and Frequency	$C_{max,ss}$ Mean (%CV)	$AUC_{0-24\ hr,ss}$ Mean (%CV)	$C_{min,ss}$ Mean (%CV)
35 mg QD	[redacted]		
75 mg QD			

$AUC_{0-24\ hr,ss}$=area under the concentration–time curve from 0 to 24 hours at steady state; $C_{max,ss}$=maximum concentration at steady state; $C_{min,ss}$=minimum concentration at steady state; CV=coefficient of variation.

[redacted]

[redacted]

[redacted]

In summary, based on existing data and analysis, the proposed randomized dosing regimens of 35 mg QD and 75 mg QD provide an adequate safety margin and PK exposure separation to explore the PK, safety, and efficacy objectives in this Phase Ib dose-finding study in patients with high-risk aGVHD.

3.3.2 Rationale for Patient Population

aGVHD remains a life-threatening complication of allogeneic HSCT. Based on its mechanisms of action and nonclinical efficacy data in animal models of GVHD (see Section 1.2.1), treatment with the RIP1-inhibitor GDC-8264 has the potential to improve clinical response in patients with aGVHD. Although RIP1 inhibition may confer benefit to a broad aGVHD population, Grade I aGVHD (limited skin rash) and aGVHD limited to the upper GI tract (a subset of Grade II aGVHD) are often not treated with systemic corticosteroids and thus are not appropriate for inclusion in this study. This study will test the hypothesis that RIP1 inhibition with GDC-8264, when added to systemic corticosteroid treatment, will improve the clinical response in patients with high-risk aGVHD.

As outlined in Section 1.1.1, the Minnesota risk score at the onset of aGVHD treatment with corticosteroids identifies patients who are less likely to respond at [redacted] and have higher mortality (MacMillan et al. 2015; MacMillan et al. 2020). Patients with high-risk GVHD were less likely to respond at [redacted] (odds ratio 0.3, 95% CI:0.2 to 0.4; $p < 0.001$) and had higher risks of mortality (relative risk 2.1, 95% CI: 1.7 to 2.6; $p < 0.001$) and transplant-related mortality (relative risk 2.5, 95% CI: 2.0% to 3.2%; $p < 0.001$) compared with patients with standard-risk GVHD (MacMillan et al. 2015).

Patients who have high-risk aGVHD as determined by Minnesota risk score will be enrolled in this study. These patients have a poor prognosis and stand to benefit from novel treatment approaches.

Enrollment of patients with high-risk aGVHD is not expected to generate additional patient risk, as the risk score is not anticipated to correlate with increased safety risk or reduced efficacy to treatment with GDC-8264. Moreover, as GDC-8264 is being developed as an add-on therapy, all study patients will receive current, approved standard-of-care therapies (with the exception of prohibited therapies outlined in

Section 4.4.3). Participation in the study will not delay patient treatment and/or expose patients to any excessive safety risks.

3.3.3 Rationale for Biomarker Assessments

Blood samples will be collected and residual tissue samples will be obtained for exploratory pharmacodynamic (PD) biomarker assessments. These assessments will be used to demonstrate evidence of biologic activity of GDC-8264, to advance the understanding of the mechanism of action of GDC-8264, and to increase the knowledge and understanding of disease biology. As the biomarkers collected may also have prognostic value, their potential association with disease progression may also be explored.

Serum biomarker samples will be collected at screening and during the study for measurement of MAGIC biomarkers ST2 and REG3α for retrospective exploratory biomarker analysis of a high-risk cohort predefined by Ann Arbor score (see Section 1.1.2 and Appendix 3) (Srinagesh 2019).

3.3.4 Rationale for Pharmacokinetic Assessments

This study is the first in which GDC-8264 is given to patients with aGVHD. PK sampling will be performed in all patients to assess variability in GDC-8264 exposure and effects of covariates on the pharmacokinetics of GDC-8264 to inform future dosing of GDC-8264 in the aGVHD patient population.

In addition, because of the varied pathophysiology of aGVHD and the dynamic nature of aGVHD progression, intrapatient variability in GDC-8264 pharmacokinetics will be assessed using intensive PK sampling o [redacted] If the PK profile of GDC-8264 for these patients differs from that previously observed in healthy subjects, PK sampling timepoints may be changed for subsequent patients (with no change in the total number of PK samples).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 40 patients will be enrolled in this study and receive open-label treatment with GDC-8264.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form from the patient or legal representative
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- Diagnosis of post–allogeneic HSCT aGVHD at screening, with the following aspects of HSCT permissible:
  - Any malignant or non-malignant indication leading to HSCT
  - Any HSCT donor type (e.g., related, unrelated) or stem cell source (i.e., bone marrow, peripheral blood, cord blood)
  - Any GVHD prophylaxis regimen
  - Any conditioning regimen (i.e., myeloablative, reduced intensity, and non-myeloablative)
- Evidence of engraftment post-transplant, as indicated by the following values: ANC $\geq 500/\mu L$ ($0.5 \times 10^9/L$) and platelet count $\geq 10{,}000/\mu L$ ($100 \times 10^9/L$)

  ANC and platelet counts may be repeated once during screening.

  Use of growth-factor supplementation to maintain neutrophil count is allowed.

  If platelet-transfusion refractoriness is suspected, platelet count will be measured approximately 1 hour after transfusion.
- Diagnosis of high-risk aGVHD, defined as meeting any <u>one</u> criterion from either of the following sets of refined Minnesota high-risk aGVHD criteria during screening, with staging determined through use of MAGIC aGVHD Target Organ Staging: (see Appendix 4)
  - Single-organ involvement

    Stage 4 skin

    Stage 3–4 lower GI

    Stage 1–4 liver
  - Multiple-organ involvement

    Stage 1–2 lower GI plus any liver

    Stage 2 lower GI plus any skin

    Stage 3–4 lower GI plus any liver or skin

    Any three-organ involvement
- Initiation of treatment with systemic corticosteroids for aGVHD at a dose of prednisone ≥ 2 mg/kg/day PO or methylprednisolone ≥ 2 mg/kg/day intravenously (or equivalent) in divided doses at diagnosis and up to 3 days prior to or on the same day as initiation of GDC-8264 (Day 1), with no taper planned prior to Day 3

  As clinically indicated, corticosteroid treatment may be initiated at a lower dose and increased on Day 1 to the doses specified above.

In exceptional cases of administrative delays or other logistical reasons (i.e., due to the potential participant's health insurance provider[s] issues, screening of a patient during weekends, or extended holidays), a participant who has received systemic corticosteroids up to [redacted] *prior to initiation of GDC-8264 (Day 1), may be enrolled, provided that the participant is not experiencing worsening of aGVHD. The MAGIC Principal Investigator and Medical Monitor are available to advise as needed. The investigator will maintain a record of reasons for the delay in enrollment.*

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for [redacted] after the final dose of GDC-8264.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for [redacted] after the final dose of GDC-8264 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of relapsed, progressing, or persistent malignancy, or treatment for relapse after transplant, or requirement for rapid immune suppression withdrawal as preemergent treatment of early malignancy relapse
- Prior receipt of more than one allogeneic HSCT
- *Prior receipt of solid organ transplantation that are target organs for aGVHD (e.g., liver transplant)*
- Prior systemic treatment for aGVHD, except for the standard-of-care corticosteroid treatment initiated as part of this trial (see Section 4.3.2.2)

  Topical skin corticosteroid treatment and non-absorbable oral corticosteroid treatment for GI aGVHD are permissible.
- Diagnosis of chronic GVHD or overlap syndrome
- Uncontrolled active infection (i.e., progressive symptoms related to infection despite treatment, or persistently positive blood cultures despite treatment, or any other evidence of severe sepsis)

  Persistent fever without signs or symptoms will not be interpreted as an uncontrolled active infection.

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).
- Severe organ dysfunction (e.g., acute liver failure, renal failure requiring dialysis, ventilator support, or vasopressor therapy)
- Direct bilirubin >2 mg/dL within 3 days prior to initiation of GDC-8264 unless the elevation is due to Gilbert syndrome or aGVHD
- ALT/SGPT and AST/SGOT $>5\times$ the upper limit of normal (ULN) within [redacted] prior to initiation of GDC-8264, unless due to aGVHD

- Creatinine clearance or estimated glomerular filtration rate < 30 mL/min as calculated by institutional practice (e.g., Cockcroft-Gault equation, CKD-EPI equation)
- Treatment with an investigational small molecule therapy within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264

  An investigational therapy is defined as a drug that has not been approved or authorized by the U.S. Food and Drug Administration for any use.
- Treatment with an investigational biologic therapy (e.g., monoclonal antibody) within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264, unless the investigator determines, after consultation with the MAGIC Principal Investigator and the Medical Monitor, that the treatment would not interfere with patient safety or achievement of study objectives
- Initiation or planned use of a marketed small molecule (excluding corticosteroids) or biologic therapy as treatment for aGVHD from the start of screening through the treatment period
- History of seizure or convulsions, except history of childhood febrile seizures
- Higher risk of seizure, as determined by the investigator (including, but not limited to, history of stroke; known Alzheimer's disease or non-Alzheimer's dementia; structural brain disease including arteriovenous malformations or other mass lesions; clinical diagnosis of traumatic brain injury or concussion within previous 6 months)

  Patients with mass lesion on brain imaging with evidence of vasogenic edema are excluded.

  Patients on concomitant medications known to increase the risk of seizure may continue taking those medications, provided they have not previously experienced a seizure at or below the dose level being administered prior to initiation of GDC-8264.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within [redacted] after the final dose of GDC-8264

  Women of childbearing potential must have a negative serum pregnancy test result within [redacted] prior to initiation of GDC-8264. A negative urine pregnancy test result may be substituted if obtaining results from a serum pregnancy test would delay enrollment.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- QT interval corrected through use of Fridericia's formula (QTcF) > 500 ms demonstrated by at least two ECGs > 30 minutes apart

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is an open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number from the MAGIC Data Coordinating Center (DCC) and treatment assignment through a central interactive voice or web-based response system (IxRS). Patients will be randomly assigned in a 1:1 ratio to GDC-8264 treatment cohorts using permuted block randomization.

The patient, investigator, site personnel, $DSMB$, and Sponsor will be unblinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is GDC-8264.
Standard-of-care therapies with systemic corticosteroids as described in Section 4.3.2.2 are considered non-investigational medicinal products (NIMPs).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 GDC-8264

GDC-8264 will be supplied by the Sponsor as [redacted], and 75 mg [redacted] tablets. For information on the GDC-8264 formulation, see the pharmacy manual and the GDC-8264 Investigator's Brochure.

