

CLINICAL STUDY PROTOCOL

PRODUCT: GLASSIA

STUDY TITLE: A Two-Part, Multi-Center, Prospective, Phase 2/3 Clinical Study to Evaluate the Safety and Efficacy of GLASSIA as an Add-On Biopharmacotherapy to Conventional Steroid Treatment in Subjects with Acute Graft-Versus-Host Disease with Lower Gastrointestinal Involvement

STUDY SHORT TITLE: A Phase 2/3 Study of GLASSIA for the Treatment of Acute GvHD

PROTOCOL IDENTIFIER: CT2/3-GVHD-IV-Multi-Center-KAM/BAX; 471501

CLINICAL TRIAL PHASE 2/3

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ALL VERSIONS:

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Study Sponsor(s):

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1. STUDY PERSONNEL

1.1 Authorized Representative (Signatory) / Responsible Party

Judit Koranyi, MD

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Global Clinical Development Operations

Baxalta US Inc. / Baxalta Innovations GmbH

1.2 Study Organization

The name and contact information of the responsible party and individuals involved with the study (eg, investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees and oversight committees [including ethics committees (ECs)], as applicable) will be maintained by the sponsor and provided to the investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs.

ALL SAEs, INCLUDING SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARs), ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT (SAER) FORM AND TRANSMITTED TO THE SPONSOR WITHIN 24 HOURS AFTER BECOMING AWARE OF THE EVENT

**Drug Safety contact information: see SAE Report form.
Refer to SAE Protocol Sections and the study team roster for further information.**

For definitions and information on the assessment of these events, refer to the following:

- Adverse event (AE), Section [12.1](#)
- SAE, Section [12.1.1.1](#)
- SUSARs, Section [12.1.1.2](#)
- Assessment of AEs, Section [12.1.2](#)

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	GLASSIA
Name(s) of Active Ingredient(s)	Alpha-1 Proteinase Inhibitor
CLINICAL CONDITION(S)/INDICATION(S)	
Treatment of acute graft-versus-host disease (GvHD) with lower gastrointestinal (GI) involvement resulting from allogeneic hematopoietic stem cell transplant (HSCT)	
PROTOCOL ID	CT2/3-GVHD-IV-Multi-Center-KAM/BAX; 471501
PROTOCOL TITLE	A Two-Part, Multi-Center, Prospective, Phase 2/3 Clinical Study to Evaluate the Safety and Efficacy of GLASSIA as an Add-On Biopharmacotherapy to Conventional Steroid Treatment in Subjects with Acute Graft-Versus-Host Disease with Lower Gastrointestinal Involvement
Short Title	A Phase 2/3 Study of GLASSIA for the Treatment of Acute GvHD
STUDY PHASE	Ph2/3
PLANNED STUDY PERIOD	
Initiation	2016 OCT
Primary Completion	2018 SEP (all subjects complete Day 56 in Part 2 or discontinue study treatment)
Study Completion	2019 JUL
Duration	Approximately 3 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
The purpose of the study is to evaluate the safety and efficacy of GLASSIA as an add-on biopharmacotherapy to standard-of-care steroid treatment as the first-line treatment in subjects with acute GvHD with lower GI involvement.	
Primary Objective	
This study has 2 study parts:	
<u>Part 1:</u>	
To confirm the safety and efficacy of GLASSIA administered at a dose of 90 mg/kg (Day 0) followed by 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49), when added to conventional steroid therapy, in subjects with acute GvHD with Stage 1 to 4 lower GI involvement, as assessed by treatment response at Day 28, and to determine whether continuation to Part 2 is warranted.	
<u>Part 2:</u>	
To confirm the safety and efficacy of the GLASSIA dose regimen studied in Part 1 versus albumin (control), when added to conventional steroid therapy, in subjects with acute GvHD with Stage 1 to 4 lower GI involvement, as assessed by treatment response at Day 28.	

Secondary Objective(s)

Efficacy

Part 1:

To evaluate the treatment effects of GLASSIA, when added to conventional steroid therapy, on other clinical outcomes, such as rate, duration and magnitude of response; all-cause, transplant-related, infection-related and GvHD-related mortality; overall survival; GvHD-free survival; treatment failure-free survival and incidence of chronic GvHD.

Part 2:

To determine the efficacy of GLASSIA versus albumin (control), when added to conventional steroid therapy, on other clinical outcomes, such as rate, duration and magnitude of response; all-cause, transplant-related, infection-related and GvHD-related mortality; overall survival; GvHD-free survival; treatment failure-free survival and incidence of chronic GvHD.

Safety (Parts 1 and 2):

1. To evaluate the safety and tolerability of GLASSIA in addition to conventional steroid therapy (Part 1) and compared with conventional steroid treatment alone (Part 2)
2. To assess the incidence of recurrence of primary malignancies
3. To assess the incidence and type of infection

Pharmacokinetics (Part 1 Only):

1. To characterize the pharmacokinetic (PK) profile of GLASSIA, when added to conventional steroid treatment, using noncompartmental analysis methodology

Exploratory (Parts 1 and 2):

1. To assess alpha-1 proteinase inhibitor (A₁PI) plasma and stool concentrations and clearance in stool
2. To characterize the PK profile of GLASSIA, when added to conventional steroid treatment, using a population PK approach
3. To assess biomarkers in plasma (ie, inflammatory cytokines interleukin [IL]-2, IL-6, IL-8, and IL-10; IL-1 receptor antagonist [IL-1RA] and T cell subpopulations, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ regulatory T cells [Tregs]) and stool (ie, calprotectin concentrations)
4. To assess quality-of-life (QoL), GvHD symptoms and healthcare resource utilization for GLASSIA treatment as a first-line add-on therapy

Exploratory (Part 2 Only):

1. To assess the following additional biomarkers in plasma on Day 0 and Day 28: Reg3 α , ST2, and TNFR1

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, PK, Pharmacodynamic, Safety, Tolerability
Control Type	Part 1: No control Part 2: Concurrent control (albumin control)
Study Indication Type	Treatment
Intervention model	Part 1: Single group Part 2: Parallel groups
Blinding/Masking	Part 1: Open-label Part 2: Double-blind
Study Design	<p>This is a 2-part Phase 2/3, prospective, controlled, randomized, multicenter study in subjects with acute GvHD with Stage 1 to 4 lower GI involvement. Part 1 will evaluate the safety, efficacy, and PK of GLASSIA in approximately 20 evaluable subjects. Part 2 will compare the safety and efficacy of GLASSIA versus albumin (control) in a total of approximately 148 randomized subjects (74 subjects/group).</p> <p>All eligible subjects in Parts 1 and 2 will be given 2 mg/kg/day of methylprednisolone or equivalent steroid and intravenous (IV) study treatment (defined as GLASSIA in Part 1; GLASSIA or control in Part 2). Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.</p> <p>Results from Part 1 will be used to determine whether continuation to Part 2 is warranted. All efficacy data will be adjudicated by an Adjudication Committee.</p> <p>All subjects will be treated with study treatment in combination with conventional steroid treatment through Day 49, or until treatment failure, withdrawal from treatment or withdrawal from the study, whichever comes first. Thereafter, subjects will be treated with standard-of-care for the remainder of their participation in the study based on the investigator's discretion. Subjects who are withdrawn from study treatment will continue to be followed through at least Day 28, unless the subject withdraws consent.</p>

Part 1

Part 1 of this study is a nonrandomized, open-label, active treatment, multicenter study evaluating GLASSIA in combination with conventional steroid treatment.

Cohort 1 (20 evaluable subjects): GLASSIA loading dose of 90 mg/kg (Baseline/Day 0) followed by GLASSIA 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49), in combination with 2 mg/kg/day methylprednisolone or equivalent steroid. Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.

For Part 1, subjects who are treated but subsequently found to have a lower GI biopsy inconsistent with GvHD will be replaced to ensure a total of 20 evaluable subjects.

Interim Analysis

An analysis will take place when the last subject in Part 1 has completed the GvHD response assessment at Day 28, to determine whether continuation from Part 1 to Part 2 is warranted.

Part 2

Criteria for Initiation of Part 2

The following decision criteria will be followed for the initiation of Part 2 of the study:

- The study may be terminated by the sponsor for toxicities or adverse safety findings observed in Part 1 of the study
- The study may proceed to Part 2 if an overall response rate of $\geq 55\%$ is observed at Day 28 in Part 1, as determined by the sponsor
- The study may be stopped for futility if the overall response rate is $< 55\%$ at Day 28
- The sponsor will be the final arbiter of the decision to move into Part 2. The decision will be based on the totality of cumulative data available (eg, rate of GvHD complete response [CR], partial response [PR] and very good partial response [VGPR]; rate of GI CR and PR, including response at Days 28 and 56; duration of any overall and any GI response; and GvHD-free survival)

	<p>Study Design for Part 2</p> <p>Part 2 of this study is a randomized, parallel-group, double-blind, placebo (albumin)-controlled, clinical study comparing GLASSIA in combination with conventional steroid treatment versus albumin (control) in combination with conventional steroid treatment. Part 2 of the study is planned to enroll approximately 148 randomized subjects (74 subjects/group) in order to obtain 134 evaluable subjects, provided that the study does not stop early for futility. Eligible subjects will be randomized 1:1 in a double-blind fashion to 1 of the following groups:</p> <p>Group 2a: GLASSIA loading dose of 90 mg/kg (Baseline/Day 0) followed by GLASSIA 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49), in combination with 2 mg/kg/day methylprednisolone or equivalent steroid. Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.</p> <p>Group 2b: Albumin (control), in combination with 2 mg/kg/day methylprednisolone or equivalent steroid. Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.</p> <p>Randomization will be stratified, using a single stratification factor: lower GI involvement severity (2 strata). Subjects who are randomized to treatment in Part 2 and subsequently discontinue treatment or withdraw from the study will not be replaced.</p> <p>Interim Analysis</p> <p>An interim analysis will take place when approximately 50% of the primary endpoint data in Part 2 has been collected. The study will be analyzed for futility based on the primary endpoint. A Data Monitoring Committee (DMC) will provide recommendations to the Sponsor based on the interim analysis. However, the sponsor may decide to stop the trial even if statistical criteria for futility are not observed.</p>
<p>Planned Duration of Subject Participation</p>	<p>Approximately 52 weeks from enrollment to study completion, including the follow-up period</p>
<p>Primary Outcome Measure (Parts 1 and 2)</p> <ol style="list-style-type: none"> 1. Proportion of subjects achieving overall response at Day 28. Overall response is defined as GvHD CR + PR, which are defined as follows: <ul style="list-style-type: none"> • GvHD CR is complete resolution of all signs and symptoms of acute GvHD in all organs without intervening salvage • GvHD PR is improvement of 1 stage in 1 or more organs involved in GvHD without progression in other organs 	

Secondary Outcome Measures

Key Secondary Efficacy Outcome Measure (Parts 1 and 2)

1. Proportion of subjects achieving GI response at Day 28. Gastrointestinal response is defined as GI CR + PR, as defined below:
 - GI CR is defined as
 - a) Able to eat; not requiring parenteral nutrition, and
 - b) Passing primarily formed stools
 - GI PR is defined as
 - a) Decrease in need for parenteral nutrition to $\leq 50\%$ of required calories; and
 - b) Reduction of stool volume by $\geq 50\%$, without ileus

Other Secondary Efficacy Outcome Measures (Parts 1 and 2)

1. Proportion of subjects achieving overall response at Day 56
2. Change from baseline in acute GvHD grading at Days 28, 56 and 180
3. Incidence of chronic GvHD at Days 100, 180 and 365
4. Duration of any overall response
5. Duration of any GI response
6. Overall survival through Days 100, 180 and 365
7. Transplant-related mortality at Days 28, 56, 100 and 180
8. Failure-free survival at Days 100 and 180
9. GvHD-free survival at Days 28, 56, 100 and 180
10. Infection-related mortality at Days 28, 56, 100 and 180
11. GvHD-related mortality at Days 28, 56, 100 and 180
12. All-cause mortality at Days 28, 56, 100 and 180

Safety Outcome Measures (Parts 1 and 2)

1. The incidence and severity of all AEs, related AEs, all serious adverse events (SAEs), related SAEs and temporally-associated AEs
2. Change from baseline in clinical laboratory safety parameters and vital signs
3. Incidence of recurrence of primary malignancies through Days 180 and 365
4. Incidence and type of infection (eg, bacterial, fungal, viral, etc) at Days 28, 56, 180 and 365

Pharmacokinetic Outcome Measures (Part 1 only)

The following noncompartmental analysis PK parameters by day and/or dosing frequency, as applicable, will be assessed:

1. Area under the plasma concentration curve (AUC) from time zero to the last quantifiable activity
2. AUC from time zero to time "t"
3. Systemic clearance at steady state
4. Maximum plasma concentration at steady state

5. AUC from time zero to infinity
6. Apparent volume of distribution at steady state
7. The terminal half-life
8. Mean residence time
9. Trough plasma A₁PI levels at steady state

Exploratory Outcome Measures

Efficacy (Parts 1 and 2)

1. Proportion of subjects achieving GvHD VGPR at Day 28. A GvHD VGPR is defined as follows:
 - Skin: no rash, or residual erythematous rash involving <25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
 - Liver: total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment
 - Gut: tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abdominal cramping and no more than occasional nausea or vomiting
2. Cumulative steroid dose at Days 28, 56, 100 and 180
3. Steroid dose at Days 28, 56 and 100
4. Proportion of subjects achieving GI CR and GI PR at Days 28, 56 and 180 at each baseline GvHD severity grade (B, C and D)

Pharmacokinetics (Parts 1 and 2)

An exploratory, mixed-effects population PK model will be developed from the Part 1 and Part 2 data. Potential exploratory outcome measures include, but are not limited to, the following:

1. Systemic clearance at steady state
2. Maximum plasma concentration at steady state
3. Apparent volume of distribution at steady state
4. The terminal half-life
5. Trough plasma A₁PI levels at steady state

Pharmacodynamics (Parts 1 and 2)

1. Change from baseline in plasma and stool concentrations of A₁PI
2. A₁PI clearance in stool
3. Change from baseline in plasma biomarkers (eg, cytokines IL-2, IL-6, IL-8, and IL-10; and IL-1RA) and stool calprotectin concentrations
4. T cell subpopulations from serum, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs

Pharmacodynamics (Part 2 Only)

1. Change from baseline in additional plasma biomarkers on Day 0 and Day 28 (Reg3 α , ST2, and TNFR1)

Health Outcomes (Parts 1 and 2)	
<ol style="list-style-type: none"> 1. Change from baseline in QoL as measured by the Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale version 4.0 instrument (FACT-BMT) 2. Change from baseline in acute GvHD symptoms as measured by the Chronic GvHD Symptom Scale 3. Change from baseline in health utility as measured by European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) 4. Healthcare resource utilization: <ul style="list-style-type: none"> • Type of admission (Hospital, Intensive Care Unit and/or transplant unit) • Length of stay • Number of unscheduled physician office visits • Number of emergency room visits 5. Medication: <ul style="list-style-type: none"> • Days on steroids 	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Active Product	<p>GLASSIA (human A₁PI). Subjects will receive a loading dose of 90 mg/kg Baseline/Day0) followed by 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49).</p> <p>Dosage form: injection, solution</p> <p>Dosage frequency: every other day (Days 0 to 12), then weekly (Days 14 to 49)</p> <p>Mode of Administration: IV</p> <p>In combination with assigned therapy, all subjects in Parts 1 and 2 will receive 2 mg/kg/day of methylprednisolone or equivalent steroid (either oral or IV per investigator's discretion). Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.</p>
Control (Part 2 only)	<p>Human albumin in normal saline solution (see Pharmacy Manual for details)</p> <p>Dosage form: injection, solution</p> <p>Dosage frequency: every other day (Days 0 to 12), then weekly (Days 14 to 49)</p> <p>Mode of Administration: IV</p> <p>In combination with assigned therapy, all subjects will receive 2 mg/kg/day of methylprednisolone or equivalent steroid (either oral or IV per investigator's discretion). Steroids will be tapered as appropriate, according to institutional practice and guidance provided in the protocol.</p>

