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1. INTRODUCTION AND OBJECTIVES

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 graft-versus-host disease (GvHD) with lower gastrointestinal (GI) involvement. This is a 2-part study. Part 1 will evaluate the safety, efficacy and pharmacokinetic (PK) of GLASSIA in approximately 20 subjects. Start of any Part 2 activities was pending results from statistical analysis of Part 1 data.

GLASSIA was approved in the United States for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of human alpha-1 proteinase inhibitor (A₁PI). The preclinical literature for A₁PI, in combination with the interim efficacy results from a Phase 1/2 study, suggests that GLASSIA has the potential to provide significant clinical benefit as a first-line treatment in acute GvHD. There is currently no FDA-approved treatment for acute GvHD. The study population is selected because severe acute GI GvHD is associated with high mortality and patients with acute GvHD with lower GI involvement have a lower response rate to steroid treatment.

On 2 June 2017, Shire (sponsor) prematurely terminated the entire study (both Part 1 and Part 2) following an internal portfolio prioritization exercise which took into consideration difficulties in enrolling subjects and a reduced probability of success of the study. As of the decision date, only 1 subject had been enrolled in the study and no additional subject will be enrolled. That subject was treated with study drug under the original protocol because Protocol Amendment 1, while approved on 19 April 2017, prior to the study termination date, could not be implemented.

This SAP is for Part 1 of the 2-part study and is based on the original protocol and thus documents all derivations of outcome variables, statistical analyses and summaries preplanned in the original protocol. Derivations of outcome variables, statistical analyses and summaries in this SAP are no longer applicable, as indicated by “Not Applicable” in the appropriate sections, but the analysis content is retained only for alignment with the original protocol. Only data listings will be produced for the single-enrolled subject, and the listings will include raw (actual) values. In addition, since no adjudication of the response assessment data will be done, only the data based on the investigators’ assessments will be presented in the listings.

There will be no SAP for Part 2 since the entire study (Part 1 and Part 2) was terminated before start of Part 2. No subjects were enrolled in Part 2 at time of termination.

1.1 Study Objectives

1.1.1 Primary Objective

To confirm the safety and efficacy of GLASSIA administered at a dose of 90 mg/kg (Day 1) followed by 30 mg/kg every other day (Days 3 to 13), then followed by 120 mg/kg weekly (Days 15 to 50), 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.

1.1.2 Secondary Objective(s)

1.1.2.1 Efficacy

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.

1.1.2.2 Safety

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

1.1.2.3 Pharmacokinetics

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

1.1.2.4 Exploratory

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, IL-10 and IL-32; heparan sulfate; regenerating islet-derived protein 3 α [Reg3 α]; suppression of tumorigenicity 2 (ST2); tumor necrosis factor receptor 1 [TNFR1]; 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

2. STUDY DESIGN

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 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 subjects (Cohort 1). The overall study design of Part 1 is illustrated in Figure 1 in Section 14.1. Part 2 of the study is not discussed in this SAP.

Screening for eligibility will occur from Days -2 to -1. After screening, all eligible subjects will be given GLASSIA with a loading dose of 90 mg/kg (Day 1) followed by GLASSIA 30 mg/kg every other day (Days 3 to 13), then followed by 120 mg/kg weekly (Days 15 to 50) in combination with 2 mg/kg/day of methylprednisolone or equivalent steroid. Tapering of steroids may commence after a subject responds to therapy.

All subjects will be treated through Day 50, 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. Prior to Day 28, subjects must be withdrawn from study treatment if a second-line treatment for acute GvHD is introduced. Subjects who experience recurrent malignancy will also be withdrawn from study treatment. Subjects who are withdrawn from study treatment will continue to be followed through at least Day 28, unless the subject withdraws consent.

Steroid treatment after Day 50 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 requiring second-line treatment after Day 56 may be eligible to receive 1-time retreatment with GLASSIA with the same loading and maintenance dosing regimen (50 days of treatment). Regardless of whether the subject receives retreatment, all subjects will be followed up at Days 100, 180 and 365.

Subjects classified as treatment failures will be included in the analysis but not be counted as either complete response (CR) or partial response (PR) for the primary

(overall response) or key secondary (GI response) endpoints. Subjects classified as treatment failures will not be replaced. Assessments of vital signs, clinical laboratory data (hematology and chemistry), local tolerability and adverse events (AEs) will be performed throughout the study.

2.1 Study Population

The population for this study will consist of male and female subjects ≥ 18 years of age who are recipients of an allogeneic hematopoietic stem cell transplantation (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). 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.

2.2 Sample Size and Power Calculations

The sample size for Part 1 was determined from an operational perspective and was not based on statistical power considerations. With 20 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%.

2.3 Randomization and Blinding

Part 1 is a nonrandomized, open-label, active treatment clinical study.

2.4 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.

2.5 Study Assessments

A schedule of assessments for Part 1 is provided in Section [14.2](#). Details on clinical laboratory assessments can be found in Section [14.3](#).