4.3.1.2 Standard-of-Care Corticosteroid aGVHD Treatment

Standard-of-care corticosteroid aGVHD treatment (prednisone or methylprednisolone) will be provided by the site. For information on the formulation and packaging of prednisone and methylprednisolone, see the local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.1.

Details on treatment administration (e.g., dose and timing) should be noted on the electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for GDC-8264 treatment interruption or discontinuation for patients who experience adverse events are provided in Sections 5.1.2.2 and 4.6.1, respectively.

4.3.2.1 GDC-8264

Patients will receive an oral dose of GDC-8264 once a day for 28 days. Patients with PR, VGPR, or CR (as defined in Section 3.1.4) on Day 29 may receive an additional

28 days of treatment with GDC-8264 at the same dose level (for a total of 56 days) at the discretion of the investigator. GDC-8264 should be taken at approximately the same time each day, with or without food. *If necessary, a planned dose may be delayed for up to* [redacted] *per the investigator's clinical judgment.* The tablets should be swallowed whole and should not be crushed, broken, or chewed prior to swallowing. If a dose of GDC-8264 is missed ([redacted]) or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose (i.e., the next day).

For patients who are hospitalized, the investigator will maintain a record of dosing time. For patients who are not hospitalized or for patients following discharge, any doses not yet taken will be self-administered on an outpatient basis. To assess patient compliance with self-administration of GDC-8264, patients will be required to record the time and date of each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring their bottles of GDC-8264 and medication diaries to each study visit.

On days that PK sampling is required, patients should be instructed to not take GDC-8264 at home. On these PK sampling days, GDC-8264 dosing should occur after all predose assessments are completed to ensure accurate timing of the *dosing time and* PK sampling *times*.

4.3.2.2 Standard-of-Care Corticosteroid aGVHD Treatment

All patients enrolled in the study will receive standard-of-care treatment with systemic corticosteroids. Corticosteroid treatment may be initiated up to [redacted] prior to Day 1. Eligible patients must be receiving prednisone ≥2 mg/kg/day PO or methylprednisolone ≥2 mg/kg/day intravenously (or equivalent) in divided doses on Day 1 (see Section 4.1.1). The dose of corticosteroids may not be tapered prior to study Day 3; thereafter, the corticosteroid tapering protocol (based on BMT CTN GVHD therapy studies) described below should be followed:

- 2 mg/kg/day divided once or twice/day on Days 2–7
- 1.5 mg/kg/day QD on Days 8–14
- 1 mg/kg/day QD on Days 15–22
- 0.5 mg/kg/day QD on Days 23–29

In exceptional cases of administrative delays or other logistical reasons (i.e., due to the potential participant's health insurance provider[s] issues, screening of a patient during weekends, or extended holidays), a participant who has received systemic corticosteroids up to [redacted] *prior to initiation of GDC-8264 (Day 1), may be enrolled, provided that the participant is not experiencing worsening of aGVHD. The MAGIC Principal Investigator and Medical Monitor are available to advise as needed. The investigator will maintain a record of reasons for the delay in enrollment.*

Patients should be tapered, as tolerated, to no less than 0.5 mg/kg/day, in the absence of corticosteroid toxicity requiring a lower dose. After [redacted], taper should proceed according to institutional guidelines, with a goal to reach ≤0.2 mg/kg/day of prednisone or ≤0.16 mg/kg/day of methylprednisolone by [redacted].

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug accountability log.

Refer to the pharmacy manual and/or the GDC-8264 Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to GDC-8264

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (GDC-8264) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue

providing GDC-8264 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from [redacted] prior to initiation of GDC-8264 through the safety follow-up period, unless otherwise indicated.

Standard-of-care corticosteroid aGVHD treatment will be reported from up to 3 days prior to initiation of GDC-8264 through study [redacted].

All such medications should be reported to the investigator and recorded on the concomitant medication eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Growth-factor supplementation to maintain neutrophil count
- GVHD prophylaxis medications

  Marketed small molecule or biologic therapy (such as cyclosporine, tacrolimus, sirolimus, mycophenolate, or methotrexate) if used as GVHD prophylaxis and initiated prior to screening should be continued at therapeutic doses (according to institutional standards) and adjusted as necessary (e.g., for renal, CNS, or other toxicity or intolerance) using conventional management guidelines.
- Topical and ancillary aGVHD therapies

  Topical therapy for aGVHD of the skin and non-absorbable oral corticosteroids for GI aGVHD are allowed.

  Ancillary/supportive care measures for aGVHD such as the use of anti-motility agents for diarrhea, including octreotide, are allowed at the discretion of the treating physician. Use of ursodiol to prevent or reduce gall bladder sludging or prevent hepatic transplant complications is also allowed according to institutional guidelines.
- Medications known to increase the risk of seizure (e.g., tacrolimus), provided the patient has not previously experienced a seizure at or below the dose level being administered prior to initiation of GDC-8264

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

[redacted]

[redacted]

[redacted]

The investigator should contact the MAGIC Principal Investigator and the Medical Monitor if questions arise regarding such medications.

Refer to the following for the list of common CYP inhibitors, inducers, and substrates. (FDA) Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational small molecule therapy is prohibited within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264 through the safety follow-up period.

  An investigational therapy is defined as a drug that has not been approved or authorized by the U.S. Food and Drug Administration for any use.

- Investigational biologic therapy is prohibited within [redacted] drug elimination half-lives, whichever is longer, prior to initiation of GDC-8264 through the safety follow-up period, unless the investigator determines, after consultation with the MAGIC Principal Investigator and the Medical Monitor, that the treatment would not interfere with patient safety or achievement of study objectives. A shorter drug washout period prior to the initiation of GDC-8264 may be acceptable in select circumstances. The investigator should consult with the MAGIC Principal Investigator and the Medical Monitor for guidance.

- Initiation or planned use of a marketed small molecule (excluding corticosteroids) or biologic therapy as treatment for aGVHD is prohibited from the start of screening through the treatment period.

Patients requiring a prohibited therapy or new systemic therapy for corticosteroid-refractory aGVHD will be discontinued from GDC-8264 and will undergo follow-up assessments as described in Section 4.6.1 and Appendix 1.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Records

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened, to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at screening. *Significant*

non-serious events or conditions that occur after informed consent but prior to initiation of GDC-8264 should be reported as medical history. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within [redacted] prior to initiation of GDC-8264 *(or* [redacted] *prior if initiation of GDC-8264 is delayed due to administrative or logistical reasons)* will be recorded. Information on the HSCT (e.g., donor type, HLA status), preparative regimen, and the prophylaxis regimen for GVHD will be recorded. An interval medical history should be obtained at subsequent clinic visits, and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race or ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

The targeted neurologic examination will be focused on motor abnormalities and may include an assessment of orientation, facial and eye movement assessment (e.g., through evaluation of cranial nerves III–VII, XI, XII), and a check for postural tremor or myoclonic movements in the outstretched arm(s). The same assessment performed at baseline should be repeated at each timepoint indicated in Appendix 1.

Limited, symptom-directed physical examinations should be performed at specified visits and as clinically indicated. Changes from abnormalities identified at screening should be recorded in patient notes.

Any abnormality identified at screening or prior to initiation of study drug should be recorded on the appropriate eCRF (unless considered related to a protocol-mandated intervention; see Section 5.3.1). After initiation of study drug, any new or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature.

Any abnormality identified at screening or prior to initiation of study drug should be recorded on the eCRF (unless considered related to a protocol-mandated intervention). After initiation of study drug, any new or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event eCRF (see Section 5.3.5.5).

4.5.5 Clinical Response Assessment

Overall response will be determined by the investigator at specified timepoints according to the response criteria as defined in Section 3.1.4. Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Endpoints (e.g., ORR, DOR, OS, NRM) will be calculated programmatically on the basis of investigator assessments of response at each specified timepoint.

4.5.6 MAGIC Acute Graft-versus-Host Disease Target Organ Staging

The MAGIC aGVHD Target Organ Staging (see Appendix 4) assigns a stage to each of four aGVHD target organs (skin, liver, upper GI tract, and lower GI tract) based on severity of organ involvement. The stages range from 0 to 4, with Stage 4 being the most severe, except for upper GI that is 0 or 1 (yes or no). An overall grade ranging from 0 to IV is then determined on the basis of stages for the four target organs, with Grade IV being the most severe (Harris et al. 2016).

4.5.7 Chronic Graft-versus-Host Disease Staging

Chronic GVHD severity will be independently assessed according to the National Institutes of Health Chronic GVHD Diagnosis and Staging score (see Appendix 5) on the basis of Karnofsky Performance Score and investigator quantification of patient chronic GVHD signs and symptoms. The chronic GVHD target organs (skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, and genital tract) are scored from 0 to 3, with 3 as the most severe (Jagasia et al. 2015).

4.5.8 Corticosteroid-Refractory Acute Graft-versus-Host Disease Assessment

Assessment of aGVHD severity (grade) and patient response to treatment will be performed after the initiation of study treatment. Patients who demonstrate progression of disease or non-response according to the criteria in Sections 3.1.4.7 and 3.1.4.4, respectively, should be evaluated for corticosteroid-refractory aGVHD. If criteria for corticosteroid-refractory aGVHD are met (see Section 3.1.4.5), the investigator should evaluate the patient's condition to guide the clinical decision on initiation of second-line therapy. The MAGIC Principal Investigator may be consulted. Initiation of any second-line therapy will require discontinuation of GDC-8264 (see Section 4.6.1).

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, and AST
- Coagulation: INR, aPTT, and PT
- Pregnancy test

    All women of childbearing potential (defined in Section 4.1.1) will have a serum pregnancy test performed at screening. If obtaining results from a serum pregnancy test would delay enrollment, a urine pregnancy test is acceptable.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis
- Serum samples for biomarker analysis of ST2 and REG3α to calculate MAP
- Serum samples for exploratory research on biomarkers (including biomarker assay development)
- Residual biopsy tissue samples from involved aGVHD target organs (e.g., GI, skin) obtained up to 2 weeks prior to study enrollment or during the study for exploratory research on biomarkers

    Patients may undergo biopsies of involved organs to inform the diagnosis of aGVHD and/or to inform clinical management decisions according to institutional guidelines. Biopsies of involved aGVHD target organs are encouraged but not required for this study.