SUBJECT SELECTION	
Targeted Accrual	Part 1: approximately 20 evaluable subjects Part 2: approximately 148 randomized subjects
Number of Groups/Arms/Cohorts	Part 1: 1 cohort Part 2: 2 groups (GLASSIA or control) of 74 randomized subjects per group
Inclusion Criteria	
<ol style="list-style-type: none"> 1. Male or female subjects aged ≥ 18 years at the time of screening 2. Recipient of an HSCT 3. The disease indication for which the subject required HSCT must be in remission 4. Newly diagnosed acute GvHD, including lower GI involvement (modified International Bone Marrow Transplant Registry [IBMTR] Severity Stage 1 to 4 [>500 mL diarrhea/day]), with or without other organ system involvement. 5. Willing to undergo or must have had a lower GI biopsy within 7 days of informed consent to confirm GI GvHD. Biopsy results are not needed to initiate treatment; however, if biopsy results are not consistent with aGvHD, treatment with GLASSIA will be discontinued. 6. Subjects must be receiving systemic corticosteroids. Treatment with methylprednisolone/systemic steroids must have been initiated within 72 hours prior to the first dose of study treatment after enrollment. 7. Evidence of myeloid engraftment (absolute neutrophil count $\geq 0.5 \times 10^9/L$) 8. Lower GI GvHD manifested by diarrhea must have other causes of diarrhea ruled out (eg, negative for <i>Clostridium difficile</i> or cytomegalovirus [CMV] infection or oral magnesium administration) 9. Karnofsky Performance Score $\geq 50\%$ 10. If female of childbearing potential, subject presents with a negative blood pregnancy test 11. Females of childbearing potential with a fertile male sexual partner must agree to employ adequate contraception for the duration of the study. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or a condom 12. Males must use adequate contraception and must not donate sperm for the duration of the study. Adequate contraception for the male subject and his female partner is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or a condom 13. Subject is willing and able to comply with the requirements of the protocol 	

Exclusion Criteria

1. Subject with manifestations of chronic GvHD
2. Subject with acute/chronic GvHD overlap syndrome
3. Subject whose GvHD developed after donor lymphocyte infusion
4. Subject with myocardial infarction within 6 months prior to enrollment or New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to the first dose of study treatment, any electrocardiogram (ECG) abnormality at screening must be documented by the investigator as not medically relevant
5. Subject with evidence of recurrent malignancy
6. Subject with veno-occlusive disease (ie, sinusoidal obstruction syndrome)
7. Subject receiving GvHD treatment other than continued prophylaxis (eg, cyclosporine and/or mycophenolate mofetil, etc) or corticosteroid therapy. In addition, a subject who received the first dose of corticosteroid therapy for acute GvHD with lower GI involvement more than 72 hours before the first dose of study treatment is not eligible for the study
8. Subject with severe sepsis involving at least 1 organ failure
9. Subject who is seropositive or positive in the nucleic acid test for human immunodeficiency virus (HIV)
10. Subject with active hepatitis B or C
11. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. If female, subject is pregnant or lactating at the time of enrollment, or has plans to become pregnant during the study
13. Subject with a serious medical or psychiatric illness likely to interfere with participation in the study
14. Subject is a family member or employee of the investigator

STATISTICAL ANALYSIS

Sample Size Calculation

The sample size for Part 1 was determined from an operational perspective and was not based on statistical power considerations. With 20 evaluable subjects and an assumed true response rate of 65%, the probability of observing an overall response rate of at least 55% is 87.8%. If the true response rate is 40%, the probability of observing an overall response rate of 55% or higher is less than 13%.

The sample size for Part 2 is based on the assumptions of a control group overall response rate of 40% across strata; GLASSIA group overall response rate of 65% across strata; randomization ratio 1:1; 1-sided family wise Type I error rate of 0.025; Type II error rate of 0.20; and a group sequential design with 1 interim look. Based on the sample size calculations, using a Cochran-Mantel-Haenszel chi-squared test, controlling the stratification factor, to detect the difference between the 2 groups, the primary analysis will require 67 evaluable subjects per group. Assuming a 10% early withdrawal rate, the target number of subjects will include 74 randomized subjects per group for a total of 148 randomized subjects.

Planned Statistical Analysis

For Part 1, all endpoints will be summarized with descriptive statistics.

For Part 2, all statistical tests will be conducted at a 1-sided significance level of 2.5% unless otherwise specified. For Part 2, the primary endpoint of overall response rate at Day 28 will be analyzed using the Cochran-Mantel-Haenszel chi-squared test, controlling the stratification factor (lower GI involvement severity), to test the null hypothesis that the odds ratio is equal to 1 for Part 2 of the study. An unstratified comparison of the overall response rate at Day 28 will be conducted as a sensitivity analysis. The binary types of secondary efficacy endpoints, such as GI response rate, will be analyzed similarly to the primary endpoint. The time-to-event type of secondary endpoints, including overall survival and failure-free survival rate; all-cause, transplant-related, infection-related and GvHD-related mortality; and durations of any overall and any GI response will be analyzed using the Cox proportional hazard model. The change from baseline in acute GvHD grading will be analyzed with a shift table. All other secondary endpoints will be summarized with descriptive statistics.

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5. LIST OF ABBREVIATIONS

Abbreviation	Definition
A ₁ PI	alpha-1 proteinase inhibitor, also known as alpha-1 antitrypsin
AE	adverse event
AUC	area under the plasma concentration curve
CMV	Cytomegalovirus
CR	complete response
CRF	case report form
CTA	Clinical Trial Agreement
DMC	Data Monitoring Committee
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Level
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale version 4.0 instrument
FA set	Full Analysis set
FDA	Food and Drug Administration
GI	Gastrointestinal
GI CR/PR	Complete/partial gastrointestinal response Gastrointestinal response is defined as GI CR + PR
GvHD	graft-versus-host disease
GvHD CR/PR/VGPR	Complete/partial/very good partial graft-versus-host disease response Overall response is defined as GvHD CR + PR
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
IB	investigator's brochure
IBMTR	International Bone Marrow Transplant Registry
ICH GCP	International Council for Harmonisation Guideline for Good Clinical Practice
IgA	immunoglobulin A
IL	Interleukin
IL-1RA	interleukin-1 receptor antagonist
INR	international normalized ratio

Abbreviation	Definition
IP	investigational product
IRT	Interactive Response Technology
IV	intravenous(ly)
LOCF	last-observation-carried-forward
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMC	Non-medical complaint
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality-of-life
Reg3 α	regenerating islet-derived protein 3 α
SAE	serious adverse event
SAER	serious adverse event report
SAF set	Safety Analysis set
SIC	subject identification code
ST2	suppression of tumorigenicity 2
Study treatment	GLASSIA or albumin (control)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	tumor necrosis factor
TNFR1	tumor necrosis factor receptor 1
Tregs	regulatory T cells
US	United States
US CFR	United States Code of Federal Regulations
VGPR	very good partial response

6. BACKGROUND INFORMATION

6.1 Description of Investigational Product

6.1.1 GLASSIA

GLASSIA (human alpha-1 proteinase inhibitor [A₁PI]; also known as human alpha-1 antitrypsin, Kamada-AAT or Kamada-API) is a stable, liquid, ready-to-use preparation of human A₁PI. Alpha-1 proteinase inhibitor belongs to the family of serine protease inhibitors and is primarily produced in the liver and secreted into the circulation. In addition to its anti-protease activity, A₁PI has anti-inflammatory, anti-apoptotic and immunomodulatory properties.^{1,2,3,4}

GLASSIA is an injection solution prepared from human plasma collected from healthy volunteer blood donors in accordance with Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulations. GLASSIA was approved in the United States (US) in 2010 JUL for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of A₁PI.

In this 2-part study, GLASSIA will be administered intravenously (IV) in subjects with acute graft-versus-host disease (GvHD) with lower gastrointestinal (GI) involvement. GLASSIA will be administered at a dose of 90 mg/kg (Day 0) followed by 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49). Results from Part 1 will be used to determine whether continuation to Part 2 is warranted, if the criteria to initiate Part 2 are met.

Rationale for Dosing Regimen

The GLASSIA dosing regimen for this study was selected based on results from nonclinical mouse models of GvHD and the interim efficacy and pharmacokinetic (PK) results from an ongoing Phase 1/2 study in subjects with steroid-refractory GI GvHD (Study FHCRC 2571). In the interim analysis of Cohorts 1 and 2 in Study FHCRC 2571, efficacy was observed with doses of 30 or 60 mg/kg every other day (after induction with 90 mg/kg on the first day of treatment), which resulted in plasma A₁PI concentrations of 2.5 to 3.5 mg/mL. The dose that Cohort 1 received (30 mg/kg every other day [after induction with 90 mg/kg]) led to a plasma level of A₁PI in the high-normal range. Cohort 2 received 60 mg/kg every other day (after induction with 90 mg/kg) and had plasma A₁PI levels that overlapped with Cohort 1 (especially the trough plasma concentration). In addition, the overall response in Cohort 1 was numerically greater than the overall response in Cohort 2. Recently published preliminary data with another A₁PI product suggests that a dose similar to the Cohort 1 dose results in a similar outcome.⁵

As of 2016 JAN, 1 subject had been enrolled in Cohort 3; Cohort 3 receives 90 mg/kg every other day. The subject in Cohort 3 had a GI partial response (PR), a partial resolution of GI signs and symptoms. As the dose of A₁PI was increased, there was not an increased rate of response, suggesting that the 30 mg/kg dose every other day (after induction with 90 mg/kg) may be sufficient to replace intestinal losses and to promote healing of the gut and resolution of GvHD.

In Study FHCRC 2571, 3 subjects who had responded at Day 28 subsequently relapsed 2 or more weeks after the last dose of A₁PI. This suggests that continued therapy beyond 15 days may allow sustained response and reduce or prevent relapses of acute GvHD. Therefore, in the current protocol, subjects will receive weekly infusions (120 mg/kg) until Day 49 for maintenance. The dose and regimen will allow for the maintenance of plasma levels of A₁PI in the high-normal range, despite ongoing losses of A₁PI due to diarrhea. Less frequent doses can be justified by the data from Study FHCRC 2571 showing healing of the mucosal lesions and reduction of GI clearance of A₁PI.

A loading dose of 90 mg/kg was used in Study FHCRC 2571 and is used in this study in order to reduce the time needed to achieve steady state plasma A₁PI concentrations.

In the key nonclinical mouse models of GvHD, A₁PI was dosed at 50 to 200 mg/kg every other day.^{6,7} Refer to Section 6.4 for a summary of the relevant nonclinical and clinical studies with GLASSIA and A₁PI.

6.1.2 Control

In this protocol, study treatment is defined as GLASSIA or control. During Part 2 of the study, human albumin in normal saline solution will serve as the matching control (in volume, color and foaming characteristics) to GLASSIA. Albumin was chosen as the control because, as a protein, its physical properties will match those of GLASSIA, allowing the double-blind to be maintained. The placebo (albumin)-controlled, double-blind design used in Part 2 of this study is appropriate because there are currently no FDA-approved treatments for acute GvHD. In this study, subjects will receive study treatment in addition to conventional steroid therapy, which is the current standard-of-care for acute GvHD; thus, the use of albumin as a control will allow the comparison of GLASSIA, in combination with the current standard-of-care, versus the current standard-of-care alone.

6.2 Clinical Condition/Indication

Graft-versus-host disease is one of the most common complications of allogeneic hematopoietic stem cell transplantation (HSCT), a component of a treatment program for blood cancer and other blood disorders. Despite prophylactic treatment with immunosuppressive agents, acute GvHD occurs in 30% to 70% of patients undergoing HSCT and is associated with significant morbidity and mortality. Severe GI acute GvHD is estimated to have a mortality rate as high as 70% to 80%.⁸ Standard, frontline therapy for acute and chronic GvHD consists of glucocorticoids, but less than 40% of patients treated with steroids have durable complete responses (CRs) or PRs, a complete or partial resolution of all signs and symptoms of GvHD in all organs.^{9;10} The 1-year survival rate for subjects who do not respond to steroid therapy ranges from 5% to 30%.^{8;9;11;12,13,14} There is currently no FDA-approved treatment for acute GvHD.

6.3 Population to be Studied

The population for this study will consist of male and female subjects ≥ 18 years of age who are recipients of an allogeneic HSCT and who have been newly diagnosed with acute GvHD with lower GI involvement (modified International Bone Marrow Transplant Registry [IBMTR] Severity Stage 1 to 4).^{15;16} Subjects with Stage 1 to 4 lower GI involvement have diarrhea >500 mL/day. Subjects must have evidence of myeloid engraftment. There are no restrictions on the prior conditioning treatments.

This population was selected because it has a high unmet medical need; as described in Section 6.2, severe acute GI GvHD is associated with high mortality. Furthermore, patients with acute GvHD with lower GI involvement with or without other organ involvement have a lower response rate to steroid treatment.¹³

In addition, nonclinical and clinical data support the hypothesis that administration of exogenous A₁PI blocks pro-inflammatory cytokines and replaces intestinal losses (Section 6.4). This includes clinical data from Study FHCRC 2571 evaluating the treatment of subjects with GI GvHD with GLASSIA, in which endoscopic evaluation of patients with severe GI GvHD 1 week after completion of GLASSIA administration showed evidence of re-epithelialization of the bowel wall.¹⁷ Thus, it is expected that subjects with GI GvHD will benefit most from first-line treatment with GLASSIA, as the anticipated clinical benefit of healing of GvHD-related gut injury should be accompanied by a reduction in intestinal losses.

Refer to Section 6.4 for additional details of the nonclinical and clinical studies with A₁PI and the rationale for GLASSIA in the treatment of acute GvHD with lower GI involvement.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Nonclinical Studies

Results from nonclinical studies demonstrated that administration of exogenous A₁PI significantly reduced the incidence and severity of GvHD in murine bone marrow transplant models.^{6,7} In addition, results from nonclinical studies showed that A₁PI administration interfered with the expression of pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF) and IL-32, and was associated with increased numbers of CD4⁺ CD25hi FoxP3⁺ regulatory T cells (Tregs) and CD8⁺/CD205⁺ dendritic cells in comparison with albumin-treated controls.¹⁸ Additionally, subjects with GI GvHD have been shown to lose endogenous A₁PI in their stool. A correlation of stool content of A₁PI (and A₁PI clearance) with GvHD of the small bowel has been confirmed in pediatric¹⁹ and in adult subjects.²⁰ The loss of A₁PI in stool is an expression of intestinal injury and presumably compromises the protective systemic and local effects of A₁PI. On the basis of these results, the administration of exogenous A₁PI may a) replace intestinal losses and b) block pro-inflammatory cytokines. The expected result would be healing of GvHD-related gut injury, which should also contribute to a reduction in intestinal losses. Furthermore, the resulting shifts in the cytokine milieu should lead to an environment that facilitates the establishment of T cell tolerance.³

Nonclinical PK studies in rabbits treated with a single bolus IV administration of GLASSIA showed that the half-life of GLASSIA during the Phase 1 elimination was 16.3 hours; the maximum concentration, terminal half-life (Phase 2 half-life) and Phase 2 elimination rate constants were $42\,264 \pm 3443$ ng/mL, 68.13 ± 13.53 hours and -0.0046 ± 0.0014 hours⁻¹, respectively. Nonclinical toxicology studies have evaluated acute and repeated dosing with GLASSIA in rats and rabbits; GLASSIA was well tolerated with no overt toxicities reported. Refer to the investigator's brochure (IB) for further information on nonclinical studies with GLASSIA.

6.4.2 Clinical Studies

GLASSIA has been evaluated in 2 clinical studies in adult subjects with A₁PI deficiency, 1 clinical study in subjects aged 9 to 18 years with type 1 diabetes mellitus and 1 Phase 4 clinical study in healthy adult subjects. GLASSIA was generally safe and well tolerated in all studies; the majority of adverse events (AEs) reported were of mild or moderate severity. All serious adverse events (SAEs) reported in the clinical studies were assessed by the investigator as unrelated to GLASSIA. Three treatment-emergent SAEs were reported in the studies: cholangitis, exacerbation of chronic obstructive pulmonary disease and pulmonary emboli. All 3 SAEs were reported in the Phase 2/3 study of adult subjects with A₁PI deficiency.

One subject in the Phase 2/3 study experienced a treatment-emergent serious adverse reaction (infective exacerbation of chronic obstructive pulmonary disease), considered possibly related to GLASSIA due to its temporal association.