2.6 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action). 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.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject has a lower GI biopsy that in the opinion of a pathologist is inconsistent with acute GvHD
- The subject becomes pregnant
- The subject begins lactating
- The subject starts a second-line treatment for acute GvHD prior to Day 28
- The subject experiences recurrent malignancy

2.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) will independently evaluate safety and efficacy data. 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 periodically to evaluate safety during Part 1 and use the results from Part 1 to determine whether continuation to Part 2 is warranted. 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.

3. STUDY OUTCOME MEASURES

3.1.1 Primary Outcome Measure

The primary outcome measure for Part 1 is the proportion of subjects achieving overall response (GvHD CR + PR) at Day 28.

3.1.2 Secondary Outcome Measures

3.1.2.1 Efficacy

Key Secondary Efficacy Outcome Measures

1. Proportion of subjects achieving GI response (GI CR + PR) at Day 28

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

3.1.2.2 Safety

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

3.1.3 Exploratory Outcomes Measure

3.1.3.1 Efficacy

1. Proportion of subjects achieving GvHD very good partial response (VGPR) at Day 28
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)

3.1.3.2 Pharmacokinetics

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

3.1.3.3 Pharmacodynamics

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, IL-10 and IL-32; heparan sulfate; Reg3 α ; ST2; TNFR1 and IL-1RA) and stool calprotectin concentrations
4. T cell subpopulations from serum, including CD4+ CD25+ CD127+ FoxP3+ Tregs

3.1.3.4 Health Outcomes

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)
1. Change from baseline in acute GvHD symptoms as measured by the Chronic GvHD Symptom Scale
2. Change from baseline in health utility as measured by European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L)
3. 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
4. Medication:
 - Days on steroids

4. ANALYSIS SETS

4.1 Efficacy Analysis Set

The Efficacy Analysis set will include all subjects who are evaluable for overall response at Day 28. Subjects who do not receive at least 1 dose or who are withdrawn due to a lower GI biopsy that is inconsistent with acute GvHD will not be considered evaluable.

The Efficacy Analysis set will be used for the primary analysis of the primary outcome measure and the analyses of selected secondary efficacy outcome measures and health outcomes.

4.2 Safety Analysis Set

The Safety Analysis (SAF) set will consist of all subjects who receive at least 1 dose of study treatment and will be used in the analyses of safety variables, and the sensitivity analyses of the GvHD overall response rate at Day 28 and GI response rate at Day 28.

4.3 PK Analysis Set

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

4.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will consist of all subjects in the SAF set who have at least 1 postdose biomarker sample collected.

5. STATISTICAL CONSIDERATIONS

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

For Part 1, all the outcome variables will be summarized descriptively. Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects will not be performed.

Statistical summaries described will be provided for all subjects in the analysis set of interest unless otherwise stated.

For efficacy outcome measures, the point estimate and 95% confidence interval will be provided. For the other outcome measures, continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each

category. Unless otherwise stated, percentages will be calculated out of the total in the analysis set. The number of missing values will be presented where necessary.

For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. For categorical data, percentages will be rounded to 1 decimal place.

For time-to-event outcome measures, Kaplan-Meier estimates will be provided, and the estimates will include 25th percentile, median and 75th percentile, if estimable, and the corresponding 95% confidence intervals.

5.1 Handling of Missing, Unused, and Spurious Data

For Part 1, for the primary analysis of GvHD overall response, the non-responder imputation (NRI) approach will be used to impute the response status at Day 28 as no response for subjects without a response assessment at Day 28 due to any reason. The NRI approach will also be applied to GI response at Day 28 and other time point responses, including overall response at Day 56.

Regarding missing data in AE records:

- Handling of unknown causality assessment:
 - If a subject experiences an AE with a missing causality assessment, the relationship of the AE will be counted as “related”.
- Handling of unknown severity grades:
 - If a subject experiences more than one AE categorized under the same preferred term, the subject will be counted under the most severe toxicity grade reported for that AE.
 - If a subject experiences an AE and the toxicity grade was not provided, the toxicity grade of this AE should be counted as “unknown”. A row or column labelled “Unknown” should be inserted for those AEs in tables where AEs are summarized by toxicity grade.

5.2 Definition of Baseline

Baseline will be the last non-missing assessment of the variable under consideration prior to initial administration of study treatment (GLASSIA in Part 1).

Assessments on the day of first dose of study treatment where time is not captured will be considered as after the first dose unless a nominal pre-dose indicator is available or such procedures are required by the protocol to be conducted before the first dose of study treatment.

5.3 Changes from the Planned Statistical Analysis in Protocol

As indicated in Section 1, Shire (sponsor) prematurely terminated the entire study (both Part 1 and Part 2) on 2 June 2017 following an internal portfolio prioritization exercise which took into consideration difficulties in enrolling subjects and a reduced probability of success of the study. As of the decision date, only 1 subject had been enrolled in the study and no additional subject will be enrolled. That subject was treated with study drug under the original protocol because Protocol Amendment 1, while approved on 19 April 2017, prior to the study termination date, could not be implemented.