    For patients with residual biopsy tissue samples available, the samples will be submitted to the Sponsor or designated laboratory only after the tissue samples are no longer required for clinical care
- Buccal scraping sample for exploratory research on biomarkers

Exploratory biomarker research may include, but will not be limited to, analysis of *ATG16L1* polymorphisms and protein biomarkers. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling. Genomic research may include exploration of germline variants. Genomic profiling may include whole genome sequencing (WGS) or whole exome sequencing (WES) of buccal scraping samples, but only at participating sites (see Section 4.5.12).

Residual plasma PK samples may be used for exploratory biomarker research described above.

For sampling procedures, storage conditions, and shipment instructions, see the appropriate laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional PK and biomarker research and biomarker assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Serum samples collected for biomarker analysis of ST2 and REG3α to calculate MAP will be destroyed no later than10 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Serum samples collected for biomarker research (including biomarker assay development) will be destroyed no later than 10 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Residual biopsy tissue samples that are shared for biomarker research will be returned to the site upon request or no later than 5 years after the final Clinical Study Report has been completed.
- Buccal scraping samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of samples that undergo WGS or WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.10 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal, if possible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The MAGIC Principal Investigator and the Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, a PK sample may be obtained, at the discretion of the MAGIC Principal Investigator or the Medical Monitor. A decision on GDC-8264 discontinuation should be made, as described in Section 5.1.2.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.11 Use of Screen-Fail Samples (Patients at Participating Sites)

At participating sites, screening blood samples collected from patients who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools.

If a site does not permit research on screen-fail samples, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.12 Buccal Scraping Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, buccal scraping samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to GDC-8264, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease

biology and drug safety. Research will include exploration of germline variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of buccal scraping samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.12) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the appropriate laboratory manual.

Buccal scraping samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.9 for details on use of samples after patient withdrawal and confidentiality standards for data.

Data generated from buccal scraping samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her buccal scraping sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.13 Optional Samples for Research Biosample Repository and Mount Sinai Acute GVHD International Consortium Biorepository

4.5.13.1 Overview of the Research Biosample Repository and Mount Sinai Acute GVHD International Consortium Biorepository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

The MAGIC Natural History Study is a database and biorepository that contains detailed longitudinal biomarker and clinical data prospectively obtained according to an institutional review board–approved protocol at each MAGIC participating center. Samples retained in the MAGIC biorepository will be used for research activities related to GVHD.

Samples for the RBR and the MAGIC biorepository will be collected from patients who give specific consent to participate in this optional research.

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR and MAGIC biorepository samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by the Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR and MAGIC biorepository sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to GVHD or GDC-8264, or drug safety:

- Leftover blood, serum, plasma, and tissue samples (with the exception of residual biopsy tissue samples from involved aGVHD target organs, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

The following samples will be stored in the MAGIC biorepository and used for research purposes, including, but not limited to, research on GVHD or complications of HSCT that mimic GVHD:

- Leftover serum samples for biomarker analysis of ST2 and REG3α to calculate MAP

Alongside samples, the information collected from patients during the trial may also be shared with MAGIC, but only after personal information that can identify the patient has been removed.

For sampling procedures, storage conditions, and shipment instructions, see the appropriate laboratory manual.

RBR and MAGIC biorepository samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR and MAGIC biorepository storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.13.4 Data Protection, Use, and Sharing

RBR and MAGIC biorepository samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR and MAGIC biorepository samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RBR and MAGIC biorepository samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR and MAGIC biorepository samples, data derived from these analyses will generally not be provided to study investigators or patients, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR and MAGIC biorepository samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR and MAGIC biorepository data will become and remain the exclusive and unburdened property of the Sponsor and MAGIC, respectively, except where agreed otherwise.

4.5.13.5 Consent to Participate in the Research Biosample Repository and Mount Sinai Acute GVHD International Consortium Biorepository

The Informed Consent Form will contain a separate section that addresses participation in the RBR and the MAGIC biorepository. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR and the MAGIC biorepository. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's

agreement to provide optional RBR and MAGIC biorepository samples. Patients who decline to participate will not provide a separate signature. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the appropriate eCRF.

In the event of an RBR and MAGIC biorepository participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR and MAGIC research.

4.5.13.6 Withdrawal from the Research Biosample Repository and Mount Sinai Acute GVHD International Consortium Biorepository

Patients who give consent to provide RBR and MAGIC biorepository samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR and MAGIC biorepository samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR and MAGIC biorepository samples during the study, the investigator must inform the Medical Monitor or the MAGIC Principal Investigator (as applicable) in writing of the patient's wishes through use of the appropriate Subject Withdrawal Form and must enter the date of withdrawal on the appropriate eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR and MAGIC biorepository samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR and MAGIC biorepository samples. Likewise, a patient's withdrawal of consent for testing of RBR and MAGIC biorepository samples does not constitute withdrawal from this study.

4.5.13.7 Monitoring and Oversight

RBR and MAGIC biorepository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR and the MAGIC biorepository for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR and MAGIC biorepository samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Drug Discontinuation

Patients must permanently discontinue study drug if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study drug
- Investigator or Sponsor determination that study drug discontinuation is in the best interest of the patient
- Confirmed anaphylaxis to study drug
- Pregnancy
- Use of a new line of systemic therapy for corticosteroid-refractory aGVHD
- Use of a prohibited therapy (see Section 4.4.3)
- Confirmed seizure
- *Newly discovered brain lesion associated with a higher risk of seizure (e.g., new mass lesion with surrounding vasogenic edema)*
- Patient noncompliance with the study treatment regimen
- Receipt of fewer than 10 doses of study drug within the [redacted] of the treatment period due to noncompliance, voluntary withdrawal, or reasons other than safety or (lack of) efficacy
- [redacted]

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely due to safety or (lack of) efficacy will continue participation in the study.

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study drug. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

If patients discontinue from the study during the study treatment period or prior to completion of the safety follow-up period, patients will return to the clinic for an early termination visit [redacted] after the last dose of GDC-8264.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent

- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. For patient-replacement rules, refer to Section 3.1.1.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- [redacted] and upon review of the data the $DSMB$ recommends study termination

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study was developed on the basis of nonclinical data on the RIP1 pathway and GDC-8264, as well as clinical experience with GDC-8264 in

Study GP41678 in healthy subjects and the ongoing Study GP42995 in subjects with renal impairment and matched healthy volunteers with normal renal function. There is currently no identified risk associated with GDC-8264. The anticipated important potential safety risks for GDC-8264 are outlined below. Please refer to the GDC-8264 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken in this study to ensure the safety of participating patients. Eligibility criteria have been designed to exclude patients at higher risk for potential toxicities, including patients with active infections or with risk factors for seizures. Patients will undergo safety monitoring during the study, including, but not limited to, neurologic examinations (described in Section 4.5.3) and assessment of the nature, frequency, and severity of adverse events. [redacted] Ongoing review of safety data will be performed by the MAGIC Principal Investigator, the Sponsor, and the *DSMB* (see Section 3.1.3) for early identification of potential new safety signals. [redacted] In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

Patients with uncontrolled active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., ASCO or ESMO). Although testing for SARS-CoV-2 infection is not mandated by the protocol, a positive test performed for any other reason, including local institutional or health authority requirements, may require investigator assessment and management. The majority of patients in this study are hospitalized, allowing for study assessments to continue as scheduled. Depending on the clinical situation, alternative methods and revised timing for assessments may be required for outpatient patients who test positive for SARS-CoV-2 infection and are quarantined.

5.1.1 Potential Risks Associated with GDC-8264

5.1.1.1 Serious Bacterial or Viral Infections with Blunted Clinical Response

Mice that are homozygous for a knock-in mutation of RIP1 that inhibits kinase activity (i.e., KD mice) are viable, healthy, and born in Mendelian ratios (Newton et al. 2014). RIP1 inactivation or inhibition does not affect RIP1 stability and also does not affect TNF-induced nuclear factor–kappa B or MAPK activation (Newton et al. 2014; Patel et al. 2020). When challenged with certain pathogens, such as vaccinia virus, some published reports suggest that RIP1 KD mice exhibit impaired pathogen clearance and can therefore manifest more severe infections compared with WT controls (Polykratis et al. 2014, Shutinoski et al. 2016). However, other studies conducted under similar experimental conditions have failed to reproduce these results (Kuriakose et al. 2016,

Zhang et al. 2020). Similarly, infection with murine gamma herpes virus MHV68 showed no significant differences in levels of MHV68 in lungs or spleens or changes in leukocyte populations between RIP1 KD and WT mice (Webster et al. 2020). In addition, RIP1 inactivation does not affect cellular nuclear envelope rupture (a critical step for viral replication) or proinflammatory cytokine production during influenza A–virus infection (Kuriakose et al. 2016). However, considering the uncertainty of the translatability of some of these reported findings to humans, the Sponsor cannot exclude the potential risk that inhibition of RIP1 with GDC-8264 could increase the risk of serious infections.

RIP1 KD mice may demonstrate a blunted systemic inflammatory response to certain inflammatory stimuli. For example, in WT mice, TNF causes hypothermia (a manifestation of severe systemic inflammation) and shock; however, hypothermia and shock do not occur after TNF administration to RIP1 KD mice (Newton et al. 2014). Also, it has been reported that RIP1 KD mice may be impaired in their inflammatory response to lipopolysaccharide, although other published data have not replicated this finding (Newton et al. 2016, Saleh et al. 2017). Nevertheless, if this result translates to humans, it is possible that patients exposed to GDC-8264 who have active infections may exhibit a blunted clinical response. As such, patients with uncontrolled active infections are excluded from this study (see Section 4.1.2).

Although data are limited regarding human experience following pharmacologic inhibition of RIP1, no indication of serious infection risk has been reported for several different RIP1 inhibitors dosed up to 12 weeks in healthy subjects or patients, including patients taking concomitant immunomodulatory drugs such as methotrexate. GSK2982772, a potent orally administered RIP1 inhibitor, has been tested in healthy human subjects in a SAD/MAD trial (Weisel et al. 2017), patients with active plaque-type psoriasis (Weisel et al. 2020), patients with moderate to severe rheumatoid arthritis (Weisel et al. 2021a), and patients with active ulcerative colitis (Weisel et al. 2021b). One non-serious adverse event of herpes zoster (moderate in severity) in the GSK2982772 psoriasis study in a patient in the high-dose group (60 mg twice a day) led to the patient's discontinuation from study treatment, but no serious infections were reported (Weisel et al. 2020). Similarly, no indication of a risk of serious infections was reported for DNL104, another RIP1 inhibitor, when administered to healthy subjects in a SAD/MAD study (Grievink et al. 2020). To date, no serious infection has been reported in any participant from the studies of GDC-8264. For additional information, refer to the GDC-8264 Investigator's Brochure.