One ongoing Phase 1/2 study is being conducted in subjects with steroid-refractory acute GvHD (Study FHCRC 2571). An interim analysis was conducted with the 12 subjects in Cohorts 1 and 2 in Study FHCRC 2571. Cohort 1 received a loading dose of GLASSIA of 90 mg/kg IV on Day 1, followed by 30 mg/kg every other day through Day 15. Cohort 2 received a loading dose of GLASSIA of 90 mg/kg IV on Day 1, followed by 60 mg/kg every other day through Day 15. In the interim analysis, most AEs were of mild or moderate severity. Two subjects experienced bowel perforation 3 weeks and 2 months, respectively, after the last dose of GLASSIA. Neither AE resulted in death. Both AEs were assessed by the investigator as possibly related to GLASSIA; the study's Data Safety Monitoring Board reviewed the events and concluded that the 2 bowel perforation events were not related to GLASSIA, but instead were related to viral infections. One fatal SAE in the study was assessed as possibly related to GLASSIA: liver failure, which occurred <30 days after the last dose of GLASSIA. Most AEs during the study were consistent with those expected in subjects undergoing HSCT or experiencing GvHD and do not preclude further investigation of GLASSIA in GvHD.

The interim efficacy data from Study FHCRC 2571 showed that 8 of the 12 subjects had overall responses, 4 of which were CRs, and 4 of which were PRs. Six of the 12 subjects (50%) were alive at follow-up of up to 820 days at the time of the interim analysis. One of the 12 subjects died following the interim analysis. The subject in Cohort 3 died due to a fungal infection after the Day 28 assessments but was not included in the interim analysis.

6.5 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

GLASSIA was generally safe and well tolerated in the clinical studies of healthy adult subjects and subjects with A₁PI deficiency and type 1 diabetes mellitus. In the 2 clinical studies in subjects with A₁PI deficiency, the adverse reactions (ie, AEs assessed as related or possibly related to GLASSIA or temporally related to administration of GLASSIA) reported by >1 subject consisted of headache (6%) and dizziness (3%). In the ongoing clinical study in subjects with steroid-refractory acute GvHD, most AEs have been consistent with those expected in subjects undergoing HSCT or experiencing GvHD.

GLASSIA may contain trace amounts of immunoglobulin A (IgA). Subjects with selective or severe IgA deficiency and with known antibodies to IgA have a greater risk of developing severe hypersensitivity and anaphylactic reactions. However, reactions due to IgA deficiency and anti-IgA antibodies are not expected in this study because of the immunosuppressive nature of the transplant procedure.

Because the product is produced from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease agent. The risk of transmitting an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process. The risk of Creutzfeldt-Jakob disease transmission has been reduced by donor restriction and selection and the plasma derivative manufacturing process. In addition to the risks associated with GLASSIA, IV administration of GLASSIA could lead to inflammation or infection at the catheter contact area.

The preclinical literature for A₁PI, in combination with the interim efficacy results from Study FHCRC 2571, suggests that GLASSIA has the potential to provide significant clinical benefit as a first-line treatment in acute GvHD.

Refer to the IB for further guidance related to GLASSIA.

6.6 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Union Directives 2001/20/EC and 2005/28/EC and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The purpose of the study is to evaluate the safety and efficacy of GLASSIA as an add-on biopharmacotherapy to standard-of-care steroid treatment as the first-line treatment in subjects with acute GvHD with lower GI involvement.

7.2 Primary Objective

This study has 2 study parts:

The primary objective of Part 1 is to confirm the safety and efficacy of GLASSIA administered at a dose of 90 mg/kg (Baseline/Day 0) followed by 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49), when added to conventional steroid therapy, in subjects with acute GvHD with Stage 1 to 4 lower GI involvement, as assessed by treatment response at Day 28, and to determine whether continuation to Part 2 is warranted.

The primary objective of Part 2 is to confirm the safety and efficacy of the GLASSIA dose regimen studied in Part 1 versus albumin (control), when added to conventional steroid therapy, in subjects with acute GvHD with Stage 1 to 4 lower GI involvement, as assessed by treatment response at Day 28.

7.3 Secondary Objectives

7.3.1 Efficacy

Part 1:

1. To evaluate the treatment effects of GLASSIA, when added to conventional steroid therapy, on other clinical outcomes, such as rate, duration and magnitude of response; all-cause, transplant-related, infection-related and GvHD-related mortality; overall survival; GvHD-free survival; treatment failure-free survival and incidence of chronic GvHD.

Part 2:

1. To determine the efficacy of GLASSIA versus albumin (control), when added to conventional steroid therapy, on other clinical outcomes, such as rate, duration and magnitude of response; all-cause, transplant-related, infection-related and GvHD-related mortality; overall survival; GvHD-free survival; treatment failure-free survival and incidence of chronic GvHD.

7.3.2 Safety (Parts 1 and 2)

1. To evaluate the safety and tolerability of GLASSIA in addition to conventional steroid therapy (Part 1) and compared with conventional steroid treatment alone (Part 2)
2. To assess the incidence of recurrence of primary malignancies
3. To assess the incidence and type of infection

7.3.3 Pharmacokinetics (Part 1 Only)

1. To characterize the PK profile of GLASSIA, when added to conventional steroid treatment, using noncompartmental analysis methodology

7.4 Exploratory Objectives (Parts 1 and 2)

1. To assess A₁PI plasma and stool concentrations and clearance in stool
2. To characterize the PK profile of GLASSIA, when added to conventional steroid treatment, using a population PK approach
3. To assess biomarkers in plasma (ie, inflammatory cytokines IL-2, IL-6, IL-8, and IL-10; IL-1 receptor antagonist [IL-1RA] and T cell subpopulations, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs) and stool (ie, calprotectin concentrations)
4. To assess quality-of-life (QoL), GvHD symptoms and healthcare resource utilization for GLASSIA treatment as a first-line add-on therapy

7.5 Exploratory Objectives (Part 2 Only)

1. To assess the following additional biomarkers in plasma on Day 0 and Day 28: Reg3 α , ST2, and TNFR1

8. STUDY DESIGN

8.1 Brief Summary

This is a 2-part Phase 2/3, prospective, controlled, randomized, multicenter study in subjects with acute GvHD with Stage 1 to 4 lower GI involvement. Part 1 will be a nonrandomized, open-label, active treatment, multicenter study to evaluate the safety, efficacy and PK of GLASSIA in approximately 20 evaluable subjects. Part 2 will be a randomized, parallel-group, double-blind, multicenter study to compare the safety and efficacy of GLASSIA versus albumin (control) in a total of 148 randomized subjects (74 subjects/group).

Eligible subjects for Parts 1 and 2 must be recipients of an allogeneic HSCT and have been newly diagnosed with acute GvHD with Stage 1 to 4 lower GI involvement (modified IBMTR).^{15;16} Subjects must have evidence of myeloid engraftment. There are no restrictions on the prior conditioning treatments. Subjects may continue any prior therapy used for prophylaxis (eg, cyclosporine and/or mycophenolate mofetil) at a stable dose from baseline if the therapy agent was not discontinued and restarted after initiating first-line steroid treatment for acute GvHD. Subjects may have been treated with corticosteroids for acute GvHD with lower GI involvement for a maximum of 72 hours prior to initiation of GLASSIA administration.

All eligible subjects in Parts 1 and 2 will be given 2 mg/kg/day of methylprednisolone or equivalent steroid (either IV or oral per investigator discretion) and IV study treatment (defined as GLASSIA in Part 1; GLASSIA or control in Part 2). Steroids will be tapered as appropriate, according to institutional practice and guidance provided in Section 8.2.

Results from Part 1 will be used to determine whether continuation to Part 2 is warranted. All efficacy data will be adjudicated by an Adjudication Committee (Section 11.13).

8.2 Overall Study Design

The overall study design is illustrated in [Figure 1](#) (Part 1) and [Figure 2](#) (Part 2).

For Parts 1 and 2, screening for eligibility will occur from Days -2 to -1. After screening, subjects will undergo the baseline visit, which is also Day 0.

Subjects will complete study visits either as inpatient or outpatient visits, in accordance with institutional practice. Following the first 2 weeks of every other day study treatment (GLASSIA in Part 1; GLASSIA or control in Part 2), subjects will undergo visits on the following days to have study treatment administered (through Day 49) and to perform safety follow-up and study procedures: Days 14, 21, 28, 35, 42, 49 and 56.

All subjects will be treated with study treatment in combination with conventional steroid treatment through Day 49, or until treatment failure, withdrawal from treatment or withdrawal from the study, whichever comes first. Thereafter, subjects will be treated with standard-of-care for the remainder of their participation in the study based on the investigator's discretion. Subjects who are withdrawn from study treatment will continue to be followed through at least Day 28 (refer to Section 10.6), unless the subject withdraws consent.

Steroid treatment after Day 49 will be at the investigator's discretion. Subjects will visit the site for follow-up visits on Days 56, 100, 180 and 365. In the event that it is not feasible for the subject to visit the site at Day 365, the visit may be conducted with a phone call.

Subjects will also receive standard antibiotic, antifungal and antiviral prophylactic treatment through Day 180 or per institutional guidelines.

Assessments of vital signs, clinical laboratory data (hematology and chemistry), local tolerability and AEs will be performed throughout the study.

Steroid Taper

Tapering of steroids may commence after a subject responds to therapy (overall response, also referred to as GvHD response, as defined in Section 8.4.1); however, the dose of steroid should not be tapered below 2 mg/kg/day (methylprednisolone or equivalent dose) before Day 2 or below 0.25 mg/kg/day (methylprednisolone or equivalent dose) before Day 28.

Subjects who discontinue study treatment (GLASSIA or control) will be treated with standard-of-care for the remainder of their participation in the study.

Treatment Failures

Prior to Day 28 in Parts 1 and 2, subjects must be withdrawn from study treatment if a second-line treatment for acute GvHD is introduced. Second-line treatment may be introduced per investigator discretion prior to Day 28 if a subject experiences disease progression and/or new organ involvement or no change in acute GvHD status after at least 7 days of study treatment (Day 6). Subjects who experience recurrent malignancy will also be withdrawn from study treatment (Section 12.11).

An increase in steroid dose following steroid taper does not constitute second-line treatment; however, steroid treatment at methylprednisolone doses (or equivalent) of greater than 2 mg/kg/day for GvHD treatment will be considered a treatment failure.

Subjects classified as treatment failures will be included in the analysis, but will not be counted as either CR or PR for the primary (overall response) or key secondary (GI response) endpoints. Subjects classified as treatment failures will not be replaced.

All subjects will be followed up at Days 100, 180 and 365.

Data Monitoring Committee

A Data Monitoring Committee (DMC) will independently evaluate safety and efficacy data (Section 15.4). The recommendations of the DMC will be based on the analysis of safety in Parts 1 and 2 and the interim analysis of Part 2 (Section 8.2.2).

8.2.1 Part 1 Study Design

Part 1 of this study is a nonrandomized, open-label, multicenter, clinical study evaluating GLASSIA in combination with conventional steroid treatment.

The target population for Part 1 will include approximately 20 evaluable subjects (Cohort 1).

All eligible subjects will be given GLASSIA with a loading dose of 90 mg/kg (Day 0) followed by GLASSIA 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49) in combination with 2 mg/kg/day of methylprednisolone or equivalent steroid.

For Part 1, subjects who are treated but subsequently found to have a lower GI biopsy inconsistent with GvHD will be replaced to ensure a total of 20 evaluable subjects.

Interim Analyses

An analysis will take place when the last subject in Part 1 has completed the GvHD response assessment at Day 28, to determine whether continuation from Part 1 to Part 2 is warranted (Section 13.5).

8.2.2 Part 2 Study Design

Criteria for Initiation of Part 2

The following decision criteria will be followed for the initiation of Part 2 of the study:

- The study may be terminated by the sponsor for toxicities or adverse safety findings observed in Part 1 of the study
- The study may proceed to Part 2 if an overall response rate of $\geq 55\%$ is observed at Day 28 in Part 1, as determined by the sponsor

- The study may be stopped for futility if the overall response rate is <55% at Day 28
- The sponsor will be the final arbiter of the decision to move into Part 2. The decision will be based on the totality of cumulative data available (eg, rate of GvHD CR, PR and very good partial response [VGPR]; rate of GI CR and PR, including response at Days 28 and 56; duration of any overall and any GI response; and GvHD-free survival)

Study Design for Part 2

Part 2 of this study is a randomized, parallel-group, double-blind, placebo (albumin)-controlled, clinical study comparing GLASSIA in combination with conventional steroid treatment versus albumin (control) in combination with conventional steroid treatment. Part 2 of the study is planned to enroll approximately 148 randomized subjects (74 subjects/group) in order to obtain 134 evaluable subjects, provided that the study does not stop early for futility.

On Day 0, eligible subjects will be randomized 1:1 in a double-blind fashion to the following groups:

Group 2a: GLASSIA with a loading dose of 90 mg/kg (Day 0) followed by GLASSIA 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49), in combination with 2 mg/kg/day methylprednisolone or equivalent steroid

Group 2b: Albumin (control) in combination with 2 mg/kg/day methylprednisolone or equivalent steroid

Randomization will be stratified, using a single stratification factor: lower GI involvement severity (2 strata), as described in Section 8.5.1. Subjects who are randomized to treatment in Part 2 and subsequently discontinue treatment or withdraw from the study will not be replaced.

Interim Analyses

An interim analysis will take place when approximately 50% of the primary endpoint data in Part 2 has been collected (Section 13.5). An independent, unblinded biostatistics team will perform the interim analysis and present the results to the DMC. The study will be analyzed for futility based on the primary endpoint. The DMC will provide recommendations to the sponsor based on the interim analysis. However, the sponsor may decide to stop the trial even if statistical criteria for futility are not observed.

8.3 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 3 years from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The recruitment period is expected to be approximately 2 years.

The subject participation period is approximately 52 weeks from enrollment to subject completion (ie, last study visit), unless prematurely discontinued.

8.4 Outcome Measures

8.4.1 Primary Outcome Measure (Parts 1 and 2)

The primary outcome measure for Parts 1 and 2 is the proportion of subjects achieving overall response at Day 28. The overall response is defined as GvHD CR + PR, as defined below:

- GvHD CR is complete resolution of all signs and symptoms of acute GvHD in all organs without intervening salvage
- GvHD PR is improvement of 1 stage in 1 or more organs involved in GvHD without progression in other organs

8.4.2 Secondary Outcome Measures

8.4.2.1 Efficacy (Parts 1 and 2)

Key Secondary Efficacy Outcome Measures

1. Proportion of subjects achieving GI response at Day 28. Gastrointestinal response is defined as GI CR + PR, which are defined as follows:
 - GI CR is defined as
 - a) Able to eat; not requiring parenteral nutrition, and
 - b) Passing primarily formed stools
 - GI PR is defined as
 - a) Decrease in need for parenteral nutrition to $\leq 50\%$ of required calories; and
 - b) Reduction of stool volume by $\geq 50\%$, without ileus

Other Secondary Efficacy Outcome Measures

1. Proportion of subjects achieving overall response at Day 56
2. Change from baseline in acute GvHD grading at Days 28, 56 and 180
3. Incidence of chronic GvHD at Days 100, 180 and 365

4. Duration of any overall response
5. Duration of any GI response
6. Overall survival through Days 100, 180 and 365
7. Transplant-related mortality at Days 28, 56, 100 and 180
8. Failure-free survival at Days 100 and 180
9. GvHD-free survival at Days 28, 56, 100 and 180
10. Infection-related mortality at Days 28, 56, 100 and 180
11. GvHD-related mortality at Days 28, 56, 100 and 180
12. All-cause mortality at Days 28, 56, 100 and 180

8.4.2.2 Safety Outcome Measures (Parts 1 and 2)

1. The incidence and severity of all AEs, related AEs, all SAEs, related SAEs and temporally-associated AEs
2. Change from baseline in clinical laboratory safety parameters and vital signs
3. Incidence of recurrence of primary malignancies through Days 180 and 365
4. Incidence and type of infection (eg, bacterial, fungal, viral, etc) at Days 28, 56, 180 and 365

8.4.2.3 Pharmacokinetic Outcome Measures (Part 1 Only)

The following noncompartmental analysis PK parameters by day and/or dosing frequency, as applicable, will be assessed:

1. Area under the plasma concentration curve (AUC) from time zero to the last quantifiable activity
2. AUC from time zero to time “t”
3. Systemic clearance at steady state
4. Maximum plasma concentration at steady state
5. AUC from time zero to infinity
6. Apparent volume of distribution at steady state
7. The terminal half-life
8. Mean residence time
9. Trough plasma A₁PI levels at steady state

8.4.3 Exploratory Outcome Measures

Efficacy (Parts 1 and 2)

1. Proportion of subjects achieving GvHD VGPR at Day 28. A GvHD VGPR is defined as follows:
 - Skin: no rash, or residual erythematous rash involving <25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
 - Liver: total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment
 - Gut: tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abdominal cramping and no more than occasional nausea or vomiting
2. Cumulative steroid dose at Days 28, 56, 100 and 180
3. Steroid dose at Days 28, 56 and 100
4. Proportion of subjects achieving GI CR and GI PR at Days 28, 56 and 180 at each baseline GvHD severity grade (B, C and D)

Pharmacokinetics (Parts 1 and 2)

An exploratory, mixed-effects population PK model will be developed from the Part 1 and Part 2 data. Potential exploratory outcome measures include, but are not limited to, the following:

1. Systemic clearance at steady state
2. Maximum plasma concentration at steady state
3. Apparent volume of distribution at steady state
4. The terminal half-life
5. Trough plasma A₁PI levels at steady state

Pharmacodynamics (Parts 1 and 2)

1. Change from baseline in plasma and stool concentrations of A₁PI
2. A₁PI clearance in stool
3. Change from baseline in plasma biomarkers (eg, cytokines IL-2, IL-6, IL-8, and IL-10; and IL-1RA) and stool calprotectin concentrations
4. T cell subpopulations including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs

Pharmacodynamics (Part 2 Only)

1. Change from baseline in additional plasma biomarkers on Day 0 and Day 28 (Reg3 α , ST2, and TNFR1)

Health Outcomes (Parts 1 and 2)

1. Change from baseline in QoL as measured by the Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale version 4.0 instrument (FACT-BMT)
2. Change from baseline in acute GvHD symptoms as measured by the Chronic GvHD Symptom Scale
3. Change from baseline in health utility as measured by European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L)
4. Healthcare resource utilization:
 - Type of admission (hospital, Intensive Care Unit and/or transplant unit)
 - Length of stay
 - Number of unscheduled physician office visits
 - Number of emergency room visits
5. Medication:
 - Days on steroids

8.4.4 Rationale for Endpoints

The primary efficacy endpoint of overall response (GvHD response) was chosen because multiple studies have shown an association between overall response at fixed time points and an improvement in mortality up to 2 years post-transplant.^{21;22;23;24;25;26;27;28} Overall response 28 days after initiating treatment was associated with lower non-relapse mortality at up to 2 years and has been supported as an endpoint in the guidelines issued by an expert panel of the American Society for Blood and Marrow Transplant and results from other studies.^{25;26;27;28}

The key secondary endpoint of GI response was chosen because of the evidence of the role of A₁PI in GvHD with lower GI involvement (Section 6).

The IBMTR Severity Index was chosen to allow comparison with other studies using the IBMTR criteria, including Study FHCRC 2571.

The exploratory endpoint of GvHD VGPR was chosen on the basis of the recommendation of Martin et al.²³ A VGPR approximates a GvHD CR and identifies subjects with excellent responses who may have outcomes similar to subjects with a GvHD CR.

8.5 Randomization and Blinding

8.5.1 Randomization

Part 1 is a nonrandomized, open-label, active treatment clinical study. In Part 1, if the subject has met all eligibility criteria, the Eligibility Criteria Form will be completed by the site, signed by the investigator and faxed to the Medical Monitor for review. The form must be signed by the Medical Monitor prior to proceeding with enrolling the subject in the Interactive Response Technology (IRT).

Part 2 is a randomized, double-blind, concurrent, placebo (albumin)-controlled clinical study. In order to minimize/avoid bias, subjects will be randomly assigned to 1 of 2 treatment regimens (investigational product [IP] or control) in equal numbers. Randomization codes will be maintained by the sponsor or the sponsor's representative.

In Part 2, if the subject has met all eligibility criteria, the Eligibility Criteria Form will be completed by the site, signed by the investigator and faxed to the Medical Monitor for review. The form must be signed by the Medical Monitor prior to proceeding with randomizing the subject. The site will then request the study treatment assignment using the IRT system.

All randomized subjects will be managed by IRT. The IRT will assign subjects their 6-digit subject number at the time of randomization and will provide the vial number of the blinded study treatments to be administered at each visit. Subjects will not be re-randomized.

Subjects will be randomized to treatment via stratified randomization, using a single stratification factor. Separate randomization schedules will be used within each strata of lower GI involvement severity, based on the modified IBMTR grading system (Section 11.4). The 2 strata will be as follows:

- Lower GI Stage 4, or Stage 3 with other organ(s) involved
- Lower GI Stage 1 to 2, or Stage 3 with no other organ involvement

8.5.2 Blinding

The solutions for GLASSIA and albumin (control) in Part 2 will be identical in volume, color and foaming characteristics. Blinding of the study treatment will be performed by an unblinded pharmacist at the study site, who will also prepare the study treatment for administration.

An independent, unblinded biostatistics team will perform the interim analysis of Part 2 and will present the results to the DMC (Section 13.5).

The treatment each subject receives will not be disclosed to the investigator, study site staff, subject, sponsor or contract research organization, including at the interim analysis of Part 2, unless the subject meets criteria for unblinding (Section 8.5.3).

8.5.3 Unblinding

The process for breaking the blind in Part 2 will be handled through the IRT. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management. Any site that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the subject in question.

The sponsor and the contract research organization must be notified immediately if a subject and/or investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and electronic case report forms (eCRFs).

The study will be unblinded after all subjects complete Day 56 of Part 2 or discontinue study treatment and the Adjudication Committee adjudicates all efficacy data through Day 56 of Part 2 (Section 11.13).

8.6 Study Stopping Rules

Stopping rules will not be established for Part 1 of this study. The study may be stopped at the sponsor's discretion for any reason, including lack of efficacy, toxicities or adverse safety findings.

Part 2 of the study may be stopped based on the DMC's nonbinding recommendation from the interim analysis (Section 13.5) if the statistical criteria for futility are met. The study may also be stopped at the sponsor's discretion for any reason.

8.7 Investigational Product(s)

8.7.1 Packaging, Labeling, and Storage

8.7.1.1 GLASSIA and Control

Dosage Form: Injection, solution

Packaging: GLASSIA and albumin (control) are supplied by the sponsor as ready-for-use, sterile, non-pyrogenic liquid preparations in single-dose containers of 50 mL. GLASSIA containers contain approximately 1 g of functional A₁PI in glass vials. The control vials contain human albumin 20% in 50 mL normal saline solution in glass vials (for EU/ROW), or Flexbumin 25% in 50 mL in normal saline solution in plastic IV bags (for US).

Labeling: The product is labeled according to the valid regulatory requirements for clinical studies. For Part 2, an unblinded pharmacist will prepare and blind the study treatment.

Storage: GLASSIA and control must be stored under refrigerated conditions (2°C to 8°C or 36°F to 46°F). Do not freeze the product. If removed from refrigeration, the product must be used in 1 month. Do not use if expiration date is exceeded or carton is damaged.

8.7.1.2 Conventional Steroid Treatment

The conventional steroid treatment (methylprednisolone or equivalent steroid) will be supplied by the investigators per their institutional practice. The conventional steroid treatment will be labeled by the manufacturer and will not be re-labeled by the sponsor; the product must be stored in accordance with the package label.

8.7.1.3 Anti-infective Prophylaxis

Subjects will receive standard antibacterial, antifungal and antiviral prophylactic treatment including that for herpes simplex virus, varicella-zoster virus and CMV (eg, acyclovir or valacyclovir), through Day 180 or per institutional guidelines.

8.7.2 Administration

For instructions for the preparation, blinding and administration of study treatment, please refer to the Pharmacy Manual. GLASSIA and control will be administered by IV infusion, through either a central indwelling catheter or peripheral line, per the investigator's discretion.

The dose (in mg) will be calculated based on the subject's body weight at screening. The screening body weight will be used for the dose calculation throughout the study.

Study treatment will be prepared for administration and blinded by an unblinded pharmacist at the site. The volume of infusion solution (in mL) will be calculated based on the content of functional A₁PI (potency) in the study treatment vials, as specified in the certificate of analysis to be provided with a particular GLASSIA lot and as printed on the vial. Note that the functional activity of A₁PI is independent from the particle load of a GLASSIA manufacturing lot. Single-dose containers of albumin will have a corresponding label with a "hypothetical" functional A₁PI potency.

The investigator will record in the eCRF whether study treatment was administered via a central indwelling catheter or peripherally and whether the line was flushed after administration.

The conventional steroid treatment (either IV or oral per investigator discretion) should be administered according to the package label.

8.7.3 Description of Treatment

In Part 1, Cohort 1 will receive a GLASSIA loading dose of 90 mg/kg (Baseline/Day 0) followed by GLASSIA 30 mg/kg every other day (Days 2 to 12), then followed by 120 mg/kg weekly (Days 14 to 49). Refer to Section 6.1.1 for the rationale for the dose selection.

In Part 2, subjects will receive GLASSIA (Group 2a) or control (Group 2b). Group 2a will receive the same dose and regimen of GLASSIA that was used in Part 1.

In Parts 1 and 2, all subjects will receive 2 mg/kg/day of methylprednisolone or equivalent steroid (either oral or IV per investigator's discretion). Steroids will be tapered as appropriate, according to institutional practice and the guidance provided in Section 8.2.

8.7.4 Investigational Product Accountability

The investigator will ensure that the IP(s) is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP(s) was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP(s) must be dispensed only at the study site or other suitable location (eg, infusion center; home, as applicable per study design). Records will be maintained that includes the subject identification code (SIC), dispensation date and amount dispensed.

All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

8.8 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the case report form (CRF).

For additional information on study documentation and CRFs, see Section [17.2](#). The use of subject diaries is described in Section [10.5](#).

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for Parts 1 and 2 of this study:

1. Male or female subjects aged ≥ 18 years at the time of screening
2. Recipient of an HSCT
3. The disease indication for which the subject required HSCT must be in remission
4. Newly diagnosed acute GvHD, including lower GI involvement (modified International Bone Marrow Transplant Registry [IBMTR] Severity Stage 1 to 4 [>500 mL diarrhea/day]), with or without other organ system involvement.
5. Willing to undergo or must have had a lower GI biopsy within 7 days of informed consent to confirm GI GvHD. Biopsy results are not needed to initiate treatment; however, if biopsy results are not consistent with aGvHD, treatment with GLASSIA will be discontinued.
6. Subjects must be receiving systemic corticosteroids. Treatment with methylprednisolone/systemic steroids must have been initiated within 72 hours prior to the first dose of study treatment after enrollment.
7. Evidence of myeloid engraftment (absolute neutrophil count $\geq 0.5 \times 10^9/L$)
8. Lower GI GvHD manifested by diarrhea must have other causes of diarrhea ruled out (eg, negative for *Clostridium difficile* or cytomegalovirus [CMV] infection or oral magnesium administration)
9. Karnofsky Performance Score $\geq 50\%$ ²⁹
10. If female of childbearing potential, subject presents with a negative blood pregnancy test
11. Females of childbearing potential with a fertile male sexual partner must agree to employ adequate contraception for the duration of the study. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or a condom
12. Males must use adequate contraception and must not donate sperm for the duration of the study. Adequate contraception for the male subject and his female partner is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or a condom
13. Subject is willing and able to comply with the requirements of the protocol

9.2 Exclusion Criteria

Subjects who meet **ANY** of the following criteria are not eligible for this study:

1. Subject with manifestations of chronic GvHD
2. Subject with acute/chronic GvHD overlap syndrome
3. Subject whose GvHD developed after donor lymphocyte infusion
4. Subject with myocardial infarction within 6 months prior to enrollment or New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to the first dose of study treatment, any electrocardiogram (ECG) abnormality at screening must be documented by the investigator as not medically relevant
5. Subject with evidence of recurrent malignancy
6. Subject with veno-occlusive disease (ie, sinusoidal obstruction syndrome)
7. Subject receiving GvHD treatment other than continued prophylaxis (eg, cyclosporine and/or mycophenolate mofetil, etc) or corticosteroid therapy. In addition, a subject who received the first dose of corticosteroid therapy for acute GvHD with lower GI involvement more than 72 hours before the first dose of study treatment is not eligible for the study
8. Subject with severe sepsis involving at least 1 organ failure
9. Subject who is seropositive or positive in the nucleic acid test for human immunodeficiency virus (HIV)
10. Subject with active hepatitis B or C
11. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
12. If female, subject is pregnant or lactating at the time of enrollment, or has plans to become pregnant during the study
13. Subject with a serious medical or psychiatric illness likely to interfere with participation in the study
14. Subject is a family member or employee of the investigator

9.3 Withdrawal from Study Participation and Discontinuation of Study Treatment

Any subject may voluntarily withdraw at any time consent for continued participation in the study and data collection. Every effort should be made prior to enrollment to ensure subjects are willing to comply with study procedures and assessments. The reason for withdrawal will be recorded on the End of Study CRF. Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject. Assessments to be performed at the termination visit (including in cases of withdraw or discontinuation) are described in Section 10.6 and Section 20.2.

Whenever possible, all subjects who prematurely withdraw from the study will be followed through Day 28 or 2 weeks after the last dose of study treatment, whichever comes later (refer to Section 10.6 for additional details), unless otherwise indicated below.

Subjects will be discontinued from study treatment for the following reasons:

- The subject has a lower GI biopsy within 7 days of informed consent that in the opinion of a pathologist is inconsistent with acute GvHD (Section 11.3). If the results are obtained prior to the first dose of study treatment, the subject will be withdrawn from the study prior to study treatment for Part 1 and without being randomized for Part 2.
- The subject becomes pregnant.
- The subject starts a second-line treatment for acute GvHD prior to Day 28 (Section 8.2).
- The subject experiences recurrent malignancy (Section 12.11).
- If the Sponsor medical monitor or the investigator deem it is in the best interest of the subject

Subjects who discontinue study treatment and/or the study will not be replaced.

10. STUDY PROCEDURES

10.1 Informed Consent

Any patient who provides informed consent (ie, signs and dates the informed consent form and assent form, if applicable) is considered a subject in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (eg, 090701) to be provided by the sponsor, 2- or 3-digit number study site number (eg, 02) to be provided by the sponsor and 3- or 4-digit subject number (eg, 0003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 090701-020003. All study documents (eg, CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted as long as it does not contain a combination of information that allows identification of a subject (eg, collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

10.3 Screening and Study Visits

The study site is responsible for maintaining a screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new ICF, new SIC and new CRF are required for that subject.

The overall study design is illustrated in [Figure 1](#) (Part 1) and [Figure 2](#) (Part 2). Details on the procedures to be performed at each study visit, including screening, can be found in Supplement [20.2](#) Schedule of Study Procedures and Assessments and Supplement [20.3](#) Clinical Laboratory Assessments.

On visits at which study treatment is administered, all assessments and sample collections, except for PK and stool samples as indicated in [Table 2](#), must be performed prior to the start of study treatment administration.

10.4 Medications and Non-Drug Therapies

The following medications and non-drug therapies are **not** permitted within 30 days before study entry and during the course of the study:

- Medications:

- Any IP other than GLASSIA (GLASSIA is also not permitted prior to the first administration of study treatment)
- Any GvHD treatment (eg, antithymocyte globulin, anti-TNF drugs) other than 1) prophylactic therapies started prior to study entry and 2) corticosteroid therapy as described below
- Prophylactic GvHD therapies started after study entry
- Enteral corticosteroids
- Non-drug therapies:
 - Any investigational device

A subject who has taken any of these medications or received any of these non-drug therapies will be discontinued from study treatment, and the medication/non-drug therapy will be considered a protocol deviation.

Second-line GvHD treatment may be introduced per investigator discretion prior to Day 28 if a subject experiences disease progression and/or new organ involvement or no change in acute GvHD status after at least 7 days of study treatment (Day 6). Subjects receiving second-line treatment prior to Day 28 must be withdrawn from study treatment; if the subject meets the criteria for introducing second-line treatment prior to Day 28, the second-line treatment will not be considered a protocol deviation. Refer to Section 8.2 for additional details about second-line treatment.