This SAP is for Part 1 of the 2-part study and is based on the original protocol and thus documents all derivations of outcome variables, statistical analyses and summaries preplanned in the original protocol. Unless otherwise specified in this SAP, only data listings will be produced for the single-enrolled subject, and the listings will include raw (actual) values. In addition, since no adjudication of the response assessment data will be done, only the data based on the investigators' assessments will be presented in the listings.

6. STUDY SUBJECTS

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

6.1 Disposition of Subjects

Subject disposition will be summarized and presented with the number and percentage of subjects who were screened, screen-failed, treated, completed the study, and discontinued early (including reasons for discontinuations). The number and percentage of subjects in each analysis set (SAF, Efficacy, PK) will be displayed. A listing of subject disposition will be produced. Inclusion/exclusion criteria violations will be listed for screen-failed subjects.

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age (years), sex, race (where applicable), ethnicity (where applicable), height (cm), weight (kg), BMI (kg/m²),

baseline GvHD stages as measured as the degree of skin, GI, liver involvement, severity grade of acute GvHD, stage of lower GI involvement, status of recurrent malignancy at baseline, and transplant history (source of HSCT, donor related or not, sex of donor, primary or repeated transplant) will be summarized using descriptive statistics. Age will be calculated as the integer of (Date of Informed Consent – Date of Birth)/365.25.

Smoking history will be categorized (never, current, former) for each nicotine type and presented separately. Details of smoking history, including the age of starting and quitting smoking, daily amount, and pack years, will be listed only.

Summaries will be provided for the SAF and Efficacy Analysis sets for all subjects in each analysis set. Demographics and baseline characteristics will also be presented in subject data listings.

6.3 Medical History

The medical and surgical history of subjects will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 or a later version and summarized separately for the SAF set, presenting the number and percentage of subjects with a history in each system organ class (SOC) and preferred term. For summary tables, a subject will be counted only once per body system and preferred term. Medical and surgical history will be included in data listings. Acute GvHD history will be listed only.

6.4 Concomitant Medications

Other than the study drug, any medications or therapies administered on or after the first dose of study treatment but not starting after the last dose of study treatment, or with a start date prior to and an end date on or after the date of the first dose of study treatment, or marked as ongoing will be considered concomitant medications. Medications that ended prior to the date of the first dose of the study drug will be considered as prior medications. Concomitant and prior medications will be coded using the latest version of the WHO Drug dictionary and summarized separately.

Concomitant anti-infective medications will be summarized by re-grouping antibiotics, antivirals, and antifungals agents, with the number and percentage of subjects using each concomitant medication according to the WHODRUG Anatomic Therapeutic Class (ATC) and preferred term for the SAF set. Subjects with multiple uses of a concomitant medication will be counted once by the drug class and preferred term.

Prior and concomitant medications will be presented in the subject data listings.

6.5 Protocol Deviations

Protocol deviations will be classified as Minor, Important/Major or Critical/Priority. For analysis and reporting purposes, deviations leading to exclusion from the Efficacy Analysis set will include, but are not limited to: deviation from eligibility criteria, administration of prohibited medications and erroneous administration of study treatment. The criteria for grading protocol deviations will be proposed according to Quintiles SOP by the Quintiles Therapeutic Medical Advisor and aligned with the Baxalta Physician. All protocol deviations leading to exclusion from the Efficacy Analysis set are determined together with the Baxalta Physician on a case-by-case basis by the medical reviewer prior to each database lock of Part 1.

The number and percentage of subjects for each type of protocol deviation will be tabulated for the SAF set and a listing will be produced showing individual subjects for all protocol deviations.

7. EFFICACY EVALUATION

7.1 Analysis of Primary Efficacy Outcome Measure

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

The primary outcome measure is the GvHD overall response rate, the proportion of subjects achieving overall response at Day 28. The overall response is defined as GvHD CR + PR, which are defined as follows:

- 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

Overall response at Day 28 will be based on the response assessments at Day 28 with a +1- day window for this assessment. For the primary analysis in the efficacy analysis set, the NRI approach will be used to impute the missing response assessment at Day 28. For the GvHD overall response rate at Day 28 95% exact confidence intervals of the proportion will be calculated with Clopper-Pearson method.

The primary analysis of the GvHD overall response rate in the efficacy analysis set will use the investigators' response assessment collected on the CRF Investigator Response Assessment [INVRES] module and use NRI approach for missing response assessment.

A sensitivity analysis in the efficacy analysis set will use the adjudicated response assessments by an adjudication committee and use NRI approach for missing response assessment.

All the planned analyses of the GvHD overall response rate at Day 28 are listed in the table below.

Analysis	Analysis set	Response assessment data	Approach for missing response assessment imputation
Primary analysis	Efficacy analysis set	Investigators' assessment	NRI
Sensitivity analysis	Efficacy analysis set	Adjudicated data	NRI

Response assessments for each subject will be listed by visit.

7.2 Analysis of Secondary Efficacy Outcome Measure

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

7.2.1 Key Secondary Efficacy Outcome Measures

The key secondary efficacy outcome is the GI response rate, the proportion of subjects achieving GI response at Day 28. GI 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

GI response at Day 28 based on investigator assessments (CRF INVRES module) and adjudicated data will be analyzed using the same approach as described for the primary outcome in Section 7.1.