5.1.1.2 Seizures (Convulsions)

HSCT is associated with a range of complications including involvement of the CNS. Several clinical studies have indicated that seizures are a relatively uncommon neurologic complication after HSCT, with incidence ranging from 1.6 to 15.4% (Wang et al. 2021). Etiologies of epileptic seizures after HSCT mainly focus on drug-related neurotoxicity, metabolic disorder, cerebrovascular events, intracranial infection, and CNS recurrence. However, sometimes seizures may be the result of the coexistence of multiple contributing factors. Seizures can manifest as strange sensations and behaviors, or sometimes convulsions, muscle spasms, and loss of consciousness, and could eventually lead to serious impairments of normal CNS function and even death. Management and prognosis are determined by whether the etiology of the seizures is systemic and usually reversible, such as derangement (e.g., hyponatremia, drug toxicity), or is due to a structural CNS disorder.

Patients with a history of seizure or convulsions or at higher risk of seizure are excluded from this study (see Section 4.1.2) and patients will be monitored by neurologic examination over the treatment period. If a patient in this study experiences a seizure,

GDC-8264 treatment will be withheld (see Table 7), and a PK sample should be obtained as soon as possible. Patients on concomitant medications known to increase the risk of seizure may continue taking those medications, provided they have not previously experienced a seizure at or below the dose level being administered prior to initiation of GDC-8264.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Dose modification is not permitted in this study for any patient.

5.1.2.2 Treatment Interruption

GDC-8264 treatment may be temporarily suspended in patients who experience toxicity considered to be related to GDC-8264. If GDC-8264 has been withheld for $>$14 days because of toxicity, the patient should be discontinued from GDC-8264, unless resumption of treatment is recommended by the investigator after discussion with the MAGIC Principal Investigator and the Medical Monitor.

GDC-8264 treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) in consultation with the MAGIC Principal Investigator and the Medical Monitor. The investigator should consult with the MAGIC Principal Investigator and the Medical Monitor to determine an acceptable length of treatment interruption.

5.1.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 7. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Hematologic toxicity	
ANC $\leq 500/\mu L$ ($0.5 \times 10^9/L$) for 3 days	• Continue GDC-8264 and monitor ANC. • If ANC remains $\leq 500/\mu L$ ($0.5 \times 10^9/L$) after 3 days, withhold GDC-8264. • Monitor ANC and resume GDC-8264 when ANC $> 500/\mu L$ ($0.5 \times 10^9/L$). • If not resolved in ≤ 14 days while withholding GDC-8264, permanently discontinue GDC-8264. Note that growth factor use is permitted.
Platelet count $< 10,000/\mu L$ ($100 \times 10^9/L$) for 7 days	• Continue GDC-8264 and monitor platelet count. • If platelet count remains $< 10,000/\mu L$ ($100 \times 10^9/L$) after 7 days, withhold GDC-8264. • If platelet count sustainable at $> 10,000/\mu L$ ($100 \times 10^9/L$) (with transfusions, if necessary), resume GDC-8264. • If not resolved in ≤ 14 days while withholding GDC-8264, permanently discontinue GDC-8264. Note that transfusions are permitted.
Hepatic events	
Total bilirubin, ALT, or AST increased, and cause is not clearly attributable to aGVHD or other transplant-related complication (e.g., veno-occlusive disease)	**For patients with normal bilirubin, ALT, and AST values at screening:** • Withhold GDC-8264 for any Grade ≥ 3 increase. • If not resolved in ≤ 14 days, permanently discontinue GDC-8264. **For patients with elevated bilirubin, ALT, and AST values at screening:** • If any values $> 3 \times$ baseline, withhold GDC-8264 until values resolve to baseline. • If not resolved in ≤ 14 days, permanently discontinue GDC-8264.

aGVHD = acute graft-versus-host disease; PK = pharmacokinetic; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Seizure	
Any grade	• Immediately withhold GDC-8264 and report event as an adverse event of special interest (see Section 5.2.3). • Obtain PK sample as soon as possible. • Evaluate event and if not confirmed as seizure, resume GDC-8264. • If event confirmed as seizure, permanently discontinue GDC-8264.
ECG abnormalities	
Any one of the following: • Torsades de pointes • Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and >60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment) • Sustained absolute QTcF that is >515 ms (at least two ECG measurements >30 minutes apart) • New ECG finding of clinical concern	• Withhold GDC-8264. For torsades de pointes, permanently discontinue GDC-8264. For sustained QTcF events or all other ECG findings of clinical concern, permanently discontinue GDC-8264 when there is no clear alternative cause. If there is a clear alternative cause, GDC-8264 may be resumed at investigator's discretion following consultation with the MAGIC Principal Investigator and the Medical Monitor, provided abnormalities have resolved and patient is appropriately monitored. • Contact the MAGIC Principal Investigator and the Medical Monitor as soon as possible. • Obtain PK sample if not already scheduled for that timepoint. • Initiate standard-of-care treatment at investigator's discretion. Management of sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. • Evaluate patient for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia). • Consult with cardiologist or electrophysiologist to confirm ECG changes and ascertain the likelihood of drug-induced arrhythmia versus background occurrence of arrhythmias, as it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring.

aGVHD = acute graft-versus-host disease; PK = pharmacokinetic; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

Table 7 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

GDC-8264-related toxicity not described above	
Grade 3 laboratory or non-laboratory abnormality attributable to GDC-8624	• Withhold GDC-8264. Resume GDC-8264 only after the toxicity has resolved to Grade 1 or better. • If no improvement to Grade 2 or better in ≤ 14 days while withholding GDC-8264, permanently discontinue GDC-8264.
Grade 4 laboratory or non-laboratory abnormality attributable to GDC-8624 that is not clearly attributable to aGVHD or other transplant-related complication	• Immediately withhold GDC-8264. • If improvement to Grade 2 or better, resume GDC-8264. • If no improvement to Grade 2 or better in ≤ 14 days while withholding GDC-8264, permanently discontinue GDC-8264.

aGVHD = acute graft-versus-host disease; PK = pharmacokinetic; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from GDC-8264 (see Section 5.3.5.4 for more information)
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to GDC-8264
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by GDC-8264, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the GDC-8264 is suspected.
- Seizure, any grade
- Grade ≥3 syncope

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the adverse event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the adverse event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the adverse event eCRF.

After informed consent has been obtained but prior to initiation of GDC-8264, *all* serious adverse events should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of GDC-8264, all adverse events will be reported until [redacted] after the final dose of GDC-8264.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The investigator will use the NCI CTCAE (v5.0) grading scale for assessing the severity of each adverse event reported during the study. The investigator will use the grading scale in Table 8 for assessing the severity of adverse events that are not specifically listed in NCI CTCAE.

For infection adverse events, the investigator will also use the Blood and Marrow Transplant Clinical Trial Network (BMT CTN) infection severity grading system (see Appendix 7) for assessing the severity of infection adverse events (i.e., in addition to using the NCI CTCAE grading scale).

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the GDC-8264, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of GDC-8264
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of GDC-8264, or reintroduction of GDC-8264 (as applicable)
- Known association of the event with GDC-8264 or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–GDC-8264–related factors that are known to be associated with the occurrence of the event (e.g., adverse events associated with standard-of-care treatment with systemic corticosteroids or medications commonly used in the management of aGVHD)

Table 9 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the adverse event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the adverse event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the adverse event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the adverse event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the adverse event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the adverse event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the adverse event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the adverse event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The adverse event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the adverse event eCRF. Investigators should use clinical judgment to assess each event as recurrent or intermittent. An intermittent adverse event should be recorded as a single event.

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the adverse event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated creatinine," as opposed to "abnormal creatinine"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, low albumin level of 2.0 g/dL should be recorded as "hypoalbuminemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the adverse event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the adverse event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the adverse event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the adverse event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator to progression of aGVHD should be recorded as a clinical event. All other deaths that occur during the adverse event reporting period, regardless of relationship to GDC-8264, must be recorded on the adverse event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent $DSMB$ will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the adverse event eCRF. Generally, only one such event should be

reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the adverse event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the adverse event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Acute Graft-Versus-Host Disease

Events that are clearly consistent with worsening of aGVHD should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, worsening will be based on aGVHD grading scale but may be based on symptomatic deterioration. Every effort should be made to document aGVHD worsening through use of objective criteria. If there is any uncertainty as to whether an event is due to disease aGVHD worsening, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization for patients who are not otherwise hospitalized at the initiation of the study should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due to worsening of aGVHD (see Section 5.3.5.9

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations and adverse events associated with special situations are to be reported separately on the adverse event eCRF, as outlined in the sections below.

Reporting Special Situations

All special situations associated with GDC-8264, regardless of whether they result in an adverse event, should be recorded on the adverse event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

Reporting Adverse Events Associated with Special Situations

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the adverse event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For GDC-8264, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the adverse event eCRF, one entry to report the accidental overdose (special situation) and one entry to report the headache (adverse event). The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor and the MAGIC DCC immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor and the MAGIC DCC within 24 hours after learning of the event, regardless of relationship to GDC-8264:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor and the MAGIC DCC immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to GDC-8264 Initiation

After informed consent has been obtained but prior to initiation of GDC-8264, *all* serious adverse events should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

Significant non-serious events or conditions that occur after informed consent, but prior to initiation of GDC-8264, should be reported as medical history.