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

- Medications:
 - Corticosteroid therapy for acute GvHD with lower GI involvement (treatment must have been initiated no more than 72 hours prior to the first administration of study treatment)
 - Prophylactic GvHD therapies started prior to study entry (eg, cyclosporine and/or mycophenolate mofetil, etc)
 - Topical corticosteroids including ophthalmic steroids
 - Any medications other than those listed as not permitted above
- Non-drug therapies:
 - Any non-drug therapies other than those listed as not permitted above

10.5 Subject Diary

A paper subject diary will be provided to each subject at each visit as outlined in Table 1 to record the following information:

Healthcare resource utilization

- Unscheduled physician office visits
- Emergency room visits
- For any admissions after the initial hospitalization, the type of admission (hospital, Intensive Care Unit or transplant unit); the reason for admission and the length of stay

Subjects will be trained on use of the diary to record all healthcare utilization at baseline and following at their discharge for treatment of acute GvHD. The diary will be provided in paper format and remain with the subject for the duration of the study. The investigator will review the diary for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the diary will be reported as AEs according to the investigator's discretion and clinical judgment.

The subject diary will serve as a primary source record and remain at the study site. Entries in the subject diary will be transferred into the appropriate collection device. Any entry in the collection device that does not correspond with an entry in the subject diary will be explained by the investigator in source documentation.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study according with the protocol (with or without protocol deviations).

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation CRF, including: completed, screen failure, AE (eg, death), discontinuation by subject (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (eg, pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by sponsor, or other (reason to be specified by the investigator, eg, technical problems). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation through the study follow-up period should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion/termination visit. If the study completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the study completion/termination visit. If a subject terminates participation in the study and does not return for the study completion/termination visit, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the study completion/termination visit (including in cases of withdraw or discontinuation) can be found in Supplement 20.2 Schedule of Study Procedures and Assessments.

Subjects who discontinue study treatment prior to Day 28 will complete the Day 28 visit on Day 28 (± 1 day). If at least 2 weeks have passed since the last dose of study treatment, the Day 28 visit will serve as the study completion/termination visit. If Day 28 is less than 2 weeks following the last dose of study treatment, subjects will complete the Day 28 visit and then the study completion/termination visit 2 weeks (± 1 day) after the last dose of study treatment. In this event, the study completion/termination visit will consist of an office visit with the same assessments as the Day 365 visit.

Subjects who discontinue study treatment after Day 28 will complete the study completion/termination visit as an office visit 2 weeks (± 1 day) after the last dose of study treatment. Subjects who withdraw from the study after Day 56 will be encouraged to complete the study completion/termination visit at the time of discontinuation. In the event that it is not feasible for the subject to visit the site at the study completion/termination visit after Day 56, the visit may be conducted with a phone call.

Subjects who discontinue study treatment will not attend any other subsequent visits other than Day 28 and the study completion/termination visit (if applicable), except as needed for follow-up of recovering/resolving AEs (see Section 12.1.2).

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

10.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

11.1 Demographics and Baseline Characteristics

At screening, the following subject demographics will be collected:

- Gender
- Date of birth
- Race and ethnicity (where permitted by local regulations)
- Smoking status

At screening, the following subject baseline characteristics will be collected: medical, surgical and transplant history, including the date and source of HSCT.

11.2 CMV and HIV Testing

At screening and at the visits indicated in [Table 1](#), subjects will be tested for CMV, using antigenemia or polymerase chain reaction–based assays according to institutional guidelines. Subjects with evidence of CMV viremia (based on either assay) will receive antiviral therapy based on the investigator’s standard practice. Subjects may be tested for CMV at additional visits not indicated in [Table 1](#), per institutional guidelines.

At screening, subjects will be tested for HIV using the antibody or nucleic acid test. If HIV testing was performed within the 3 months prior to screening, the results of the earlier tests may be used instead.

11.3 Lower GI Biopsy

Subjects will have a lower GI biopsy within 7 days of informed consent. If a biopsy was performed within 3 days prior to screening, results from that biopsy may be used instead. The type of lower GI biopsy is at the investigator’s discretion based on their standard institutional practice. If in the opinion of a pathologist, the results of the lower GI biopsy are inconsistent with acute GvHD, the subject will be withdrawn from the study. Results of the biopsy will not be required to assess eligibility prior to the first dose of study treatment, but are required for continuation in the study.

11.4 GvHD Staging/Assessment

At screening and at the visits indicated in [Table 1](#), GvHD will be assessed for severity. Grading of GvHD will be performed by the investigator according to the modified IBMTR grading system¹⁵, which classifies the degree of involvement of each organ system by stage on a scale of 0 to 4 and the grade of severity of acute GvHD on a scale of A to D. The IBMTR grading system is modified on the basis of UpToDate¹⁵ and is summarized below.

The degree of **skin involvement** is staged depending upon the degree and severity of the lesions as follows:

- Stage 1: Maculopapular rash over <25% of body area
- Stage 2: Maculopapular rash over 25 to 50% of body area
- Stage 3: Generalized erythroderma
- Stage 4: Generalized erythroderma with bullous formation, often with desquamation

The degree of **GI involvement** is staged based upon the severity of diarrhea as follows:

- Stage 1: Diarrhea 500 to 1000 mL/day
- Stage 2: Diarrhea 1000 to 1500 mL/day
- Stage 3: Diarrhea 1500 to 2000 mL/day
- Stage 4: Diarrhea >2000 mL/day OR pain OR ileus

The degree of **liver involvement** is staged based upon the serum total bilirubin level as follows:

- Stage 1: Bilirubin 2 to 3 mg/dL
- Stage 2: Bilirubin 3 to 6 mg/dL
- Stage 3: Bilirubin 6 to 15 mg/dL
- Stage 4: Bilirubin >15 mg/dL

The modified IBMTR grading system defines the severity of acute GVHD as follows:

- Grade A: Stage 1 skin involvement alone (maculopapular rash over <25% of the body) with no liver or gastrointestinal involvement
- Grade B: Stage 2 skin involvement and/or Stage 1 to 2 gut or liver involvement
- Grade C: Stage 3 involvement of any organ system (generalized erythroderma; bilirubin 6.1 to 15.0 mg/dL; diarrhea 1500 to 2000 mL/day)
- Grade D: Stage 4 involvement of any organ system (generalized erythroderma with bullous formation; bilirubin >15 mg/dL; diarrhea >2000 mL/day OR pain OR ileus)

The investigator will record the grade of GvHD (A through D) and the stage for each organ system (0 to 4) in the eCRF.

11.5 Overall Response, GI Response, and GvHD VGPR

At the visits indicated in [Table 1](#), the investigator will assess the subject for overall and GI response, as well as GvHD VGPR, which are defined in the following sections:

- Overall response: Section [8.4.1](#)
- GI response: Section [8.4.2.1](#)
- GvHD VGPR ²³: Section [8.4.3](#)

11.6 Chronic GvHD Assessment

At screening and Days 100, 180 and 365, the investigator will assess the subject for chronic GvHD and acute/chronic GvHD overlap syndrome, based on the investigator's standard practice. The investigator will record the assessment in the eCRF.

11.7 Pharmacokinetic, Biomarker and Stool Sample Collection

Samples of whole blood will be obtained in a 10-mL Vacutainer[®] containing heparin anticoagulant for the determination of A₁PI and selected metabolites, as well as biomarkers, in human plasma. Blood samples will be obtained prior to the first study treatment administration and at the visits and times indicated in [Table 2](#). If study treatment is administered peripherally (Section [8.7.2](#)), the PK samples should be taken from the opposite arm as the study treatment administration, if possible. If study treatment is administered via a central indwelling catheter, the PK samples may be taken from the same infusion line if the infusion line is flushed prior to collection of the sample and the first 3 mL of blood is discarded.

Stool samples will be collected for assessment of A₁PI levels and clearance and calprotectin concentrations. One sample will be collected prior to the first dose of study treatment (either during screening or on Day 0 prior to the start of study treatment administration). A stool sample will also be collected during the 24-hour period after initiation of study treatment on Days 0 and 12 and during the 24-hour period on Days 28 and 56. The Day 28 stool sample must be collected prior to the start of study treatment administration. For inpatient visits, stool samples will be collected at the site. For outpatient visits, the sample can be collected at the site or can be collected at home and returned to the study site.

Refer to the Laboratory Manual for details of sample volumes and handling.

The following information will be captured for blood and stool sample collection in each subject's eCRF:

1. Subject's SIC
2. Time and date of start of previous study treatment infusion
3. Time and date of each blood and stool sample collected
4. Time and date of subject's most recent ingestion of food prior to sample collection (blood sample only)
5. Whether the blood sample was collected through a central or peripheral line
6. If the blood sample was collected through a peripheral line, whether it was collected through the same arm or the opposite arm, as the study treatment administration

Biomarkers to be assessed in Parts 1 and 2 include cytokines IL-2, IL-6, IL-8, and IL-10; IL-1RA; T cell subpopulations, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs; and stool calprotectin concentrations; in Part 2 only, the following biomarkers will also be assessed: Reg3α, ST2, and TNFR1. The cytokines will be measured by enzyme-linked immunosorbent assay. The T cells will be measured using epigenetic cell counting.

11.8 Functional Assessment of Cancer Therapy – Bone Marrow Transplant

Quality-of-life will be assessed with the FACT-BMT at the visits indicated in [Table 1](#). The FACT-BMT is a 37-item scale comprised of a general core questionnaire, the FACT-G, which evaluates the health-related QoL of subjects receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to BMT. The FACT-G core questionnaire assesses 4 domains:

Physical Well-being, Social/Family Well-being, Emotional Well-being and Functional Well-being. Each domain can be scored, with higher scores indicating better functioning.

The FACT-BMT, Chronic GvHD Symptom Scale and EQ-5D-5L should be collected before any other assessments are performed at the visit.

11.9 Chronic GvHD Symptom Scale

Symptoms of GvHD will be assessed with the Chronic GvHD Symptom Scale at the visits indicated in [Table 1](#). The Chronic GvHD Symptom Scale is a 30-item validated scale that measures the extent to which the subject is bothered by chronic GVHD symptoms in the following domains: skin, energy, lung, nutrition, psychological, eye and mouth. Responses are captured on a 5-point Likert scale (“no symptoms, or not bothered at all,” “slightly bothered,” “moderately bothered,” “bothered quite a bit” or “extremely bothered”). Scores for each domain are converted to a 0 to 100 scale, with higher scores indicating a greater degree to which the subject is bothered by the symptoms.

Although the scale collects chronic GvHD symptoms, several of the domains are also applicable to acute GvHD. There is no validated symptom scale that is specific to acute GvHD.

The FACT-BMT, Chronic GvHD Symptom Scale and EQ-5D-5L should be collected before any other assessments are performed at the visit.

11.10 European Quality of Life – 5 Dimensions – 5 Level

Health utility will be assessed with the EQ-5D-5L³⁰ instrument at the visits indicated in [Table 1](#). The EQ-5D-5L is a standardized subject-administered measure of health-related QoL states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each of which can take 1 of 5 responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

The FACT-BMT, Chronic GvHD Symptom Scale and EQ-5D-5L should be collected before any other assessments are performed at the visit.

11.11 Healthcare Resource Utilization

Healthcare resource utilization information will be recorded by the subject in the subject diary (Section 10.5) and by the investigator in the eCRF. The investigator will record the date of hospital discharge in the eCRF for the hospitalization that was ongoing at the time of the initiation of study treatment. In the subject diary, the subject will record the number and length of stay (in days) of: emergency room visits, hospital stays, intensive care admissions and urgent care center visits. After reviewing the subject diary with the subject, the investigator will enter the healthcare resource utilization data in the eCRF at the visits indicated in Table 1. These data will be collected to assess the economic impact of treatment with GLASSIA.

11.12 Mortality and Survival Assessments

All-cause, transplant-related, infection-related and GvHD-related mortality will be calculated as the time from HSCT to death; the cause of death will be based on the investigator's assessment. The date and cause of death, if applicable, will be collected in the eCRF at the visits indicated in Table 1. The following definitions will be used by the investigator to assess the cause of death. These categories are not mutually exclusive, and the investigator will select all applicable categories:

- Transplant-related mortality: death related to transplantation (including deaths related to GvHD)
- Infection-related mortality: death related to infection (including infections related to HSCT)
- GvHD-related mortality: death related to GvHD
- Other cause: any death not related to transplant, infection or GvHD

Failure-free survival, GvHD-free survival and overall survival will be collected in the eCRF at the visits indicated in Table 1.

Failure-free survival is determined by the investigator and defined as the absence of all 3 of the following criteria:

- Need for second-line treatment for acute GvHD
Second-line treatment is defined as any additional systemic treatment used for steroid nonresponsive treatment of acute GvHD. Methylprednisolone (or equivalent steroid) doses greater than 2 mg/kg/day required for the treatment of GvHD will also be considered second-line therapy

- Non-relapse mortality
Non-relapse mortality is defined as death during continuous complete remission
- Recurrent malignancy

11.13 Adjudication Committee

An adjudication committee will review and adjudicate all efficacy data prior to statistical analysis. During Part 2 of the study, the committee will be blinded to study treatment assignment, until the committee has adjudicated all data through Day 56 and the study has been unblinded. The committee will be composed of experts in the fields of oncology, hematology or immunology who specialize in HSCT and are not participating as investigators in the study. The experts will adjudicate all efficacy data in both parts of the study. Adjudication of Part 1 efficacy data will not be required prior to initiating Part 2 of the study.

The adjudication committee's responsibilities, definitions and operating procedures will be defined in a charter; the committee will maintain records of all its meetings.

12. ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definitions

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether or not considered causally related to the IP.

12.1.1.1 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
- Results in persistent or significant disability/incapacity (ie, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
 - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
 - Reviewed and confirmed seroconversion for HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus or parvovirus B19

Uncomplicated pregnancies, following maternal or paternal exposure to IP, are not considered an (S)AE; however, any pregnancy complication or pregnancy termination by therapeutic, elective or spontaneous abortion shall be considered an SAE.

12.1.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (ie, including active comparators) that is both serious and unexpected.

The event(s) must meet all of the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

12.1.1.3 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.1.1.4 Unexpected Adverse Events

An unexpected AE is an AE whose nature, severity, specificity or outcome is not consistent with the term, representation or description used in the Reference Safety Information. “Unexpected” also refers to the AEs that are mentioned in the IB or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation. The expectedness of AEs will be determined by the sponsor using the IB and prescribing information as the Reference Safety Information. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated from the pharmacological properties of a product.

12.1.1.5 Preexisting Diseases

Preexisting diseases that are present before entry into the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration or frequency of a preexisting disease after IP exposure, the event must be described on the AE CRF.

For medical events occurring between study entry and IP exposure, see Section 12.3 Untoward Medical Occurrences.

12.1.2 Assessment of Adverse Events

For the purposes of this study, changes in the severity or duration of GvHD experienced after the first IP exposure are collected as an efficacy endpoint and thus are not reportable on the AE CRF, nor will they be included in the analysis of AEs.

Symptoms or diagnostic findings of GvHD, such as skin rashes, abnormal liver function tests, diarrhea, ileus and bowel perforation, should be collected on the AE CRF only if there is an increase in the severity, duration or frequency AND if they begin after first exposure to IP.

All other AEs from the first IP exposure until study completion will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.1). Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 12.1.1.1
- Severity as defined in Section 12.1.2.1
- Causal relationship to IP exposure or study procedure as defined in Section 12.1.2.2

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable or unknown) will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until resolution or 30 days after the study completion/termination visit, whichever comes first. The follow-up information will be documented in the AE CRF. If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (ie, the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from protocol-specified procedures of IMP use such as overdosing, underdosing, withdrawal, omission, incorrect route of administration, and use of a product other than the IMP, standard care of the underlying disease or treatment of a TEAE shall be recorded in the Protocol Deviation Form.

Any pregnancy that occurs after administration of IP will be reported on a Pregnancy Report Form.

12.1.2.1 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. In the event an AE is not described in the NCI CTCAE version 4.03, the severity grades will be mapped to the terms listed in [Table 3](#). For assessing the severity of AEs resulting from laboratory values, see section [12.7.3.2](#).