7.2.2 Other Secondary Efficacy Outcome Measures

Proportion of subjects achieving GvHD overall response at Day 56

GvHD overall response at Day 56 will be based on all the investigators' assessments or the adjudicated data of GvHD response obtained at Day 56 (with a +1 day window) in the efficacy analysis set and using the NRI approach as for the primary outcome measure in Section 7.1.

Change from baseline in acute GvHD grading at Days 28, 56 and 180

Staging of GvHD will be performed by the investigator according to the modified IBMTR grading system, and recorded on CRF STAGE module. The degree of involvement of skin, GI and liver is classified by stage on a scale of 0 to 4 and the grade of acute GvHD is classified on a scale of A to D.

Shift tables from baseline to Days 28, 56 and 180 visits will be provided for acute GvHD grading and organ system (involvement of skin, GI and liver) staging separately in the efficacy analysis set.

Incidence of chronic GvHD at Days 100, 180 and 365

At baseline and Days 100, 180 and 365, the investigator will assess the subject for chronic GvHD and acute/chronic GvHD overlap syndrome. The number and percentage of subjects who have clinical evidence of chronic GvHD will be summarized at baseline and Days 100, 180 and 365 by organ systems (skin involvement, dry mouth/mouth sores/ulcers, dry eyes, joint involvement, liver involvement with cholestasis, esophageal involvement, obstructive lung disease) in the SAF.

Duration of any overall response

Duration of overall response is defined as the time from the date of first overall response (GvHD CR or PR) until the first date of progression (GvHD progressive disease [PD] on CRF INVRES module) or death in the absence of progression. Subjects without progression or death will be censored at the date of last GvHD response assessment.

Only subjects with an overall response will be summarized for duration of overall response. Descriptive data, including 25th percentile, median and 75th percentile will be estimated using Kaplan-Meier method. The summaries will be produced separately for investigator assessment and adjudicated data. Duration of overall response will also be presented using corresponding Kaplan-Meier plots.

Duration of any GI response

Duration of GI response will be derived and summarized for subjects who achieved a GI response using the same approach as described for the duration of overall response above, based on GI response assessments.

Overall survival through Days 100, 180 and 365

Overall survival is defined as the time from the date of first dose of study treatment until death (CRF DEATH module) due to any cause in the SAF. Any subject not known to have died in Part 1 will be censored at the date of study completion/early termination (or the last recorded date during the study).

Number and percentage of subjects who have died will be provided along with median overall survival time. Overall survival through Days 100, 180 and 365 will be presented as the Kaplan-Meier estimates of the probability of subjects' being alive at Days 100, 180 and 365. The probability of overall survival will be presented in a Kaplan-Meier plot.

All-cause, transplant-related, infection-related and GvHD-related mortality at Days 28, 56, 100 and 180

All-cause, transplant-related, infection-related and GvHD-related mortality will be collected with the cause of death based on the investigator's assessment. These categories are not mutually exclusive and they are defined as:

- 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

The proportion of subjects with all-cause mortality is a reverse of the proportion of subjects alive (overall survival). The mortalities at Days 28, 56, 100 and 180 and 95% confidence intervals will be estimated using the uncorrected Kaplan-Meier method. The cumulative mortality rate will be presented in a Kaplan-Meier plot.

Time to transplant-related, infection-related and GvHD related mortality are potentially dependent and competing mortality causes for a subject, and will be analyzed using the competing risk approach. These outcomes will be defined as the time from the date of

first dose of study treatment until death due to the corresponding cause, in the presence of other mortality causes. Any subject not having death will be censored at the date of study completion/early termination (or the last recorded date during the study). For time to transplant-related mortality, subjects having death due to a reason other than transplant-related will be censored at the date of death, and handled differently in the estimation from the censoring not due to a competing cause. Time to infection-related mortality and time to GvHD-related mortality will be censored for subjects without an event in a similar fashion. The probability of transplant-related, infection-related and GvHD-related mortality at Days 28, 56, 100 and 180 will be estimated using the competing risk estimate of cumulative incidence function. GvHD-related mortality will also be presented using a cumulative incidence rate plot.

Failure-free survival at Days 100 and 180

Failure-free survival is defined as the time from the first dose date of study treatment until death or the first date of failure-free survival not achieved (CRF Mortality and Survival Assessments [MORTAL] module), whichever comes earlier. The failure-free survival are determined by investigator with 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 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

Subjects without recorded death and failure-free survival not achieved at any survival and mortality assessment will be censored at the date of last mortality and survival assessment.

Failure-free survival will be summarized at Days 100 and 180 using the same approach (Kaplan-Meier) as described for overall survival.

GvHD-free survival at Days 28, 56, 100 and 180

GvHD-free survival is defined as the time from the first dose date of study treatment until death or the first date of GvHD-free survival not achieved (CRF MORTAL module), whichever comes earlier. Subjects without recorded death and GvHD-free survival not

achieved will be censored at the date of last mortality and survival assessment. GvHD-free survival will be summarized at Days 28, 56, 100 and 180 using the same approach (Kaplan-Meier) as described for overall survival.