5.4.2.2 Events That Occur after GDC-8264 Initiation

After initiation of GDC-8264, serious adverse events and adverse events of special interest will be reported until [redacted] after the final dose of GDC-8264. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF in the electronic data capture (EDC) system. A report will be generated by the MAGIC DCC and sent to Safety Risk Management.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., within 24 hours of learning of the event) either by faxing or by scanning and/or emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > [redacted] after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within [redacted] drug elimination half-lives of GDC-8264, whichever is longer, after the final dose of GDC-8264. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the adverse event eCRF. The investigator should discontinue GDC-8264 and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus,

an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the adverse event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within [redacted] drug elimination half-lives of GDC-8264, whichever is longer, after the final dose of GDC-8264. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to GDC-8264. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion in a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the adverse event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the adverse event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to GDC-8264 or the female partner of a male patient exposed to GDC-8264 should be classified as a serious adverse event, recorded on the adverse event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the adverse event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as [redacted] after the final dose of GDC-8264), all deaths, regardless of cause, should be reported through use of the major event and death forms.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to GDC-8264, the event should be reported through use of the adverse event eCRF and by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
GDC-8264	GDC-8264 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analyses of safety, PK, and efficacy data will be performed after all enrolled patients have either completed the [redacted] visit or have discontinued from the study prior to [redacted] and all data from this period are in the database and have been cleaned and verified. The final analyses of complete data for the study will be performed when all

enrolled patients have either completed the [redacted] study period or discontinued early from the study, all data from the study are in the database, and the database is locked.

Detailed specifications of the statistical methods will be described in the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

This study is exploratory in nature. The overall purpose of the study is to identify an optimal dose for GDC-8264 for future studies, using all available safety, PK, and efficacy data. A sample size of approximately 20 patients per dose cohort is believed to be clinically appropriate to assess the preliminary safety, pharmacokinetics, and efficacy in this initial study in patients with aGVHD and to inform future development of GDC-8264. The sample size calculation is not based on a statistical power consideration.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study treatment discontinuation and study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of GDC-8264, with patients grouped according to treatment received.

Safety will be assessed through descriptive summaries of exposure to study treatment (such as treatment duration, total dose received, and dose modifications), adverse events, changes in laboratory test results, and changes in ECGs and vital signs. All adverse event data will be listed by patient number.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to the NCI CTCAE v5.0. In addition, infection adverse event severity will be graded according to the BMT CTN Severity Grading Table (see Appendix 7). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying

severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.5 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who have received at least one dose of GDC-8264 and have at least one evaluable postdose PK concentration.

Individual and mean plasma GDC-8264 concentration versus time data will be tabulated and plotted. The plasma pharmacokinetics of GDC-8264 will be summarized by estimating C_{max}, t_{max}, and $AUC_{0\text{-}24\ hr}$ on Day 1 and at steady state, apparent clearance, and apparent volume of distribution, as feasible and as appropriate for data collected. Estimates for these parameters will be tabulated and summarized (including mean, standard deviation, coefficient of variation, geometric mean, geometric %CV, median, minimum, and maximum). Assessment of protein binding may be performed on some of the PK samples.

[redacted] Additional PK analyses will be conducted as appropriate.

Details of the PK analyses will be detailed in the DAP.

PK data may be pooled across studies for population PK analyses. These analyses may be reported separately from the CSR.

6.6 EFFICACY ANALYSES

The efficacy analyses will be based on the modified intent-to-treat population defined as all enrolled patients who received at least one dose of GDC-8264 and did not miss more than four doses of the GDC-8264 within the [redacted] of the treatment period due to patient noncompliance, voluntary withdrawal, or reasons other than safety or (lack of) efficacy.

Because the study is hypothesis-generating in nature, no adjustment for multiplicity will be performed. Sensitivity/supportive analyses may be performed to evaluate the impact of missing data on the results and details will be included in the DAP.

6.6.1 Secondary Efficacy Endpoints

The efficacy of GDC-8264 will be evaluated on the basis of the following secondary efficacy endpoints:

- *Overall* response rate (ORR), defined as the proportion of patients with a complete response (CR), very good partial response (VGPR), or partial response (PR) on Day 29 with no intervening additional line of aGVHD therapy, as determined by the investigator according to the criteria defined in Section 3.1.4

  Death or aGVHD progression by Day 29 will be considered non-response for this endpoint.
- Duration of response (DOR), defined as the time from response (CR, VGPR, or PR) on Day 29 to aGVHD progression from nadir in any organ, new systemic therapy for aGVHD, or death from any cause (whichever occurs first), as determined by the investigator according to criteria defined in Section 3.1.4
- Cumulative incidence of aGVHD flares by Day 56
- Cumulative incidence of non-relapse mortality (NRM) by Day 180

All secondary efficacy endpoints will be summarized descriptively by treatment group.

6.6.2 Exploratory Efficacy Endpoints

The efficacy of GDC-8264 will also be evaluated on the basis of the following the exploratory efficacy endpoints:

- Time from initiation of GDC-8264 to first response (i.e., CR, VGPR, or PR)
- [redacted]
- FFS rate at [redacted]
- Cumulative incidence of chronic GVHD by [redacted]
- Cumulative incidence of relapse of underlying malignancy by [redacted]
- OS rate at [redacted] defined as the proportion of patients who have not experienced death from any cause at [redacted]
- Proportion of patients with maximum Grade III or IV aGVHD by [redacted]
- Cumulative corticosteroid dose at [redacted]

All exploratory efficacy endpoints will be summarized descriptively by treatment group.

6.7 BIOMARKER ANALYSES

The PD biomarker analyses will include all patients with one pretreatment and at least one post-treatment biomarker assessment. PD biomarkers will be assessed as an absolute increase over time, and/or as a percent change relative to original baseline for each patient. Results will be summarized through use of summary statistics and or other graphs as required. Descriptive statistics will be listed by clinical response status. Additional PD biomarker analyses will be conducted as appropriate.

Additional PD biomarker analyses will include all patients with one pretreatment biomarker assessment, provided there are sufficient data in each biomarker group to facilitate a meaningful analysis. Baseline values will be used to evaluate predictive biomarkers in the context of activity (clinical and/or pharmacologic), drug levels, and/or safety endpoints. Results will be summarized descriptively.

The MAGIC biomarkers will be utilized to retrospectively conduct exploratory safety and efficacy analyses on a predefined cohort of patients who have an Ann Arbor score of 2 or 3 at screening.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor, in collaboration with MAGIC, will supply eCRF specifications for this study. A contract research organization (CRO) in collaboration with the MAGIC DCC will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO and/or the MAGIC DCC will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

MAGIC will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, and ST2 and REG3α data from MAGIC laboratory via EDC system, using the Sponsor's and MAGIC standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of MAGIC's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and any data updates will be maintained in the EDC system's audit trail. System backups for data stored at on MAGIC's server(s) and records retention for the study data will be consistent with the MAGIC's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor or its designee direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical *Trials* Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent

forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, pharmacovigilance oversight, site monitoring, and medical monitoring in collaboration with the MAGIC Consortium and the CRO. Verification of the source data at each site will be performed by the contracted CRO monitors.

Approximately *20 sites* in the United States *and Canada* will participate to enroll approximately 40 patients.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected from each participating site. Biopsies collected for the diagnosis and management of aGVHD will be provided to the Sponsor on an as-available basis from each institution's pathology laboratory after the samples are no longer needed for clinical care. ECGs will be performed and read locally at each site.

A *DSMB* will be employed to monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of

the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood 2009;114:511–7.

Aziz MD, Shah J, Kapoor U, et al. Disease risk and GVHD biomarkers can stratify patients for risk of relapse and non-relapse mortality post hematopoietic cell transplant. Leukemia 2020;34:1898–1906.

[BMT CTN] Bone and Marrow Transplant Clinical Trials Network. Severity grading table and recurrence interval definitions Version 3, 19 March 2013 [resource on the Internet] 2021 [cited 17 December 2021]. Available from: https://web.emmes.com/study/bmt2/public/Definition/Severity%20Grading_Recurrence%20Interval.pdf.

Bolaños-Meade J, Logan BR, Alousi AM, et al. Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. Blood 2014;124:3221–7.

Couriel DR, Saliba R, de Lima M, et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant 2009;15:1555–62.

Degterev A, Ofengeim D, Yuan J. Targeting RIPK1 for the treatment of human diseases. Proc Natl Acad Sci USA 2019;116:9714–22.

Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010;4:28–62.

Emanuel EJ, Bedarida G, Macci K, et al. Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies. BMJ 2015; 350:h3271.

Ferrara JLM, Harris AC, Greenson JK, et al. Regenerating islet-derived 3-alpha is a biomarker of gastrointestinal graft-versus-host disease. Blood 2011;118:6702–8.

Ferrara JLM, Chaudhry MS. GVHD: biology matters. Blood Adv 2018;2:3411–17.

Fuji S, Byrne M, Nagler A, et al. How we can mitigate the side effects associated with systemic glucocorticoid after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2021;56:1248–56.

Ghimire S, Weber D, Mavin E, et al. Pathophysiology of GVHD and other HSCT-related major complications. Front Immunol 2017;8:79.

Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 1974;18:295–304.

Grievink HW, Heuberger JAAC, Huang F, et al. DNL104, a centrally penetrant RIPK1 inhibitor, inhibits RIP1 kinase phosphorylation in a randomized phase I ascending dose study in healthy volunteers. Clin Pharmacol Ther 2020;107:406–14.

Harris AC, Young R, Devine S, et al. International, multi-center standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 2016;22:4–10.

Hartwell MJ, Özbek U, Holler E, et al. An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. JCI Insight 2017; 2:e89798.

Hooker DS, Grabe-Heyne K, Henne C, et al. Improved therapeutic approaches are needed to manage graft-versus-host disease. Clin Drug Investig 2021;41:929–39.

Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics 2005;61:540–45.

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

Jagasia M, Arora M, Flowers MED, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 2012;119:296–307.

JAKAFI® (ruxolitinib tablets) U.S. Prescribing Information, Incyte Corporation.

Kekre N, Kim HT, Hofer J, et al. Phase II trial of natalizumab with corticosteroids as initial treatment of gastrointestinal acute graft-versus-host disease. Bone Marrow Transplant 2021;56:1006–12.

Kuriakose T, Man SM, Malireddi RK, ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways Sci Immunol 2016;1:aag2045.

Levine JE, Huber E, Hammer ST, et al. Low Paneth cell numbers at onset of gastrointestinal graft-versus-host disease identify patients at high risk for nonrelapse mortality. Blood 2013;122:1505–9.

Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. Lancet Haematol 2015;2:e21–9.

MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. Blood 2010;115:5412–7.

Major-Monfried H, Renteria AS, Pawarode A, et al. MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. Blood 2018;131:2846–55.

MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biol Blood Marrow Transplant 2015;21:761–7.