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

12.1.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, eg, assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met)
 - Is due to underlying or concurrent illness, complications, concurrent treatments or effects of concurrent drugs
 - Is not associated with the IP (ie, does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology)
- Unlikely related (either 1 or both circumstances are met)
 - Has little or no temporal relationship to the IP
 - A more likely alternative etiology exists
- Possibly related (both circumstances must be met)
 - Follows a reasonable temporal relationship to the administration of IP
 - An alternative etiology is equally or less likely compared to the potential relationship to the IP

- Probably related (both circumstances must be met)
 - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
 - Reappearance of a similar reaction upon re-administration (positive rechallenge)
 - Positive results in a drug sensitivity test (skin test, etc.)
 - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
 - Another etiology is unlikely or significantly less likely

For events assessed as not related or unlikely related and occurring within 1 week of study treatment administration, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

12.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The investigator may take appropriate urgent safety measures in order to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee(s) (EC(s)) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

12.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 12.1.1). However, each **serious** untoward medical occurrence experienced before the first IP exposure (ie, from the time of signed informed consent up to but not including the first IP exposure) will be described on the AE CRF and SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, also each non-serious untoward medical occurrence experienced by a subject undergoing endoscopy or other procedure to obtain a biopsy for the diagnosis of GvHD before the first IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

12.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but **did not result in an AE**. NMCs include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

12.5 Medical, Medication and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including severity (defined in Section 12.1.2.1) or surgery and start and end dates, if known: eyes, ears, nose and throat; respiratory; cardiovascular; GI; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

12.6 Physical Examinations

At screening and subsequent study visits (as described in [Table 1](#)), a physical examination will be performed including the following body systems: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin and neurological. At screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in [Section 12.1.1.5](#)), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

12.7 Clinical Laboratory Parameters

12.7.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [ie, red blood cell count] and leukocytes [ie, white blood cell count]) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin concentration and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine and glucose.

The coagulation panel will consist of prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR).

Blood will be obtained for assessment of hematology, clinical chemistry and coagulation panel parameters at screening and other study visits indicated in [Table 2](#). Clinical laboratory assessments should also be performed whenever clinically indicated.

Hematology and clinical chemistry assessments will be performed on ethylenediaminetetraacetic acid (EDTA)–anticoagulated whole blood and serum, respectively, at the local laboratory. The coagulation panel assessment will also be performed at the local laboratory.

12.7.2 Urinalysis

The urinalysis assessments will consist of color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase and microscopic examination (red and white blood cells, bacteria and casts). Urine samples will be obtained at screening and other study visits indicated in [Table 2](#). Urinalysis will be performed at the local laboratory.

12.7.3 Assessment of Laboratory Values

12.7.3.1 Toxicity Grading Scale

Laboratory values will be evaluated according to the NCI CTCAE version 4.03 toxicity grading scale by the investigator.

12.7.3.2 Assessment of Abnormal Laboratory Values

For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in [Section 12.1](#)) or if the value is related to a previously recorded AE. Any clinically significant abnormal laboratory finding associated with a pre-existing condition (described in [Section 12.1.1.5](#)) or GvHD will not constitute an AE, unless judged by the investigator to be more severe than expected for the subject's condition. The investigator will also record the severity grading (only if 3 or 4) within the respective laboratory page of the eCRF for a clinically significant laboratory value that constitutes an AE, and the severity grades for the sign, symptom or medical diagnosis in the AE page of the eCRF. Regarding clinically significant abnormal laboratory values that are adverse events, only the highest severity grading will be reported in the eCRF. Regardless of the severity grade, an AE will be followed until resolution or until no longer deemed necessary by the investigator.

If the abnormal value was not clinically significant, the investigator will indicate the reason, ie due to periodic variation, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Regarding laboratory abnormal values that are adverse events, only the highest grading will be reported in the eCRF. Regardless of the grade, the AE will be followed until resolution or until no longer deemed necessary by the investigator.

12.7.4 Backup Samples and Biobanking

Backup samples taken and stored short-term may be used for example for re-testing, follow-up of an AE(s) or other test results and/or assay development for this study only. After study testing is completed, the remaining samples may be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will be destroyed.

Backup samples from a subject who has withdrawn consent will not be used for additional testing after the subject withdraws consent.

For this study, no samples will be taken or stored long-term in biobank(s) for future analyses.

12.8 Vital Signs

Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min) and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (lb or kg) will also be collected.

Vital signs will be measured at screening and within 30 minutes before and after administration of IP at the study visits indicated in [Table 1](#). Height will be collected only at the screening visit. Blood pressure will be measured when subjects are in the sitting position; measurements in the supine position will also be acceptable if the subject is too ill to sit.

Vital sign values are to be recorded on the CRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in [Section 12.1](#)) and record the medical diagnosis (preferably), symptom or sign on the AE CRF.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

12.9 Electrocardiogram

An ECG will be performed at screening to assess eligibility. Subjects should be in a supine or semi-supine position for at least 5 minutes prior to the assessment.

All ECG printouts must be reviewed by the investigator or a medically qualified member of the site staff and annotated to indicate any clinical finding. Prior to the first dose of study treatment, any ECG abnormality must be documented by the investigator as not medically relevant

The ECG assessments (normal vs abnormal) are to be recorded on the CRF. For each assessment, the investigator will determine whether the assessment is considered an AE (see definition in Section 12.1 and record the sign, symptom, or medical diagnosis on the AE CRF). Additional tests and other evaluations required to establish the significance or etiology of an abnormal assessment, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal assessment that persists should be followed at the discretion of the investigator.

12.10 Pregnancy Test

A serum pregnancy test will be performed for females of childbearing potential only at screening and Day 56.

12.11 Recurrent Malignancy

At screening and all visits during the study, subjects will be assessed for recurrent malignancy. Recurrent malignancy must be confirmed by a biopsy, per standard institutional practice. The investigator will record the presence or absence of recurrent malignancy in the eCRF.

13. STATISTICS

13.1 Sample Size and Power Calculations

Part 1:

The sample size for Part 1 was determined from an operational perspective and was not based on statistical power considerations. With 20 evaluable subjects and an assumed true response rate of 65%, the probability of observing an overall response rate of at least 55% is 87.8%. If the true response rate is 40%, the probability of observing an overall response rate of 55% or higher is less than 13%.

Part 2:

The primary endpoint for Part 2 is the overall response rate at Day 28.

The null hypothesis for Part 2 is that there is no difference in the overall response rate at Day 28 between the 2 treatment groups. The alternative hypothesis is that the overall response rate at Day 28 of the GLASSIA group is higher than that of the control group.

To determine the sample size for Part 2, the following assumptions were used:

1. Control group overall response rate of 40% across strata
2. GLASSIA group overall response rate of 65% across strata
3. Randomization ratio 1:1
4. 1-sided family wise Type I error rate of 0.025
5. Type II error rate of 0.20 (ie, power=80%)
6. A group sequential design with 1 interim look will be applied to the study. The gamma error spending function³¹ with a parameter -2 will be used for beta spending (nonbinding). The interim analysis will take place when approximately 50% of the primary endpoint data has been accumulated

SAS version 9.4, PROC SEQDESIGN with stop=both and nonbinding option for beta, and a gamma parameter of -40 for alpha spending (and hence no alpha spent) and -2 for beta spending was used to calculate this design.

Based on the sample size calculations, using a Cochran-Mantel-Haenszel chi-squared test, controlling the stratification factor, to detect the difference between the 2 groups, the primary analysis will require 67 evaluable subjects per group. Assuming a 10% early withdrawal rate, the target number of subjects will include 74 randomized subjects per group for a total of 148 randomized subjects.

The early withdrawal rate will be monitored in a blinded manner, and if found to be greater or less than 10%, sample size assumptions may be revised.

13.2 Analysis Sets

Part 1

The **Efficacy Analysis set** will include all subjects who are evaluable for overall response at Day 28. Subjects who receive at least 1 dose of study treatment and who have a lower GI biopsy that is consistent with acute GvHD will be considered evaluable.

The **Per-Protocol Analysis set** will include all subjects who received at least 1 dose of study treatment, meet all key eligibility criteria, and have no major or clinically significant protocol deviations. Major protocol deviations that will lead to exclusion from this set will be determined prior to each database lock.

The **Safety Analysis (SAF) set** will consist of all subjects who receive at least 1 dose of study treatment.

The **PK Analysis set** will consist of all subjects in the SAF set who have at least 1 PK or stool sample collected.

Part 2

The **Full Analysis (FA) set** will include all subjects who are randomized at Day 0. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at randomization.

The **Per-Protocol Analysis set** will include all subjects who received at least 1 dose of study treatment, meet all key eligibility criteria, and have no major or clinically significant protocol deviations with a lower GI biopsy consistent with acute GvHD and without a major protocol deviation. Major protocol deviations that will lead to exclusion from this set will be prespecified prior to unblinding the treatment codes.

The **SAF set** will consist of all subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the treatment received.

The **PK Analysis set** will consist of all subjects in the SAF set who have at least 1 PK or stool sample collected.

13.3 Handling of Missing, Unused, and Spurious Data

Part 1

For the analysis of the primary and key secondary efficacy endpoints, subjects who do not have a response assessment at Day 28 will be classified as non-responders. This approach will also be applied to the analysis of other time point responses, including the overall response at Day 56. A sensitivity analysis will be performed for the primary and key secondary efficacy endpoints using the last-observation-carried-forward (LOCF) approach to impute the missing response assessment.

Part 2

For the primary analysis of the primary endpoint, subjects who do not have an overall response evaluation at Day 28 will be classified as non-responders. If there are more than 5% subjects missing for the primary endpoint in either treatment group, 2 sensitivity analyses will be carried out. In the first analysis, missing data will be imputed with a missing-at-random assumption. This approach will assume that subjects who withdraw from a treatment group had missing values similar to subjects in that treatment group who completed the study. The second analysis will be a control-based imputation for the GLASSIA group (“jump to reference”). This approach will assume that subjects who withdraw had missing values similar to subjects in the control group who completed the study, regardless of the assigned treatment.

13.4 Methods of Analysis

Baseline characteristics of the subjects will be described using summary statistics overall and by treatment group (Part 2 only).

All continuous variables will be reported with number of subjects, mean, median, SD, minimum and maximum. All categorical variables will be summarized with number of subjects and frequency.

For Part 1, all endpoints will be summarized with descriptive statistics. Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects will not be performed. However, some measures will be summarized by both point estimates and the estimation of 95% confidence limits, where appropriate.

All statistical tests for Part 2 will be conducted at a 1-sided significance level of 2.5% unless otherwise specified.

The primary analysis of Part 2 will occur after all subjects have completed Day 56 of Part 2 or discontinued from study treatment, the Adjudication Committee has adjudicated all data through Day 56 of Part 2 and the study has been unblinded. The primary analysis will evaluate the primary outcome measure and all other outcome measures up to the data cutoff. A final analysis of the secondary and exploratory outcome measures will occur after all subjects have completed or discontinued from the study.

13.4.1 Primary Outcome Measure

Part 1

The overall response rate at Day 28 (see Section 8.4) will be summarized with descriptive statistics for Part 1 of the study. The primary analysis will use the Efficacy Analysis set, with sensitivity analyses carried out on the Per Protocol Analysis set and SAF set. A subgroup analysis of baseline lower GI involvement severity (stage 1 to 2 or stage 3 with no other organ involvement, stage 4 or stage 3 with other organ(s) involved) will be performed.

Part 2

The overall response rate at Day 28 (see Section 8.4) will be analyzed using the Cochran-Mantel-Haenszel chi-squared test, controlling the stratification factor (lower GI involvement severity), to test the null hypothesis that the odds ratio is equal to 1 for Part 2 of the study. To maintain the power of the study, the gamma error spending function³¹ with a parameter -2 will be used for type II error.

An unstratified comparison of the overall response rate at Day 28 will be conducted as a sensitivity analysis.

13.4.2 Secondary Outcome Measures

Part 1

The secondary efficacy outcome measures (see Section 8.4.2.1) and the secondary PK outcome measures (see Section 8.4.2.3) will be summarized with descriptive statistics. PK parameters will be summarized with the mean, SD, median, minimum and maximum values, geometric mean and percentage of coefficient of variation.

Part 2

The key secondary endpoint of GI response rate at Day 28 (see Section 8.4.2.1) and all binary types of endpoints, including overall response at Day 56, will be analyzed similarly to the overall response rate at Day 28.

Other secondary endpoints that will be derived in the statistical analyses include, but are not limited to, the following:

- All-cause, transplant-related, infection-related and GvHD-related mortality: defined as the time from HSCT to death due to any cause, transplantation, infection and GvHD, respectively
- Duration of any overall and GI response

The secondary endpoints of overall survival and failure-free survival rate at different timepoints will be analyzed using the Cox proportional hazard model. The hazard ratio (and the corresponding 95% confidence interval) will be reported. A Kaplan-Meier plot will also be presented. All-cause, transplant-related, infection-related and GvHD-related mortality will be analyzed using a similar method with competing-risk taken into consideration.

The other time-to-event types of secondary endpoints, including duration of any overall response and any GI response, will also be analyzed using the Cox proportional hazard model and summarized using Kaplan-Meier plots.

The change from baseline in acute GvHD grading will be analyzed with a shift table.

All other secondary efficacy endpoints will be summarized with descriptive statistics.

Safety Analyses (Parts 1 and 2)

Secondary safety outcome measures will be summarized with descriptive statistics and qualitative analysis (see Section 8.4.2.2). Adverse events will be listed for each subject and summarized by system organ class and preferred term by using the Medical Dictionary for Regulatory Activities. Safety laboratory data, vital signs measurements and biomarker data will be listed for each subject and summarized with descriptive statistics by treatment group (Part 2 only), visit and assessment time.

For the purpose of summaries and listings, the durations of AEs will be calculated as follows: $(stop\ day - start\ day) + 1\ day$, which yields the number of days on which the AE was present.

13.4.3 Exploratory Outcome Measures

The exploratory outcome measures include GvHD VGPR, steroid use, GI CR and PR for each baseline GvHD severity grade, population PK, pharmacodynamics and health outcomes (see Section 8.4.3). Exploratory outcome measures will be summarized with descriptive statistics.

13.5 Planned Interim Analysis of the Study

Part 1

An analysis will be performed to determine whether continuation from Part 1 to Part 2 is warranted. It will be performed when the last subject in Part 1 has completed the GvHD response assessment at Day 28. The overall response rate at Day 28 will be analyzed, as well as the data collected at baseline, efficacy as measured by secondary efficacy outcome measures, and safety data.

The analysis will be assessed by the Sponsor. The study may proceed to Part 2 if an overall response rate of $\geq 55\%$ is observed at Day 28 in Part 1. The criteria for initiation of Part 2 are specified in Section 8.2.2.

Part 2

A group sequential design with 1 interim look (Part 2) will be applied to the study. The gamma error spending function³¹ with a parameter -2 will be used for beta spending (nonbinding). SAS version 9.4, PROC SEQDESIGN with stop=both and nonbinding option for beta, and a gamma parameter of -40 for alpha spending (and hence no alpha spent) and -2 for beta spending was used to calculate this design.

The interim analysis will take place when approximately 50% of the primary endpoint data for Part 2 has been accumulated (ie, approximately 67 evaluable subjects with Day 28 assessments).

An independent, unblinded biostatistics team will perform the interim analysis and present the results to the DMC. The study will be analyzed for futility based on the overall response at Day 28 in Part 2. The DMC will provide recommendations to the sponsor based on the interim analysis. However, the sponsor may decide to stop the trial even if statistical criteria for futility are not observed.

With the aforementioned spending functions, the DMC will recommend the study be stopped for futility if the nominal p-value is larger than 0.3430. The type II error spend at the interim analysis is 0.0538. As the interim analysis may not occur when exactly 50% of the primary endpoint data are accrued, the boundary may be adjusted at the analysis time using the specified gamma function (ie, a parameter of -2). A total of 134 evaluable subjects (67 per group) is planned.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the EC and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement (CTA). If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority and allow the sponsor to comment on any responses, as described in the CTA.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP and applicable national and local regulatory requirements as described in the CTA. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

15.1.1 Final Clinical Study Report

The investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

15.2 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the CTA. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Safety Monitoring

The safety of the subjects in this study shall be monitored by an external DMC.

The DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical study. For this study, the DMC will be composed of recognized experts in the fields of oncology, hematology and immunology clinical care and research who are not actively recruiting subjects. The DMC may make a recommendation to continue the study as is, temporarily suspend the study, continue the study after proper amendment to the protocol or terminate the study based on predefined criteria such as unacceptable toxicities or lack of treatment benefits.