8. SAFETY EVALUATION

8.1 Extent of Exposure

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

The below summaries related to study treatment will be produced for the SAF set:

- Duration of exposure of study treatment (days): date of last dose – date of first dose + 1
- Number of infusions received
- Number of subjects and reason for infusion rate change
- Number of subjects and reason for infusion interruption

8.2 Adverse Events

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

Adverse events (AEs) will be collected throughout the study, from the time the informed consent is signed until study completion. All AEs will be coded using MedDRA, version 19.1 or a later version, and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade (version 4.03).

A treatment-emergent AE (TEAE) is defined as an AE that occurred during or after study treatment application and until 30 days following the last dose of the study treatment. If the start date and time of the AE is provided, then the AE start date and time will be used to classify the AE as TEAE or not. If the start date and time or start time of an AE is unavailable, the CRF AE module asks the subject/investigator to identify whether it occurred before the first treatment, during treatment, within 24 hours after the last treatment, between 24 and 72 hours after last treatment, or more than 72 hours after the last treatment. This information will be used to determine if the AE will be considered as TEAE, when necessary.

The number and percentage of subjects reporting the following TEAEs will be tabulated by SOC, PT and severity CTCAE grade, for the SAF set:

- All TEAEs
- TEAEs related to study treatment
- TEAEs with CTCAE grade 3 or 4
- TEAEs with CTCAE grade 3 or 4, related to study treatment
- Serious TEAEs
- Serious TEAEs related to study treatment
- TEAEs leading to discontinuation of study treatment
- Temporally-associated TEAEs (occurring within 72 hours of termination of infusion)

An overall summary of the number and percentage of subjects in each category will be presented. Overview summaries of TEAEs by seriousness, severity CTCAE grade and relationship to study treatment (categories as collected and dichotomized) will be provided, separately as the subject-level and event-level summaries. Additionally, subjects with non-serious TEAEs will be presented by SOC, PT, severity CTCAE grade and dichotomized relationship to study treatment.

The following conventions will be followed in summarizing TEAEs:

- For subject incidence summaries, each subject will be counted only once within each system organ class and within each preferred term.
- If a subject reports more than one TEAE within a preferred term and/or a body system, the TEAE with the highest known CTCAE grade within each body system and within each preferred term will be included in the summaries by CTCAE grade.
- For summaries related to study treatment, AEs whose relationship to treatment are assessed as “possibly related”, “probably related” or missing will be included.

Listings of AEs that occurred before treatment application, non-serious AEs that occurred during or after treatment application, serious AEs that occurred during or after treatment application, all deaths, and AEs leading to study treatment discontinuation will be produced, including all data collected in the CRF, along with derived duration of AEs,

calculated as (end date – start date +1). If an event is ongoing at the end of the study then the duration of the event will not be calculated.

8.3 Clinical Laboratory Evaluations

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

Laboratory evaluations will be conducted at screening and during treatment period, as described in protocol and Section 14.3. For hematology and clinical chemistry variables, change from baseline will be calculated for each post-baseline visit, and the laboratory values will be evaluated according to the NCI CTCAE version 4.03 toxicity grading scale by the investigator. All the laboratory data will be analyzed for the SAF set.

Observed laboratory values will be compared to the reference range and classified as low (below range), normal (within range or on limits of range) and high (above range).

The maximum (or minimum) value during treatment will be defined for each laboratory parameter as the maximum (or minimum) post-baseline value at any time.

Summaries of laboratory results will be provided in standard international units.

For continuous laboratory assessments observed values and changes from baseline will be summarized using descriptive statistics at each visit.

Shift tables relative to the CTC grade will be produced to summarize the change from baseline to the worst CTC grade during treatment period. For specific parameters separate shift tables indicating hyper- and hypo- directionality of change will be produced. The following laboratory parameters will be included in the shift tables:

- Haematology: hemoglobin, lymphocyte absolute counts, neutrophil absolute counts, platelet counts, leukocytes
- Clinical chemistry: albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatinine, corrected calcium (increased and decreased), glucose (increased and decreased), potassium (increased and decreased), magnesium (increased and decreased), sodium (increased and decreased)

For the laboratory parameters with no CTCAE grading, shifts tables from baseline to minimum and maximum value during treatment will be created.

For urinalysis variables, a table will summarize the shift in the absence/presence of protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrate, leukocyte esterase, red blood cells, white blood cells, bacteria, and casts from baseline to each scheduled visit during treatment.

All laboratory test results (including urinalysis) will be presented in subject data listings.

8.4 Vital Signs

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

For vital signs, systolic and diastolic blood pressure (supine and standing), heart rate (supine and standing), weight, and respiratory rate and changes in these parameters from baseline will be summarized at each scheduled measurement using descriptive statistics. The summary table will be produced for the SAF set. All vital sign data will be included in a subject data listing.

8.5 Recurrent Malignancies

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

Recurrent malignancy will be assessed at screening and all visits during the study. The time to recurrent malignancies will be defined as the time interval from the first dose date of study treatment to the first onset date of recurrent malignancies. Subject without any recurrent malignancies will be censored on the last follow-up date. Subject who have died without recurrent malignancies will be censored on the date of death, and this censoring will be handled separately in the estimation. The competing risk method will be used to estimate the cumulative incidence of recurrent malignancies at Days 180 and 365.