MacMillan ML, DeFor TE, Holtan SG, et al. Validation of Minnesota acute graft-versus-host disease Risk Score. Haematologica. 2020; 105:519–524.

Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2012;18:1150–63.

Matsumura-Kimoto Y, Inamoto Y, Tajima K, et al. Association of cumulative steroid dose with risk of infection after treatment for severe acute graft-versus-host disease. Biol Blood Marrow Transplant 2016;22:1102–07.

Matsuzawa-Ishimoto Y, Shono Y, Gomez LE, et al. Autophagy protein ATG16L1 prevents necroptosis in the intestinal epithelium; J Exp Med 2017;214:3687–705.

Matsuzawa-Ishimoto Y, Hine A, Shono Y, et al. An intestinal organoid-based platform that recreates susceptibility to T-cell-mediated tissue injury. Blood 2020;135:2388–401.

Naymagon S, Naymagon L, Wong SY, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol 2017;14:711–26.

Nassereddine S, Rafei H, Elbahesh E, et al. Acute graft versus host disease: A comprehensive review. Anticancer Res 2017;37:1547–55.

[NCCN] National Comprehensive Cancer Network. Guidelines for hematopoietic cell transplantation Version 5.2021 [resource on the Internet] 2021 [cited 17 December 2021]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1501.

Newton K, Dugger DL, Wickliffe KE, et al. Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. Science 2014;343:1357–60.

Newton K, Dugger DL, Maltzman A, et al. RIPK3 deficiency or catalytically inactive RIPK1 provides greater benefit than MLKL deficiency in mouse models of inflammation and tissue injury. Cell Death Differ 2016;23:1565–76.

Newton K. Multitasking Kinase RIPK1 Regulates Cell Death and Inflammation. Cold Spring Harb Perspect Biol 2020; 12:a036368.

Patel S, Webster JD, Varfolomeev E, et al. RIP1 inhibition blocks inflammatory diseases but not tumor growth or metastases. Cell Death Differ 2020;27:161–75.

Polykratis A, Hermance N, Zelic M, et al. Cutting edge: RIPK1 Kinase inactive mice are viable and protected from TNF-induced necroptosis in vivo. J Immunol 2014;193:1539–43.

Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995;15:825–8.

RAYOS (prednisone delayed-release tablets) U.S. Prescribing Information, Horizon Pharma USA, Inc.

Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol 1997;97:855–64.

Saleh D, Najjar M, Zelic M, et al. Kinase activities of RIPK1 and RIPK3 can direct IFN-β synthesis induced by lipopolysaccharide. J Immunol 2017;198:4435–47.

Schroeder MA, Khoury HJ, Jagasia M, et al. A phase 1 trial of itacitinib, a selective JAK1 inhibitor, in patients with acute graft-versus-host disease. Blood Adv 2020;4:1656–69.

Shutinoski B, Alturki NA, Rijal D, et al. K45A mutation of RIPK1 results in poor necroptosis and cytokine signaling in macrophages, which impacts inflammatory responses in vivo. Cell Death Differ 2016;23:1628–37.

SOLU-MEDROL® (methylprednisolone sodium succinate for IV or injection, USP) U.S. Prescribing Information, Pfizer, Inc.

Srinagesh HK, Özbek U, Kapoor U, et al. The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease. Blood Adv 2019;3:4034–42.

Stark K, Goncharov T, Varfolomeev E, et al. Genetic inactivation of RIP1 kinase activity in rats protects against ischemic brain injury. Cell Death Dis 2021;12:379.

Tao P, Sun J, Wu Z, et al. A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1. Nature 2020;577:109–14.

Wang Z, Zhao M, Gao S. Epileptic seizures after allogeneic hematopoietic stem cell transplantation. Front Neurol 2021;12:675756.

Webster JD, Kwon YC, Park S, et al. RIP1 kinase activity is critical for skin inflammation but not for viral propagation. J Leukoc Biol 2020;107:941–52.

Weisel K, Scott NE, Tompson DJ, et al. Randomized clinical study of safety, pharmacokinetics, and pharmacodynamics of RIPK1 inhibitor GSK2982772 in healthy volunteers. Pharmacol Res Perspect 2017;5:e00365.

Weisel K, Berger S, Papp K, et al. Response to inhibition of receptor-interacting protein kinase 1 (RIPK1) in active plaque psoriasis: a randomized placebo-controlled study.Clin Pharmacol Ther 2020;108:808–16.

Weisel K, Berger S, Thorn K, et al. A randomized, placebo-controlled experimental medicine study of RIPK1 inhibitor GSK2982772 in patients with moderate to severe rheumatoid arthritis. Arthritis Res Ther 2021a;23:85.

Weisel K, Scott N, Berger S, et al. A randomised, placebo-controlled study of RIPK1 inhibitor GSK2982772 in patients with active ulcerative colitis. BMJ Open Gastroenterol 2021b;8:e000680.

Yu X, Ma H, Li B, et al. A novel RIPK1 inhibitor reduces GVHD in mice via a nonimmunosuppressive mechanism that restores intestinal homeostasis. Blood 2023;141:1070–86.

Zeiser R, Blazar BR. Acute graft-versus-host disease—biologic, process, prevention, and therapy. N Engl J Med 2017;377:2167–79.

Zhang J, Ramadan AM, Griesenauer B, et al. ST2 blockade reduces sST2-producing T cells while maintaining protective mST2-expressing T cells during graft-versus-host disease. Sci Transl Med 2015;7:308ra160.

Zhang T, Yin C, Boyd DF, et al. Influenza virus Z-RNAs induce ZBP1-mediated necroptosis. Cell 2020;180:1115–29.

Zhao D, Kim YH, Jeong S, et al. Survival signal REG3α prevents crypt apoptosis to control acute gastrointestinal graft-versus-host disease. J Clin Invest 2018;128:4970–79.

Appendix 1
Schedule of Activities

	Screen[a]	Treatment Periods									Safety Follow-Up Period		UV[e]	Long-Term Follow-Up[f]
		Mandatory Treatment on Days 1–28[b]					Optional Treatment Extension[b]				Follow-Up Visit 1[c]	Follow-Up Visit 2/ET Visit[d]		
Day (Window)													NA	
Informed consent[h]	X													
Demographics	X													
Medical history and baseline conditions	X													
Vital signs[i]	X	X		X		X		X		X		X	X	
Weight[j]	X	X	X	X	X	X		X		X		X		
Height	X													
Complete physical examination[k]	X					X				X				
Limited physical examination[l]		X		X								X	X	
Neurologic examination[m]	X	X[m]	X[m]			X	X[m]			X		X	X	
Single 12-Lead ECG	X	X				X				X			X	
Hematology[n]	X	X	X	X	X	X	X	X	X	X		X	X[o]	
Chemistry[p]	X	X	X	X	X	X	X	X	X	X		X	X[o]	
Coagulation (INR, aPTT, PT)	X													
Pregnancy test[q]	X					X						X[q]	X	

Appendix 1: Schedule of Activities

	Screen[a]	Treatment Periods										Safety Follow-Up Period		UV[e]	Long-Term Follow-Up[f]
		Mandatory Treatment on Days 1–28[b]					Optional Treatment Extension[b]					Follow-Up Visit 1[c]	Follow-Up Visit 2/ET Visit[d]		
Day (Window)														NA	
Serum sample (ST2 and REG3α) for MAP calculation	x	x	x	x	x	x	x	x	x	x		x	x[r]	x[s]	
MAGIC aGVHD Staging	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Residual biopsy tissue sample (if available)[t]	x[t]	x[t]													
GDC-8264 administration[u]		Once a day on Days 1–28					Once a day on Days 29–56								
Clinical response assessment			x	x	x	x	x	x	x	x	x	x	x	x	
Chronic GVHD staging[v]	x		x	x	x	x	x	x	x	x	x	x	x	x	
Corticosteroid-refractory aGVHD			x	x	x	x	x	x	x	x					
Plasma PK sample[w]		See Appendix 2											x[w]		
Serum samples for exploratory biomarkers[w, s]	x	See Appendix 2										x[w]	x[w]	x[s]	
Buccal scraping sample for WGS/WES[x, y]		x													
Concomitant medications[z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x[z]	
Adverse events[aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x[aa]	

Appendix 1: Schedule of Activities

	Screen[a]	Treatment Periods									Safety Follow-Up Period		UV[e]	Long-Term Follow-Up[f]
		Mandatory Treatment on Days 1–28[b]						Optional Treatment Extension[b]						
Day (Window)	[redacted]										Follow-Up Visit 1[c]	Follow-Up Visit 2/ET Visit[d]	NA	[redacted]
Malignancy relapse or progression follow-up[bb]												x		x
Survival follow-up[bb]												x		x

aGVHD = acute graft-versus-host disease; ET = early termination; MAGIC = Mount Sinai Acute GVHD International Consortium; MAP = MAGIC algorithm probability; NA = not applicable; PK = pharmacokinetic; Screen = screening; UV = unscheduled visit; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: All assessments should be performed within the designated window for the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within [redacted] may be used; such assessments do not need to be repeated for screening.

[b] At the investigator's discretion, patients with partial response, very good partial response, or complete response (as defined in Section 3.1.4) on [redacted] may receive GDC-8264 at the same dose level administered once a day for 28 additional days (Days 29–56). If treatment extension is anticipated, it is recommended that the [redacted] visit be scheduled such that there is no interruption in daily GDC-8264 dosing.

[c] Patients who complete the treatment period will return to the clinic for safety follow-up visit 1 at [redacted]

[d] Patients who complete the treatment period will return to the clinic for safety follow-up visit 2 at [redacted] Patients who discontinue from the study prior to completing the safety follow-up period will return to the clinic for an early termination visit [redacted]

[e] An unscheduled visit is a visit or unscheduled assessment during the treatment or safety follow-up periods (or [redacted]) that is not specified by the protocol during which a patient undergoes additional assessments for evaluation of potential adverse event(s). Assessments included in the unscheduled visit should be performed as clinically indicated.

[f] Required follow-up information will be collected via telephone calls and/or clinic visits approximately [redacted] after initiation of GDC-8264 dosing, or until death, loss to follow-up, or study termination by the Sponsor.

[g] It is recommended that all staging and efficacy measures be captured as close to [redacted] as possible, including predose biomarker samples (see Appendix 2).

[h] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than [redacted] initiation of study treatment.