The DMC will meet to evaluate safety during Parts 1 and 2 and the interim analysis of overall response at Day 28 of Part 2 when approximately 50% of the primary efficacy data has been collected (Sections 8.2.2 and Section 13.5). The DMC may meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The DMC's responsibilities, definitions and operating procedures will be defined in a charter; the committee will maintain records of all its meetings and of the interim analysis of Part 2.

15.5 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP and national and local applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the CTA. Auditing processes specific to the study will be described in the audit plan.

15.6 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor (Baxalta) will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.7 Laboratory and Reader Standardization

Local laboratories will be used for all clinical laboratory assessments (hematology, clinical chemistry, coagulation panel and urinalysis). No inter-laboratory standardization will be performed for these assessments.

16. ETHICS

16.1 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the CTA.

16.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements and any other written information will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval, as described in the CTA.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval.

16.3 Informed Consent

Investigators will choose patients for participation considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the [CTA](#).

17.2 Study Documentation and Case Report Forms

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 8.8), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable) and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

If electronic format CRFs are provided by the sponsor, only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 17.3).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the CTA.

18. FINANCING AND INSURANCE

The investigator will comply with investigator financing, investigator/sponsor insurance and subject compensation policies, if applicable, as described in the CTA.

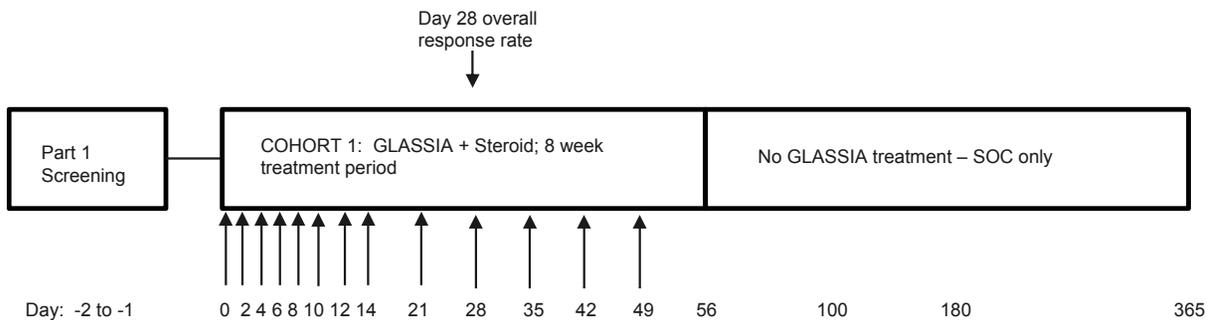
19. PUBLICATION POLICY

The investigator will comply with the publication policy as described in the CTA.

20. SUPPLEMENTS

20.1 Study Flow Chart

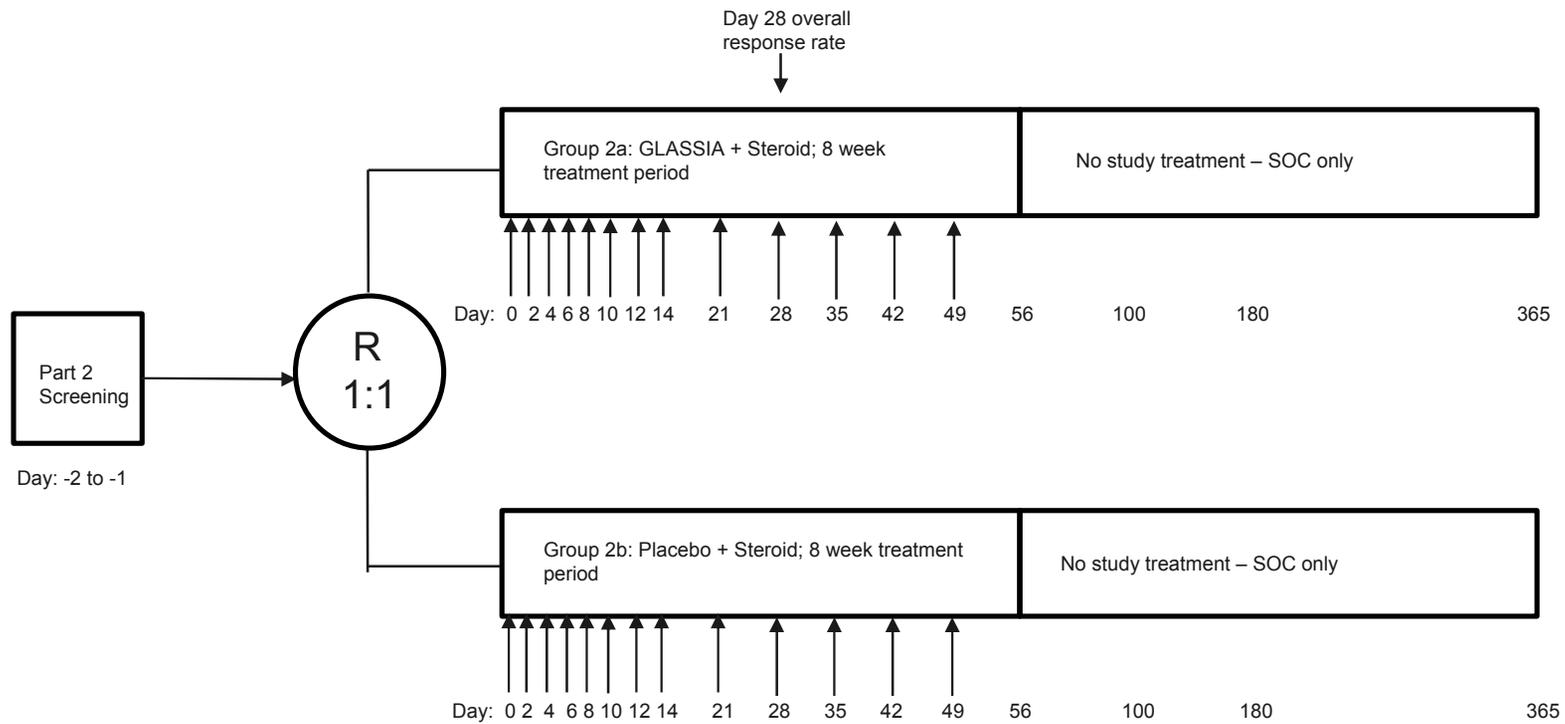
Figure 1
Study Design for Baxalta Clinical Study 471501 Part 1



Abbreviations: SOC=standard-of-care.

Note: Arrows indicate days of study treatment and the Day 28 primary endpoint assessment.

Figure 2
Study Design for Baxalta Clinical Study 471501 Part 2



Abbreviations: R=randomization; SOC=standard-of-care.

Note: Arrows indicate days of study treatment and the Day 28 primary endpoint assessment. The study will be unblinded after all subjects complete Day 56 of Part 2 or discontinue study treatment and the Adjudication Committee adjudicates all efficacy data through Day 56 of Part 2.

20.2 Schedule of Study Procedures and Assessments

Table 1 Schedule of Study Procedures and Assessments (Parts 1 and 2)																		
	Scr	Treatment Period														No Study Treatment Follow-Up		
Study Day	-2 to -1	Baseline/ day 0	2	4	6	8	10	12	14	21	28 ^a	35	42	49	56	100	180	365 ^b
Visit window (± days)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	5	5
Informed consent ^c	X																	
Inclusion/exclusion criteria	X																	
Demographics	X																	
Medical, surgical and transplant history	X																	
Medication history	X																	
Randomization (Part 2 only)		X																
Subject diary	X									X	X	X	X	X	X			
FACT-BMT, Chronic GvHD Symptom Scale, EQ-5D-5L ^d		X									X				X	X	X	X
Physical examination	X				X				X		X				X			
Vital signs ^e	X				X				X		X				X			
12-lead ECG	X																	
CMV testing	X				X				X	X	X	X	X	X	X	X	X	
HIV testing ^{f,g}	X																	
Clinical laboratory tests ^e	X		X	X	X			X	X		X				X			
Serum pregnancy test ^h	X														X			
Lower GI biopsy ⁱ	X																	
Biomarker sample collection ^e		X			X				X		X							
GvHD staging/assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1 Schedule of Study Procedures and Assessments (Parts 1 and 2)																		
	Scr	Treatment Period														No Study Treatment Follow-Up		
Study Day	-2 to -1	Baseline/ day 0	2	4	6	8	10	12	14	21	28 ^a	35	42	49	56	100	180	365 ^b
Visit window (± days)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	5	5
Overall response, GI response and GvHD VGPR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chronic GvHD assessment	X															X	X	X
Cumulative dose of steroids											X				X	X	X	
PK sample collection ^g		X ---> X						X ---> X	X	X				X ---> X				
Assessment of recurrent malignancy	X ----- > X																	
Adverse events	X ----- > X																	
Medications and non-drug therapies ⁱ	X	X ----- > X																
Mortality and survival assessments ^k											X				X	X	X	X
Study treatment administration ^l		X	X	X	X	X	X	X	X	X	X	X	X	X				
Administration of steroid treatment ^{l,m}	X	X ----->	X															
Viral prophylaxis ⁿ	X	X ----->	X															
Stool sample collection ^g	X	X						X			X				X			

Abbreviations: CMV=cytomegalovirus; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life-5 Dimensions-5 Level; FACT-BMT=Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale version 4.0 instrument; Scr=screening; GI=gastrointestinal; GvHD=graft-versus-host disease; HIV=human immunodeficiency virus; HRU=healthcare resource utilization; PK=pharmacokinetic; VGPR=very good partial response.

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- ^a Subjects who discontinue study treatment prior to Day 28 will complete the Day 28 visit on Day 28 (± 1 day). If at least 2 weeks have passed since the last dose of study treatment, Day 28 will serve as the study completion/termination visit. If Day 28 is less than 2 weeks following the last dose of study treatment, subjects will complete the Day 28 visit and then the study completion/termination visit 2 weeks (± 1 day) after the last dose of study treatment. In this event, the subject will have an office visit with the same assessments as the Day 365 visit. Subjects who discontinue study treatment will not attend any other subsequent visits other than Day 28 and the study completion/termination visit (if applicable), except as needed for follow-up of recovering/resolving AEs (see Section 12.1.2).
- ^b Study completion/termination visit after Day 28. Subjects who discontinue study treatment early but after Day 28 will complete a study completion/termination visit as an office visit 2 weeks (± 1 day) after the last dose of study treatment. Subjects who withdraw from the study after Day 56 will be encouraged to complete the study completion/termination visit at the time of discontinuation. In the event that it is not feasible for the subject to visit the site at the study completion/termination visit after Day 56, the visit may be conducted with a phone call.
- ^c Occurs prior to any study-specific procedures including screening.
- ^d The FACT-BMT, Chronic GvHD Symptom Scale and EQ-5D-5L should be collected before any other assessments are performed at the visit.
- ^e Body height will be measured at screening visit only. At visits at which study treatment is administered, vital signs will be measured within 30 minutes before and after administration of study treatment.
- ^f Antibody or nucleic acid test. The results of an HIV test performed within the 3 months prior to screening may be used instead.
- ^g See Table 2 for details.
- ^h Serum pregnancy test will be performed in females of childbearing potential only.
- ⁱ Results of a lower GI biopsy performed prior to screening may be used instead. The screening biopsy will be used to assess withdrawal criteria and will not be required to assess eligibility prior to the first dose of study treatment.
- ^j All medications taken and non-drug therapies received from providing informed consent until completion/termination will be recorded.
- ^k Investigator will assess the date and cause of death, if applicable. Cause of death will be assessed as related to transplant, infection and/or GvHD or any other cause. Failure-free, GvHD-free and overall survival will also be collected.
- ^l All assessments and sample collections, with the exception of PK and stool samples as described in Table 2, must be performed before administering study treatment and steroid treatment at each visit.
- ^m Steroid treatment for acute GvHD with lower GI involvement must have been initiated within 72 hours prior to the first study treatment administration. Steroid tapering may commence after a subject responds to therapy as described in Section 8.2. Subjects who are withdrawn from study treatment will be treated with standard-of-care at the investigator's discretion.
- ⁿ Subjects will receive standard prophylactic treatment for herpes simplex virus and varicella-zoster virus (eg, acyclovir or valacyclovir), through Day 180 or per institutional guidelines.

20.3 Clinical Laboratory Assessments

Table 2 Clinical Laboratory Assessments												
Assessments	Screening	Treatment Period										
Days	-2 to -1	Baseline/day0	2	4	6	12	14	21	28 ^a	49	56	
Visit window (± days)		1	1	1	1	1	1	1	1	1	1	
Hematology ^{b,c}	X				X	X	X		X		X	
Clinical chemistry ^{b,d}	X				X	X	X		X		X	
Coagulation panel ^{b,e}	X		X	X	X							
Urinalysis ^{b,f}	X				X	X	X		X		X	
Stool assessments ^g	X	X				X			X		X	
PK assessment ^h		X----->X				X----->X			X	X	X----->X	
Biomarker assessment ⁱ		X			X		X		X			
HIV test ^j	X											

Abbreviations: A₁PI=alpha-1 proteinase inhibitor; HIV=human immunodeficiency virus; IL=interleukin; IL-1RA=interleukin-1 receptor antagonist; PK=pharmacokinetic; RBC=red blood cell; Reg3α=regenerating islet-derived protein 3α; ST2=suppression of tumorigenicity 2; TNFR1=tumor necrosis factor receptor 1; Tregs=regulatory T cells; WBC=white blood cell.

Note: All samples, except PK and stool samples as indicated below, must be collected prior to the start of study treatment at the visit.

^a Subjects who discontinue study treatment prior to Day 28 will complete the Day 28 visit on Day 28 (±1 day). If at least 2 weeks have passed since the last dose of study treatment, Day 28 will serve as the study completion/termination visit. If Day 28 is less than 2 weeks following the last dose of study treatment, subjects will complete the Day 28 visit and then the study completion/termination visit 2 weeks (±1 day) after the last dose of study treatment. In this event, the subject will have an office visit with the same assessments as the Day 365 visit (Table 1). Subjects who discontinue study treatment will not attend any other subsequent visits other than Day 28 and the study completion/termination visit (if applicable), except as needed for follow-up of recovering/resolving AEs (see Section 12.1.2).

^b In addition to the assessments shown, clinical laboratory assessments should be performed whenever clinically indicated.

^c Hematology assessments include hemoglobin, hematocrit, RBC count and WBC count with differential (ie, basophils, eosinophils, lymphocytes, monocytes and neutrophils), mean corpuscular volume, mean corpuscular hemoglobin concentration and platelet count.

^d Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine and glucose.

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- ^e Coagulation panel includes PT, PTT and INR.
- ^f Urinalysis assessments include: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase and microscopic examination (RBC, WBC, bacteria and casts).
- ^g For the determination of stool A₁PI level and clearance and calprotectin concentrations. One sample will be collected either during screening or prior to the first study treatment administration on Day 0. On Days 0 and 12, a sample will be collected during the 24 hours after the start of study treatment infusion. On Day 28, the sample will be collected prior to the start of study treatment infusion.
- ^h If study treatment is administered peripherally, the PK samples should be taken from the opposite arm as the study treatment administration, if possible. If study treatment is administered via a central indwelling catheter, the PK samples may be taken from the same infusion line, if the infusion line is flushed prior to collection of the PK sample and the first 3 mL of blood is discarded.
The PK samples for the measurement of plasma A₁PI levels will be collected at the following timepoints:
 - Part 1, Cohort 1
 - Day 0: Prior to start of study treatment infusion, at 15 (±5) minutes, 2 hours (±12 minutes), 4 hours (±24 minutes), 8 hours (±48 minutes), 12 hours (±72 minutes) and 24 hours (±144 minutes) (ie, Day 1) following the end of study treatment infusion
 - Day 2: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 12: Within 2 hours prior to start of study treatment infusion, at 15 (±5) minutes, 2 hours (±12 minutes), 4 hours (±24 minutes), 8 hours (±48 minutes), 12 hours (±72 minutes) and 24 hours (±144 minutes) (ie, Day 13) following the end of study treatment infusion
 - Day 14: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 21: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 28: During the Day 28 clinic visit, but must be prior to the next study treatment
 - Day 49: Within 2 hours prior to start of study treatment, at 15 (±5) minutes, 2 hours (±12 minutes), 4 hours (±24 minutes), 24 hours (±144 minutes) (ie, Day 50), 72 (±7) hours (ie, Day 52) and 120 (±12) hours (ie, Day 54) following the end of study treatment infusion
 - Day 56: During the Day 56 clinic visit
 - Part 2
 - Day 0: Prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 2: Within 2 hours prior to study treatment infusion
 - Day 12: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 14: Within 2 hours prior to study treatment infusion
 - Day 21: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 28: During the Day 28 clinic visit, but must be prior to the next study treatment infusion.
 - Day 49: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 56: During the Day 56 clinic visit
- ⁱ Biomarkers to be assessed in Parts 1 and 2 will include cytokines IL-2, IL-6, IL-8, and IL-10; IL-1RA and T cell subpopulations, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs; in Part 2 only, the following biomarkers will also be assessed: Reg3α, ST2, and TNFR1.
- ^j Antibody or nucleic acid test. The results of an HIV test performed within the 3 months prior to screening may be used instead.