The incidence of recurrent malignancies will also be summarized by the number and percentage of subjects who had at least one presence of recurrent malignancy by Days 180 and 365 for the SAF set.

8.6 Infection

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

The infections and the type of infections will be identified using preferred terms of AEs by the medical team. The incidence of infection will be analyzed as a time to event outcome measure. The time to infection will be defined as the time interval from the first dose date of study treatment to the first onset date of infection. Subject without any infection or the infection of interest or death will be censored on the last follow-up date. Subject who have died without any infection will be censored on the date of death, and this censoring will be handled separately in the estimation. The competing risk method will be used to estimate the cumulative incidence function of infection at Days 28, 56, 180, and 365 for any infection and by the type of infections, including viral infection, bacterial infection, and fungal infection.

The number and percentage of subjects with infection for at least once by Days 28, 56, 180 and 365 will be summarized for any infection and by the type of infections.

9. EVALUATION OF PHARMACOKINETICS

9.1 Concentration data

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations and PK concentration data will be provided. A listing of PK stool sample collection times, sample weights and concentration and amount data will be provided where available.

Due to study discontinuation no population PK analysis is planned to be conducted based on the concentration data collected in this study.

9.2 Pharmacokinetic parameters

A listing of PK parameters by Day (Days 1, 13, and 22) will be provided.

For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ

value that occurs between quantifiable data points, especially prior to C_{max} , will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max} , BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

Blood samples for PK collected after the infusion on Day 1, Day 13 or Day 22 prior to the next infusion will be used to estimate the following PK parameters if possible. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters. The following PK parameters will be estimated for GLASSIA in plasma by non-compartmental methods using actual elapsed time from dosing, with additional parameters determined as appropriate.

$AUC_{(0-inf)}$	Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-last)} + C_{last}/\lambda_z$.
$AUC(0-t)$	Area under the concentration-time curve in the sampled matrix from zero (predose) until time "t", calculated by linear up/log down trapezoidal summation.
C_{max}	Maximum concentration in plasma, obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
$t_{1/2}$	Apparent terminal half-life (h), determined as $\ln 2/\lambda_z$.
CL	Systemic clearance after intravenous dosing (L/h), calculated as dose divided by $AUC(0-inf)$.
V_{ss}	Volume of distribution at steady state following intravenous dosing (L), calculated as mean residence time (MRT) extrapolated to infinity multiplied by clearance ($MRT_{inf} * CL$)
MRT	Mean residence time

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z .
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z . A minimum of 3 data points will be used for determination.
Rsq	Goodness of fit statistic for calculation of λ_z (Regression coefficient/coefficient of determination).
$\%AUC_{ex}$	Percentage of $AUC_{(0-inf)}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{(0-inf)}] \times 100$.

10. EVALUATION OF QUALITY OF LIFE

10.1 Quality of Life Scoring

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

10.1.1 FACT-BMT

The Functional Assessment of Cancer Therapy-Bone Marrow Transplant subscale version 4.0 instrument (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, which addresses disease and treatment-related questions specific to BMT. The FACT-G core questionnaire assesses 4 subscales: physical well-being, social/family well-being, emotional well-being and functional well-being. Each subscale can be scored, the higher the score the better the QoL.

The FACT-G scoring guide on FACIT.org identifies items that must be reversed before being added to obtain subscale totals, which are listed in Section 14.4. Negatively stated items are reversed by subtracting the response from “4”. After reversing proper items, all subscale items are summed to a total, which is the subscale score.

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered, using the formula below:

Prorated subscale score = (Sum of item scores) x (N of items in subscale) / (N of items answered)

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc).

For the “BMT Concerns” module, the procedure for scoring is the same as described above for the FACT-G. Again, over 50% of the items must be completed in order to consider the subscale score valid. The negatively stated items that must be reversed are listed in Section 14.4.

10.1.2 Chronic GvHD Symptom Scale

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, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, and mental and emotional. 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 symptom domain are converted to a 0 to 100 scale, by calculating the mean of the set of items from the domain and multiplying the result by 25. Higher scores indicate a greater degree to which the subject is bothered by the symptoms.

For each domain, if <50% of the items are missing, then the score will be divided by the number of non-missing items and multiplied by the total number of items on the domain. If at least 50% of the items are missing, then the score of that domain will be treated as missing.

10.1.3 EQ-5D-5L

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. A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions allowing for a total of 3125 health states. These data will be converted into a weighted health state utility by applying scores from EQ-5D-5L crosswalk value sets on EuroQol.org.

In addition, the EQ-VAS score record the respondent’s self-rated health on a 20 cm vertical visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health).

10.2 Analysis of QoL Data

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

For FACT-BMT, descriptive summaries of absolute value and change from baseline will be provided for FACT-G subscale scores (physical well-being, social/family well-being, emotional well-being, functional well-being), and “BMT concerns” subscale score.