[i] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. During the treatment period, for patients who are hospitalized, vital signs obtained closest to and prior to the dose of GDC-8264 should be reported as the vital signs for the scheduled study visit.

[j] Patient weight should be obtained on each day when PK samples are drawn. For the steady-state PK visit, weight should be measured once on the initial day of sample collection. See Appendix 2 for the schedule of PK samples.

[k] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[l] A limited, symptom-directed examination should be performed at specified timepoints or as clinically indicated.

[m] The targeted neurologic assessment will be focused on motor abnormalities and may include an assessment of orientation, facial and eye movement assessment (e.g., through evaluation of cranial nerves III–VII, XI, XII), and a check for postural tremor or myoclonic movements in the outstretched arm(s). The same assessment performed at baseline should be repeated at each timepoint. The neurologic examination during the treatment period should be performed postdose. On Day 1, the neurologic examination should be performed approximately 2 (±1) hours after the first dose of GDC-8264.

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[o] If patients are receiving strong inhibitors of CYP3A (such as azole anti-infectives) in combination with GDC-8264, perform safety laboratory tests twice a week during treatment with GDC-8264.

[p] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, and AST.

[q] All women of childbearing potential have a negative serum pregnancy test result within [redacted] prior to initiation of GDC-8264. A negative urine pregnancy test result may be substituted if obtaining results from a serum pregnancy test would delay enrollment. Pregnancy tests during the treatment and safety follow-up periods may be serum or urine. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] If a patient is diagnosed with corticosteroid-refractory aGVHD or aGVHD flare, a serum sample for exploratory biomarkers (see Appendix 2) and for ST2 and REG3α for MAP calculation and determination of Ann Arbor score should be obtained on the day of diagnosis.

[s] Serum sample collection for ST2 and REG3α for MAP calculation and determination of Ann Arbor score will be performed only at [redacted] during the long-term follow-up period.

[t] Residual biopsy tissue samples from involved aGVHD target organs (e.g., GI, skin) obtained as part of standard of care up to 2 weeks prior to study enrollment or during the study. Patients may undergo biopsies of involved organs to inform the diagnosis of aGVHD and/or to inform clinical management decisions according to institutional guidelines; biopsies of involved aGVHD target organs consistent with institutional guidelines are encouraged but not required for this study. For patients with residual biopsy tissue samples available, the samples will be submitted to the Sponsor or designated laboratory only after the tissue samples are no longer required for clinical care.

[u] *GDC-8264 should be taken at approximately the same time each day, with or without food. A planned dose can be delayed up to* [redacted]*, per the investigator's clinical judgment. The tablets should be swallowed whole and should not be crushed, broken, or chewed prior to swallowing. If a dose of GDC-8264 is missed (delayed by more than* [redacted] *or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose (i.e., the next day).*

[v] Chronic GVHD staging includes performance assessment through use of the Karnofsky Performance Score (see Appendix 5).

[w] See Appendix 2 for detailed schedule.

[x] Buccal scraping sample should be obtained on Day 1, unless postponing sample collection would be clinically indicated in the investigator's judgment (e.g., presence of active mucositis). If buccal scraping sample is not obtained on Day 1, it should be obtained as early during the patient's study participation as clinically feasible.

[y] Not applicable for a site that has not been granted approval for WGS or WES.

[z] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from [redacted] prior to initiation of GDC-8264 *(or* [redacted] *prior if initiation of GDC-8264 is delayed due to administrative or logistical reasons)* until [redacted] after the final dose of GDC-8264. Corticosteroid use will be documented through [redacted].

[aa] After informed consent has been obtained but prior to initiation of GDC-8264, *all* serious adverse events should be reported. After initiation of GDC-8264, all adverse events will be reported until [redacted] after the final dose of GDC-8264. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to GDC-8264 (see Section 5.6).

[bb] After the safety follow-up period, information on malignancy relapse or progression and survival status will be collected via telephone calls, patient medical records, and/or clinic visits approximately [redacted] or until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Pharmacokinetic and Exploratory Biomarker Samples

Visit	Timepoint	Sample Type	
		GDC-8264 PK (plasma)	Exploratory Biomarker (serum)
Screening	Any time	—	Biomarker
[redacted]	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] hours after dosing	GDC-8264 PK	—
	[redacted] hours after dosing	GDC-8264 PK	—
	[redacted]) hours after dosing [a]	GDC-8264 PK	—
	[redacted] hours after Day 1 dosing (and prior to Day 2 dosing) [a]	GDC-8264 PK	—
Steady-state PK visit: [redacted] (hospitalized patient) or [redacted] (outpatient) [b]	Predose (up to 2 hours before dosing)	GDC-8264 PK	
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] after dosing	GDC-8264 PK	—
	[redacted] hours after dosing	GDC-8264 PK	—
	[redacted] hours after dosing	GDC-8264 PK	—
	[redacted] hours after dosing [a]	GDC-8264 PK	—
	[redacted] hours after prior day dosing (and prior to dosing on this day) [a]	GDC-8264 PK	—
[redacted] [b]	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker

Appendix 2: Schedule of Pharmacokinetic and Exploratory Biomarker Samples

Visit	Timepoint	Sample Type	
		GDC-8264 PK (plasma)	Exploratory Biomarker (serum)
[redacted] [b]	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted] [b]	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted]	Mandatory treatment: any time Optional TE: Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted] (Optional TE only)	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted] (Optional TE only)	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted] (Optional TE only)	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
[redacted] (Optional TE only)	Predose (up to 2 hours before dosing)	GDC-8264 PK	Biomarker
Unscheduled visit [c, d, e]	—	GDC-8264 PK	Biomarker
Follow-up visit 2 [f] [redacted]	—	—	Biomarker
[redacted]	—	—	Biomarker

aGVHD = acute graft-versus-host disease; PK = pharmacokinetic; QTcF = QT interval corrected through use of Fridericia's formula; TE = treatment extension.

Notes: Please see the laboratory manual for sample details and processing instructions. See Appendix 1 for visit windows.

[a] The 12-hour and 24-hour postdose samples are optional if patient is not hospitalized. Samples for hospitalized patients should be collected.

[b] The target visit day for the steady-state PK visit is [redacted] if the patient is hospitalized or [redacted] if the patient is an outpatient. If the steady-state PK visit samples cannot be obtained on the target day, the steady-state PK visit may occur on any dosing day between [redacted], inclusive. If the steady-state PK visit is also the [redacted] visit, only one predose collection is required. If the steady-state PK visit schedule is followed on D[redacted], the 24-hour postdose collection point will also serve as the [redacted] predose collection, respectively.

[c] An unscheduled visit is a visit or unscheduled assessment during the treatment or safety follow-up periods (or [redacted]) that is not specified by the protocol during which a patient undergoes additional assessments for evaluation of potential adverse event(s).

[d] *If a patient is diagnosed with corticosteroid-refractory aGVHD or aGVHD flare, a serum sample for exploratory biomarkers should be obtained on the day of diagnosis. See Section 3.1.4 for key definitions and details on response criteria.*

[e] PK samples should be obtained if prolonged QTcF is observed or if a patient experiences seizure or convulsion (obtain PK sample as soon as possible). If an unscheduled visit occurs after [redacted] or after [redacted] for patients entering the optional treatment extension, a PK sample should not be obtained.

[f] Patients who complete the treatment period will return to the clinic for a safety follow-up visit at [redacted] (± 7 days). Patients who discontinue GDC-8264 prematurely will return to the clinic for a safety follow-up visit [redacted]

Appendix 3
Ann Arbor Scoring

The Mount Sinai Acute GVHD International Consortium (MAGIC), a group of 25 hematopoietic cellular transplantation centers conducting graft-versus-host disease(GVHD) research, has validated an algorithm that combines two gastrointestinal biomarkers (interleukin [IL]-33 receptor suppressor of tumorigenesis 2 [ST2]) and regenerating islet-derived 3-alpha [REG3α]) into a single value that estimates the probability of 6-month non-relapse mortality (NRM) for individual patients, known as the MAGIC algorithm probability (MAP). The MAP also predicts response to treatment, maximum aGVHD severity, and overall survival. The MAP is able to separate patients into three distinct risk strata (Ann Arbor scores 1, 2, and 3). The concentration of ST2 and REG3α are determined by validated ELISA. The MAP is calculated using the following formula:

MAP = 1 - EXP(- EXP(0.577*LOG(REG3α,10)+1.844*LOG(ST2,10) - 11.263))

Ann Arbor aGVHD score cut-offs are as follows:

- Ann Arbor Score 1: MAP $<$ 0.141
- Ann Arbor Score 2: 0.141 $\leq$ MAP $\leq$ 0.290
- Ann Arbor Score 3: MAP $>$ 0.290

References

Hartwell MJ, Özbek U, Holler E, et al. An early biomarker algorithm predicts lethal graft-versus-host disease and survival. JCI Insight 2017; 2:e89798.

Srinagesh HK, Özbek U, Kapoor U, et al. The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease. Blood Adv 2019;3:4034–42.

Appendix 4
Mount Sinai Acute GVHD International Consortium (MAGIC)
Acute GVHD Target Organ Staging

Table 1

GVHD Target Organ Staging

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	-	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	-	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

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

Grade 0: No stage 1–4 of any organ

Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement

Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI

Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI

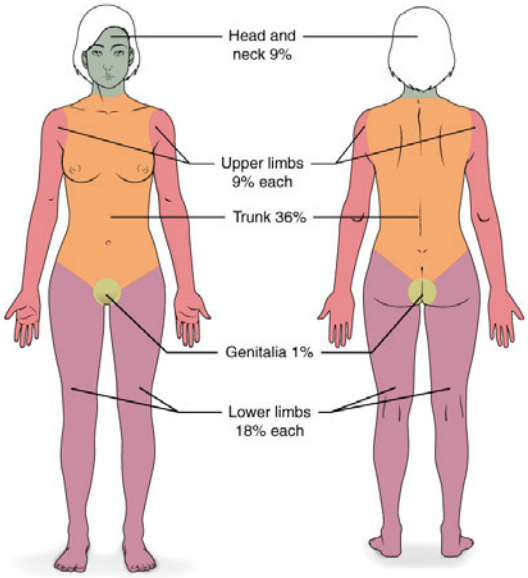
Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

Reference

Harris AC, Young R, Devine S, et al. International, multi-center standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 2016;22:4–10.