20.4 Toxicity Grading Scale for AEs

Table 3 Mapping Conventions for AE Severity (For AEs Not Described Within NCI CTCAE version 4.03)	
NCI CTCAE Grade	Corresponding AE Severity (if Not Provided in NCI CTCAE)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviations: ADL=activities of daily living; AE=adverse event;
NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

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22. SUMMARY OF CHANGES

Protocol 471501: Amendment 1 2017 APR 19

Replaces: Original: 2016 APR 19

In this section, changes from the previous version of the Protocol, dated 2016 APR 19, are described and their rationale is given.

1. Throughout the document
Description of Change: Minor grammatical and/or administrative changes have been made.
Purpose for Change: To improve the readability and/or clarity of the protocol.
2. Throughout the document
Description of Change: NCT Number added.
Purpose for Change: NCT Number provided has been obtained.
3. Throughout the document
Description of Change: IND Number added.
Purpose for Change: IND Number provided has been obtained.
4. Section 1 Study Personnel; Investigator Acknowledgement Signature Pages
Description of Change: Name of Signatory has been changed.
Purpose for Change: Sponsor Authorized Representative has changed.
5. Section 3 Synopsis and throughout document
Description of Change: Change Study Day 1 to Baseline/Day 0; all subsequent days for dosing/follow-up are in reference to the Baseline; changed Study Days 1, 3, 5, 7, 9, 11, 13, 15, 22, 36, 43, and 50 to Baseline/Day 0 and Days 2, 4, 6, 8, 10, 12, 14, 21, 35, 42, and 49.
Purpose for Change: To correct an error in calculating dosing schedule.
6. Section 3 Synopsis (Primary Objective); Section 7.2 Primary Objective
Description of Change: Change “treatment response at 28 days” to “treatment response at Day 28”.
Purpose for Change: Day 28 is a planned study visit and it’s actually on the 29th day of treatment.

7. Section 3 Synopsis (Exploratory Objectives #3; Pharmacodynamics assessment #3); Section 7.4 Exploratory Objectives (Parts 1 and 2); Section 8.4.3 Exploratory Outcome Measures; Section 11.7 Pharmacokinetic, Biomarker and Stool Sample Collection; Section 20.3 Clinical Laboratory Assessments (Table 2 footnote i)
Description of Change: Deleted IL-32 and heparin sulfate.
Purpose for Change: There is no validated assay for these analyses.
8. Section 3 Synopsis (Exploratory Objectives #3; Pharmacodynamics assessment #3); Section 7.4 Exploratory Objectives (Parts 1 and 2); Section 8.4.3 Exploratory Outcome Measures; Section 11.7 Pharmacokinetic, Biomarker and Stool Sample Collection; Section 20.3 Clinical Laboratory Assessments (Table 2 footnote i)
Description of Change: Deleted Reg3 α , ST2, and TNFR1 from Parts 1 and 2 and added these under new heading/text for Part 2 Only.
Purpose for Change: The rationale for this change is that this set of exploratory biomarkers will have limited clinical utility in the setting of Part 1 of this clinical study – given the small sample size (n=20) and the lack of an adequate controlled subject population for comparison; there might be more meaningful clinical utility of this exploratory data in Part 2 given the larger sample size, the presence of an adequately controlled population for comparison and also a disease severity stratification in this part of the clinical study.
9. Section 3 Synopsis (Study Design/Part 1); Section 8.2.1 Study Design
Description of Change: Text added that subjects who are treated but found to have a baseline lower GI biopsy inconsistent with GvHD will be replaced to ensure 20 evaluable subjects.
Purpose for Change: Conditions under which subjects are replaced clearly defined.
10. Section 3 Synopsis (Study Design/Part 1); Section 8.2.1 Study Design; Section 13.5 Planned Interim Analysis of the Study
Description of Change: Text added to describe an interim analysis that will be performed to determine continuation from Part 1 to Part 2.
Purpose for Change: Interim analysis added to determine if the study should continue from Part 1 to Part 2 based on overall response rate.
11. Section 3 Synopsis (Study Design/Part 2); Section 8.2.2 Part 2 Study Design
Description of Change: Text added that randomized subjects in Part 2 who discontinue will not be replaced.
Purpose for Change: Conditions under which subjects are replaced clearly defined.

12. Section 3 Synopsis (Study Design/Interim Analysis); Section 8.2.2 Part 2 Study Design; Section 13.5 Planned Interim Analysis of the Study
Description of Change: Text added to describe that sponsor may stop the trial following interim analysis even if futility criteria are not observed.
Purpose for Change: Text revised in response to scientific advisor's question regarding nonbinding recommendations by DMC to sponsor based on interim analysis.
13. Section 3 Synopsis (Primary Outcome Measure, Secondary Outcome Measures, and Exploratory Outcome Measures); Section 8.4.1 Primary Outcome Measure (Parts 1 and 2); Section 8.4.2.1 Efficacy (Parts 1 and 2); Section 8.4.3 Exploratory Outcome Measures
Description of Change: Outcome measures assessed "by" Day 28 changed to "at" Day 28.
Purpose for Change: Analysis wording clarified to be consistent with analyses described in the Statistical Analysis Plan.
14. Section 3 Synopsis (Health Outcomes #4); Section 8.4.3 Exploratory Outcome Measures (Health Outcomes Parts 1 and 2)
Description of Change: Text revised to "type of admission".
Purpose for Change: Changed for consistency with Statistical Analysis Plan.
15. Section 3 Synopsis (Inclusion Criterion #4); Section 9.1 Inclusion Criteria (Criterion #4)
Description of Change: Moved text "newly diagnosed" from inclusion criterion 6 to criterion 4.
Purpose for Change: Clarity of diagnosis for inclusion into the study.
16. Section 3 Synopsis (Inclusion Criterion #5); Section 8.1 Brief Summary; Section 9.1 Inclusion Criteria (Criterion #5); Section 11.3 Lower GI Biopsy
Description of Change: Inclusion criterion added for willingness to undergo lower GI biopsy within 7 days of informed consent; biopsy results not needed to start treatment; however, if biopsy results are not consistent with aGvHD, treatment will be discontinued.
Purpose for Change: Clarity on pathological basis of disease diagnosis and temporal requirements.

17. Section 3 Synopsis (Inclusion Criterion #6); Section 9.1 Inclusion Criteria (Criterion #6)
Description of Change: Moved text “newly diagnosed” from inclusion criterion 6 to criterion 4; added “subjects must be receiving systemic corticosteroids”.
Purpose for Change: Clarity of diagnosis and requirement for systemic corticosteroids for inclusion into the study.

18. Section 8.2 Overall Study Design; Section 8.7.1.3 Anti-infective Prophylaxis
Description of Change: Section heading revised to “Anti-infective Prophylaxis”; antibiotic, antifungal and antiviral added to prophylactic treatment; CMV added.
Purpose for Change: Prophylactic treatment clarified.

19. Section 8.2 Overall Study Design
Description of Change: Text added that treatment failures will be included in the analysis.
Purpose for Change: Analysis of treatment failures clarified.

20. Section 8.2 Overall Study Design
Description of Change: Retreatment allowance after Day 56 deleted.
Purpose for Change: Removed option for retreatment after Day 56 in order to focus on the primary objective of the study, which is to confirm the safety and efficacy of GLASSIA in subjects with stage 1 to 4 lower GI aGVHD as assessed by treatment response at 28 days. Retreatment could be explored in a subsequent study.

21. Section 8.2 Overall Study Design
Description of Change: Steroid taper changed from not less than 0.5 mg/kg/day to 0.25 mg/kg/day before Day 28.
Purpose for Change: To align with broad clinical practice and provide greater flexibility of steroid tapering to investigators; with the potential to reduce patient exposure to steroids.

22. Section 8.5.1 Randomization
Description of Change: An Eligibility Criteria Form has been added.
Purpose for Change: To ensure the appropriate population has been enrolled in the study.

23. Section 8.7.2 Administration
Description of Change: Reference to Pharmacy Manual added for instructions to preparation, blinding and administration of study treatment.
Purpose for Change: Specific instructions for study treatment added to Pharmacy Manual as no Study Procedures Manual will be prepared for this study.
24. Section 9.7.3.2 Withdrawal from Study Participation and Discontinuation of Study Treatment
Description of Change: Description of withdrawal and discontinuation clarified.
Purpose for Change: The description of study withdrawal and treatment discontinuation was clarified.
25. Section 10.4 Medications and Non-drug Therapies
Description of Change: Enteral corticosteroids included as medications not permitted during the study or within 30 days before study entry. Topical corticosteroids including ophthalmic steroids added to list of permitted medications.
Purpose for Change: Permitted medications clarified.
26. Section 10.5 Subject Diary; Section 20.2 Schedule of Study Procedures and Assessments
Description of Change: Subject diary will be provided to each subject once the subject is discharged; steroid dose, concomitant medications, non-drug therapies, and AEs will not be collected on the diary; text revised for clarity.
Purpose for Change: Subjects will not need diaries when they are in the hospital/clinic; steroid doses, concomitant medications, and AEs will be collected on the CRF.
27. Section 11.4 GvHD Staging/Assessment
Description of Change: GvHD grading and staging text revised.
Purpose for Change: Grading and staging clarified for GvHD.
28. Section 11.8 Functional Assessment of Cancer Therapy – Bone Marrow Transplant; Section 11.10 European Quality of Life – 5 Dimensions – 5 Levels
Description of Change: Use of an electronic patient-reported outcome device has been deleted.
Purpose for Change: No electronic device will be used.

29. Section 11.11 Healthcare Resource Utilization
Description of Change: Description of information to be included in the diary was revised.
Purpose for Change: Text revised for clarity and accuracy.
30. Section 12.1.1 Definitions
Description of Change: Definition of AEs revised by removing list of events that do not meet the definition of an AE; grading and follow-up of abnormal laboratory values reported as AEs has been added.
Purpose for Change: Text revised for clarity.
31. Section 12.1.1.5 Preexisting Diseases
Description of Change: Text regarding the reporting of changes in severity, duration, or symptoms of GvHD deleted.
Purpose for Change: The baseline state will not be captured because these signs and symptoms are part of the disease state.
32. Section 12.1.2 Assessment of Adverse Events
Description of Change: Text added to clarify that changes in severity or duration of GvHD after first IP exposure are collected as efficacy data and not AE data; symptoms or diagnostic findings of GvHD will be collected as AE data; deviations from protocol-specified IMP use will be recorded in the Protocol Deviation Form.
Purpose for Change: Clarification of language specifying collection of efficacy data vs safety data; also, text revised for clarity to indicate these above mentioned deviations from protocol-specified procedures will be recorded in the Protocol Deviation Form and not as AEs.
33. Section 12.1.2 Assessment of Adverse Events
Description of Change: Text describing investigator responsibility for reporting an SAE that occurred after study completion has been deleted.
Purpose for Change: Text deleted for accuracy of reporting.
34. Section 12.7.1 Hematology and Clinical Chemistry; Section 15.7 Laboratory and Reader Standardization; Section 20.3 Clinical Laboratory Assessments (Table 2)
Description of Change: Lipid panel removed.
Purpose for Change: Lipid panel will not be performed in this study.

35. Section 12.7.1 Hematology and Clinical Chemistry;
Section 20.3 Clinical Laboratory Assessments (Table 2 footnote f)
Description of Change: Fibrin, fibrin split products, fibrinogen and D dimer assessments replaced with PT, PTT, and INR assessments.
Purpose for Change: PT/PTT/INR are more relevant measures of coagulation function. FDP, D-Dimers and fibrinogen levels are part of a DIC panel that are not usually performed in the setting of GvHD, and the absence of these is not expected to impact clinical study safety measures.
36. Section 12.7.3.2 Assessment of Abnormal Laboratory Values
Description of Change: Abnormal laboratory values reportable as adverse events clarified.
Purpose for Change: Clarification of language for accuracy.
37. Section 12.7.4 Backup Samples and Biobanking
Description of Change: Backup samples to be used for analyses in this study only.
Purpose for Change: Use of backup samples clarified.
38. Section 12.9 Electrocardiogram
Description of Change: ECG parameters/values changed to ECG assessments (normal vs abnormal).
Purpose for Change: Revised to align with study eligibility criteria; ECG parameters will not be collected in this study.
39. Section 13.2 Analysis Sets
Description of Change: Efficacy Analysis set clarified; Per-Protocol Analysis set added to Part 1; Per-Protocol Analysis set revised in Part 2.
Purpose for Change: Analysis sets revised for accuracy and consistency.
40. Section 13.3 Handling of Missing, Unused, and Spurious Data
Description of Change: Text regarding missing efficacy response data in Part 1 revised.
Purpose for Change: Per SAP comments from Shire, there will be imputation for missing efficacy response data in Part 1 analysis.

41. Section 13.4.1 Primary Outcome Measure
Description of Change: Text regarding primary analysis in Part 1 revised.
Purpose for Change: Per SAP comments from Shire, there will be planned sensitivity analysis and subgroup analysis for primary outcome measure for Part 1 analysis.
42. Section 15.7 Laboratory Reader Standardization
Description of Change: Text regarding description of standardization methods for PK and biomarker analyses has been deleted.
Purpose for Change: Text revised for accuracy.
43. Section 20.2 Schedule of Study Procedures and Assessments (Table 2, row for PK sample collection); Section 20.3 Clinical Laboratory Assessments (PK row for PK assessment; footnote h)
Description of Change: PK samples after 15 minutes following the end of study treatment infusion on Day 21 have been deleted.
Purpose for Change: The rationale behind the change has been driven by a combination of trying to reduce sampling points during the D21 to D28 time period to ease subject participation and improve compliance with the clinical study protocol, and the ability to compute required PK data without extensive PK sampling at this time point.
44. Throughout the document
Description of Change: Deletion of legally authorized representative(s).
Purpose for Change: Patient's consent is preferred given the clinical nature and prognosis of GI GvHD. Also to exclude patients with altered mentation, etc (not Alert And Oriented X3).

INVESTIGATOR ACKNOWLEDGEMENT

PRODUCT: GLASSIA

STUDY TITLE: A Two-Part, Multi-Center, Prospective, Phase 2/3 Clinical Study to Evaluate the Safety and Efficacy of GLASSIA as an Add-On Biopharmacotherapy to Conventional Steroid Treatment in Subjects with Acute Graft-Versus-Host Disease with Lower Gastrointestinal Involvement

PROTOCOL IDENTIFIER: CT2/3-GVHD-IV-Multi-Center-KAM/BAX; 471501

CLINICAL TRIAL PHASE 2/3

AMENDMENT 1: 2017 APR 19

Replaces: ORIGINAL: 2016 APR 19

ALL VERSIONS:

AMENDMENT 1: 2017 APR 19

ORIGINAL: 2016 APR 19

OTHER ID(s)

NCT Number: NCT02956122

EudraCT Number: To be determined

IND NUMBER: 017014

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Signature of Principal Investigator

Date

Print Name of Principal Investigator

INVESTIGATOR ACKNOWLEDGEMENT

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Signature of Coordinating Investigator

Date

Print Name and Title of Coordinating Investigator

Signature of Sponsor Representative

Date

Judit Koranyi, MD

PPD

Global Clinical Development Operations
Baxalta US Inc. / Baxalta Innovations GmbH