For Chronic GvHD Symptom Scale, descriptive summaries of absolute value and change from baseline will be provided for scores of each symptom domain (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, mental and emotional).

For EQ-5D-5L, a shift table will be provided to summarize the number and percentage of subjects in each dimension with no, slight, moderate, severe and extreme problems or unable to perform the dimension from baseline to each scheduled post-baseline visit. Additionally, summary statistics and change from baseline will be provided for the utility score and EQ-VAS scores.

For each instrument, the questionnaire completion rate will be summarized by study visit, and defined as the proportion of patients who completed the questionnaire (at least one individual question within the questionnaire completed) at a certain time-point (e.g. Baseline, Day 28, Day 56, etc) using the number of patients in the study at the respective time-point as the denominator.

Efficacy Analysis set will be used for summary tables. QoL Data will also be included in listings.

11. EVALUATION OF EXPLORATORY OUTCOME MEASURES

11.1 Efficacy

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

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

The investigator assessments of whether GvHD VGPR is achieved are recorded on CRF INVRES module (response = yes). The adjudication of VGPR will be performed. The

proportion of subjects with GvHD VGPR at Day 28 based on investigator assessments and adjudicated data will be derived and summarized for the Efficacy Analysis set using the NRI approach as described for primary efficacy outcome in Section 7.1.

Cumulative steroid dose at Days 28, 56, 100 and 180

The cumulative dose of steroid will be collected at Days 28, 56, 100 and 180 and summarized at each of these visits using descriptive statistics for the Efficacy Analysis set.

Average steroid dose by Days 28, 56, 100 and 180

The average doses of steroid from Day 1 to Days 28, 56, 100 and 180 will be summarized using descriptive statistics for the Efficacy Analysis set.

Steroid dose at Days 28, 56 and 100

The daily steroid dose administered at Day 28, 56 and 100 will be summarized descriptively for the Efficacy Analysis set.

Administration of steroid treatment will be listed for the SAF set.

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)

The number and percentage of subjects achieving GI CR and GI PR will be summarized separately at Days 28, 56 and 180 by baseline GvHD severity grade for the Efficacy Analysis set, with subjects having GI CR and GI PR derived based on investigator assessments and adjudicated data of GI response at these visits using the NRI approach.

11.2 Pharmacodynamics

A listing of pharmacodynamic sample collection times will be provided. Both the absolute value and change from treatment naïve predose baseline will be presented for plasma biomarkers, serum T cell subpopulations, and A₁PI and calprotectin concentrations/amounts in stool samples will be provided where available.

The A₁PI clearance in stool may be derived if unavailable from the laboratory reported data.

11.3 Health Outcomes

All derivations, analyses and summaries are not applicable (details in Section 1 and Section 5.3).

Change from baseline in QoL outcomes

- in QoL as measured by FACT-BMT
- in acute GvHD symptoms as measured by the Chronic GvHD Symptom Scale
- in health utility as measured by EQ-5D-5L

Analyses of FACT-BMT and Chronic GvHD Symptom Scales as well as EQ-5D-5L dimensions are described in Sections 10.1 and 10.2.

Healthcare resource utilization (HRU):

- 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

This information will be collected using a paper subject diary provided to each subject at screening for all health-care professional visits that the patient made, excluding scheduled study visits.

Number of visits will be summarized descriptively as a continuous variable, for unscheduled physician office visits and emergency room visits separately. Length of stay will be summarized as the total length of stay (in days) across all the visits using descriptive statistics by the type of admission (hospital, intensive care unit, transplant unit).

Summary tables will be provided for the Efficacy Analysis set. The HRU data will be included in subject listings.

Medication:

Days on steroids is defined as (end date of last administration or Day 180 if end date missing due to steroid ongoing – start date of first administration + 1). Descriptive summaries will be provided for the Efficacy Analysis set.

12. ANALYSIS SOFTWARE

All data processing, summarization, and analyses will utilize SAS® software package, Version 9.2 or higher. If the use of other software is warranted the final statistical report will detail what software was used.

13. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2017 SEP 13	New Document

14. APPENDICES

14.1 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.

14.2 Schedule of Study Procedures and Assessments

Schedule of Study Procedures and Assessments (Parts 1)																		
	Scr	Treatment Period														No Study Treatment Follow-Up		
Study Day	-2 to -1	1	3	5	7	9	11	13	15	22	28 ^a	36	43	50	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																	
Review subject diary		X ----- > X																
FACT-BMT, Chronic GvHD Symptom Scale, EQ-5D-5L and HRU ^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 ^g	X		X	X	X			X	X		X				X			
Serum pregnancy test ^h	X														X			
Lower GI biopsy ⁱ	X																	
Biomarker sample collection ^g		X			X				X		X							
GvHD staging/assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Schedule of Study Procedures and Assessments (Parts 1)																		
	Scr	Treatment Period														No Study Treatment Follow-Up		
Study Day	-2 to -1	1	3	5	7	9	11	13	15	22	28 ^a	36	43	50	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 ^l	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																
Viral prophylaxis ⁿ	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.
- ^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 Section 14.3 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. After screening, the source for concomitant medications, including steroid use, and non-drug therapies will be the subject diary, after the investigator reviews the diary with the subject.
- ^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 Section 14.3, 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 protocol 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.