Percent Body Surface Area Calculation (Rule of Nines)

The percent body surface area (%BSA) of skin involvement is estimated assigning percentages to different body areas using the Rule of Nines (Moore et al. 2021) as shown in the figure below. The entire head is estimated as 9% (4.5% each for the anterior and posterior aspects). The entire trunk is estimated at 36% and can be divided into 18% for anterior components and 18% for the back. The anterior aspect of the trunk can further be divided into chest (9%) and abdomen (9%). The upper extremities total 18% and thus 9% for each upper extremity. Each upper extremity can further be divided into anterior (4.5%) and posterior (4.5%). The lower extremities are estimated at 36%, with18% for each lower extremity. Again, each lower extremity can be further divided into 9% each for the anterior and posterior aspects. The groin is estimated at 1%.



References

Moore RA, Waheed A, Burns B. Rule of Nines. [Updated 9 July 2021]. In: StatPearls [resource on the Internet]. Treasure Island: StatPearls Publishing, January 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513287/.

Wallace Rule of Nines for determining percent of burned body surface area. Contributed by OpenStax College, (Public Domain). In: StatPearls [resource on the Internet]. Treasure Island: StatPearls Publishing, January 2022.. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537190/figure/article-38400.image.f1/.

Appendix 5
National Institutes of Health Chronic GVHD Diagnosis and Staging

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		**S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation; Hypopigmentation; Poikiloderma; Severe or generalized pruritus; Hair involvement; Nail involvement; *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* **Yes** **No**	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs on examination **with** major limitation of oral intake
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Appendix 5: National Institutes of Health Chronic GVHD Diagnosis and Staging

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

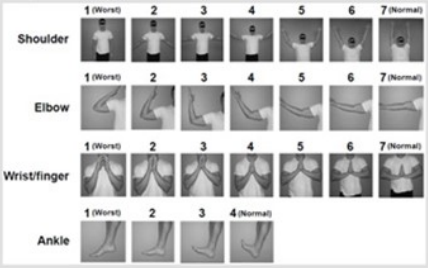
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR**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

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

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

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Reference

Jagasia MH, Grenix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant 2015;21:389–401.

Appendix 6
Primary Disease Relapse or Progression Guidance

Primary disease relapse or progression is defined in Section 3.1.4.7. Additional guidance on assessment of relapse or progression is provided below.

For acute leukemia, chronic myeloid leukemia, and myelodysplastic syndrome (MDS), relapse is defined as meeting any of the following criteria:

- Reappearance of leukemia blast cells in the peripheral blood
- Greater than 5% blasts in the bone marrow not attributable to another cause (e.g., bone-marrow regeneration)
- For patients with MDS: appearance of previous or new dysplastic changes within the bone marrow, with or without falling donor chimerism
- Development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid

For lymphoproliferative diseases, relapse or progression is defined as meeting all of the following criteria:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size

  Increased fluoro-deoxyglucose (FDG) uptake in a previously unaffected site will be considered relapsed or progressive disease (PD) only after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by computed tomography (CT) scan are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the positron emission tomography (PET) without histologic confirmation.

  At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules).

  To be considered PD, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.
- Lesion that is PET-positive if observed in a typical FDG-avid lymphoma or PET-positive before therapy, unless the lesion is too small to be detected with current PET systems (less than 1.5 cm in its long axis by CT)
- For patients with chronic lymphocytic leukemia (CLL) who present in complete remission prior to transplantation: in addition to the criteria above, reappearance of circulating malignant cells that are phenotypically characteristic of CLL

For multiple myeloma, relapse or progression is defined as meeting any one or more of the following criteria:

- Direct indicators of increasing disease and/or end-organ dysfunction (i.e., hypercalcemia, renal failure, anemia, and bone disease) related to the underlying clonal plasma-cell proliferative disorder

  This criterion is not used in calculation of time to progression or progression-free survival but can be reported optionally or for use in clinical practice

- Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)

  Definite increase in the size of existing plasmacytomas or bone lesions, defined as a 50% (and ≥to 1 cm) increase as measured serially by the sum of the product diameters of the measurable lesion.

- Hypercalcemia (> 11 mg/dL)
- Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma
- Hyperviscosity related to serum paraprotein

For the purposes of assessing relapse free survival, if patient is in complete response (CR; as defined in Section 3.1.4.1), relapse is defined as meeting any one or more of the following criteria:

- Reappearance of serum or urine M-protein by immunofixation or electrophoresis
- Development of ≥5% plasma cells in the bone marrow
- Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia; see above).

For myeloproliferative neoplasms, relapse from CR is defined as meeting one or more of the following criteria:

- Reappearance of bone-marrow disease, including blasts, monocytic blast equivalents, or fibrosis
- New extramedullary disease, including new or reappearance of splenomegaly, hepatomegaly, skin lesions, etc.

Institution of any therapy to treat persistent, progressive or relapsed malignancy, including the withdrawal of immunosuppressive therapy or treatment of relapse with donor lymphocyte infusion, will be considered evidence of relapse/progression regardless of whether the criteria described above were met. The use of preemptive

donor lymphocyte infusion is not considered as relapse. Relapse will also be considered to have occurred if the criteria described above were not met but the cause of death was attributed to relapse.

The date of relapse is the earlier of one of the following:

- Relapse criteria met
- Malignant disease that did not meet the specified relapse criteria was detected and treatment was initiated
- Death occurred and cause was reported as relapse

Non-malignant diseases will be considered to have a transplant status of persistent or active disease. Graft failures will be considered recurrence.

Appendix 7
Blood and Marrow Transplant Clinical Trials Network
Severity Grading Table and Recurrence Interval Definitions

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g., urinary tract infection)	Bacteremia (except CoNS) without severe sepsis ***	Bacteremia with deep organ involvement (e.g., with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Proprioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy d/t progression Localized or diffuse infections requiring incision with or without drain placement	Fasciitis requiring debridement
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea ≥ 1L (child ≥ 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g., oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven). Proven or probable fungal sinusistis confirmed radiologically without orbital, brain or bone involvement.	Fungemia including Candidemia Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).

Appendix 7: Bone and Marrow Transplant Clinical Trials Network Severity Grading Table and Recurrence Interval Definitions

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Fungal infections continued			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus. *Pneumocystis jiroveci* pneumonia (regardless of PaO2 level)
Viral infections	Mucous HSV infection Dermatomal Zoster Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy EBV reactivation not treated with rituximab Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy BK viremia or viruria with cystitis not requiring intervention	VZV infection with 3 or more dermatomes Clinically active CMV infection (e.g., symptoms, cytopenias) or CMV Viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy EBV reactivation requiring institution of therapy with rituximab Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment Clinically active HHV-6 infection (e.g., symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy BK viremia or viruia with clinical consequence requiring prolonged	Severe VZV infection (coagulopathy or organ involvement) CMV end-organ involvement (pneumonitis, enteritis, retinitis) EBV PTLD Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)

Appendix 7: Bone and Marrow Transplant Clinical Trials Network Severity Grading Table and Recurrence Interval Definitions

Type of Infection/ Severity Grade	Grade 1	Grade 2	Grade 3
Viral infections continued		therapy and/or surgical intervention Enterocolitis with enteric viruses Symptomatic upper tract respiratory virus Any viremia (virus not otherwise specified) requiring therapy	 Lower tract respiratory viruses Any viral encephalitis or meningitis
Parasitic infections			CNS or other organ toxoplasmosis Strongyloides hyperinfection
Nonmicrobiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation Typhlitis	Any acute pneumonia requiring mechanical ventilation Severe sepsis*** without an identified organism

*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity.
**Therapy includes both PO and IV formulations
***Severe Sepsis

Adults:

Hypotension

-A systolic blood pressure of <90 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension

Multiple Organ Dysfunction Syndrome

-2 or more of the following: Renal failure requiring dialysis, respiratory failure requiring bipap or intubation, heart failure requiring pressors, liver failure

Pediatrics:

-Pediatric SIRS definition and suspected or proven infection and cardiovascular dysfunction or ARDS or TWO or MORE other organ dysfunctions

Pediatric SIRS definition:
Two or more of the following, *one of which must be abnormal temperature or leukocyte count*

1) Core temperature >38.5C ***or*** < 36C
2) Tachycardia, otherwise unexplained persistent in absence of external stimulus, chronic drugs or painful stimuli. ***or*** bradycardia, in < 1 year old, otherwise unexplained persistent.
3) Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
4) Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands

Pediatric organ dysfunction criteria:

Cardiovavascular: despite administration of fluid bolus ≥40 ml/kg in 1 hour:

- Hypotension <5th percentile for age (***or*** per Table 1)
- Pressors at any dose
- Two of the following:
  - Capillary refill > 5 secs
  - Core to peripheral temperature gap > 3^{o}C
  - Urine output < 0.5 mL/kg/hr
  - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
  - Blood lactate > 2 x ULN

Respiratory:

- ARDS ***or***
- Intubated ***or***
- >50% FiO2 to maintain SaO2 > 92%

Neurologic:

- Glasgow Coma Score ≤ 11 ***or***
- Acute change in mental status with a decrease in GSC ≥3 pts from abnormal baseline

Renal:

- Serum creatinine ≥ 2 x ULN for age ***or*** 2-fold increase in baseline creatinine

Hepatic:

- Total bilirubin ≥4 mg/dL ***or***
- ALT ≥2 x ULN for age

Appendix 7: Bone and Marrow Transplant Clinical Trials Network Severity Grading Table and Recurrence Interval Definitions

TABLE 1: FOUR AGE GROUPS RELEVANT TO HCT:

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP mmHg
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<100
2 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<94
6 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<105
13 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<117

Disseminated Infections:

1. Two or more non-contiguous sites with the SAME organism
2. A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV, EBV, HHV6: 2 months (< 60 days)
2. VZV, HZV: 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

For infections coded as "Disseminated" per the *Infection Form*, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

Reference

[BMT CTN] Bone and Marrow Transplant Clinical Trials Network. Severity grading table and recurrence interval definitions Version 3, 19 March 2013 [resource on the Internet] 2021 [cited 17 December 2021]. Available from: https://web.emmes.com/study/bmt2/public/Definition/Severity%20Grading_Recurrence%20Interval.pdf.

Signature Page for Protocol - GA43861 - RIP1 (2) - v4 - Published
System identifier: RIM-CLIN-495937

Approval Task	[redacted] Company Signatory 20-Jul-2023 15:57:02 GMT+0000