14.3 Clinical Laboratory Assessments

Clinical Laboratory Assessments											
Assessments	Screening	Treatment Period									
Days	-2 to -1	1	3	5	7	13	15	22	28 ^a	50	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
Lipid panel ^{b,e}	X				X	X	X		X		X
Coagulation panel ^{b,f}	X		X	X	X						
Urinalysis ^{b,g}	X				X	X	X		X		X
Stool assessments ^h	X	X				X			X		X
PK assessment ⁱ		X----->X				X----->X		X----->X		X----->X	
Biomarker assessment ^l		X			X		X		X		
HIV test ^k	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 (study procedures in Section 14.2). 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.

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

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- ^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.
- ^e Lipid panel includes total cholesterol, very low density lipoprotein, low density lipoprotein, high density lipoprotein and triglycerides.
- ^f Coagulation panel includes fibrin, fibrin split products, fibrinogen and D-dimer.
- ^g Urinalysis assessments include: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate, leukocyte esterase and microscopic examination (RBC, WBC, bacteria and casts).
- ^h 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 1. On Days 1 and 13, 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.
- ⁱ 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 1: 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 2) following the end of study treatment infusion
 - Day 3: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 13: 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 14) following the end of study treatment infusion
 - Day 15: Within 2 hours prior to start of study treatment infusion, and at 15 (±5) minutes following the end of study treatment infusion
 - Day 22: Within 2 hours prior to start of study treatment infusion, at 15 (±5) minutes, 2 hours (±12 minutes), 4 hours (±24 minutes), 24 hours (±144 minutes) (ie, Day 23), 72 (±7) hours (ie, Day 25) and 120 (±12) hours (ie, Day 27) 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 50: 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 51), 72 (±7) hours (ie, Day 53) and 120 (±12) hours (ie, Day 55) following the end of study treatment infusion
 - Day 56: During the Day 56 clinic visit
- ^j Biomarkers will include cytokines IL-2, IL-6, IL-8, IL-10 and IL-32; heparan sulfate; Reg3α; ST2; TNFR1; IL-1RA and T cell subpopulations, including CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ Tregs.
- ^k Antibody or nucleic acid test. The results of an HIV test performed within the 3 months prior to screening may be used instead.

14.4 Scoring guidance for FACT-BMT version 4.0

Item	Reverse?
FACT-G physical well being (PWB)	
GP1: I have a lack of energy	4 -
GP2: I have nausea	4 -
GP3: Because of my physical condition, I have trouble meeting the needs of my family	4 -
GP4: I have pain	4 -
GP5: I am bothered by side effects of treatment	4 -
GP6: I feel ill	4 -
GP7: I am forced to spend time in bed	4 -
FACT-G social/family well-being (SWB)	
GS1: I feel close to my friends	0 +
GS2: I get emotional support from my family	0 +
GS3: I get support from my friends	0 +
GS4: My family has accepted my illness	0 +
GS5: I am satisfied with family communication about my illness	0 +
GS6: I feel close to my partner (or the person who is my main support)	0 +
GS7: I am satisfied with my sex life	0 +
FACT-G emotional well-being (EWB)	
GE1: I feel sad	4 -
GE2: I am satisfied with how I am coping with my illness	0 +
GE3: I am losing hope in the fight against my illness	4 -
GE4: I feel nervous	4 -
GE5: I worry about dying	4 -
GE6: I worry that my condition will get worse	4 -
FACT-G functional well-being (FWB)	
GF1: I am able to work (include work at home)	0 +
GF2: My work (include work at home) is fulfilling	0 +
GF3: I am able to enjoy life	0 +
GF4: I have accepted my illness	0 +
GF5: I am sleeping well	0 +
GF6: I am enjoying the things I usually do for fun	0 +
GF7: I am content with the quality of my life right now	0 +
BMT concerns	
Q1: I am concerned about keeping my job (include work at home)	4 -
Q2: I feel distant from other people	4 -
Q3: I worry that the transplant will not work	4 -
Q4: The side effects of treatment are worse than I had imagined	4 -
Q5: I have a good appetite	0 +
Q6: I like the appearance of my body	0 +

Item	Reverse?
Q7: I am able to get around by myself	0 +
Q8: I get tired easily	4 -
Q9: I am interested in sex	0 +
Q10: I have concerns about my ability to have children	4 -
Q11: I have confidence in my nurse(s)	0 +
Q12: I regret having the bone marrow transplant	4 -
Q13: I can remember things	0 +
Q14: I am able to concentrate	0 +
Q15: I have frequent colds/infections	4 -
Q16: My eyesight is blurry	4 -
Q17: I am bothered by a change in the way food tastes	4 -
Q18: I have tremors	4 -
Q19: I have been short of breath	4 -
Q20: I am bothered by skin problems (e.g., rash, itching)	4 -
Q21: I have trouble with my bowels	4 -
Q22: My illness is a personal hardship for my close family members	4 -
Q23: The cost of my treatment is a burden on me or my family	4 -