

**A Phase 2A Study of ALXN1007 in Subjects With Newly
Diagnosed Acute Graft-Versus-Host Disease Involving the
Lower Gastrointestinal Tract**

Unique Protocol ID: ALXN1007-GIGVHD-201

NCT Number NCT02245412

EudraCT Number 2015-000358-39

Date of Protocol 12 February 2016

ALXN1007
ALXN1007-GIGVHD-201
**A PHASE 2A STUDY OF ALXN1007 IN SUBJECTS WITH NEWLY
DIAGNOSED ACUTE GRAFT-VERSUS-HOST DISEASE INVOLVING
THE LOWER GASTROINTESTINAL TRACT**

IND# 119376

EudraCT Number 2015-000358-39

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Version	8.0
Date of Protocol	12 February 2016
Amended	Original Protocol Version 1.0 dated 11 December 2013 Amendment Number 1.0 dated 22 January 2014, Protocol Version 2.0 Amendment Number 2.0 dated 23 June 2014, Protocol Version 3.0 Amendment Number 3 dated 06 February 2015, Protocol Version 4.0 Amendment Number 4 dated 12 May 2015, Protocol Version 5.0 (France Only) Amendment Number 5, dated 26 June 2015, Protocol Version 6.0 (participating countries excluding France) Amendment Number 5, dated 11 August 2015, Protocol Version 7.0 (France only) Amendment Number 6, dated 12 February 2016, Protocol Version 8.0 (participating countries excluding France)
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SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2a Study of ALXN1007 in Subjects with Newly Diagnosed Acute Graft-versus-Host Disease Involving the Lower Gastrointestinal Tract

PROTOCOL NUMBER: ALXN1007-GIGVHD-201

PPD

Alexion Pharmaceuticals, Inc.
55 Cambridge Parkway, Suite 800
Cambridge, MA 02142, USA

Date

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2a Study of ALXN1007 in Subjects with Newly Diagnosed Acute Graft-versus-Host Disease Involving the Lower Gastrointestinal Tract

PROTOCOL NUMBER: ALXN1007-GIGVHD-201

I have received and read the Investigator's Brochure for ALXN1007. I have read the ALXN1007-GIGVHD-201 Study Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to conduct the study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the Good Clinical Practice guidelines of the International Council for Harmonization and applicable regulatory requirements.

Printed Name of Investigator

Signature of Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	PPD	Alexion Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 800 Cambridge, MA 02142, USA Telephone: PPD Facsimile: PPD Email: PPD
Responsible Physician	PPD	Alexion Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 800 Cambridge, MA 02142, USA Telephone : PPD Mobile: PPD Email: PPD
24-Hour Emergency Contact	PPD	Alexion Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 800 Cambridge, MA 02142, USA Telephone : PPD Mobile: PPD Email: PPD
Investigational Product Supply	Almac Clinical Services	USA: Almac Clinical Services 4204 Technology Drive Durham, NC 27704 Telephone: PPD Facsimile: PPD Europe: Almac Clinical Services 9 Charlestown Road Seagoe Industrial Estate Portadown BT63 5PW United Kingdom Telephone: PPD

Table 1: Emergency Contact Information (Continued)

Role in Study	Name	Address and Telephone Number
Clinical Laboratory	Q2 Solutions	<p>USA: Q2 Solutions Ltd. 1600 Terrell Mill Road, Suite 100 Marietta, GA 30067 Telephone: PPD Facsimile: PPD</p> <p>and</p> <p>777 Oakmont Lane Westmont, IL 60559 Telephone: PPD Facsimile: PPD</p> <p>Europe: Q2 Solutions Europe The Alba Campus Rosebank Livingston West Lothian EH54 7EG United Kingdom Telephone: PPD Facsimile: PPD</p>

1. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: ALXN1007	
Name of Active Ingredient: ALXN1007 is a humanized, anti-C5a monoclonal antibody.	
Title of Study: A Phase 2a Study of ALXN1007 in Subjects with Newly Diagnosed Acute Graft-versus-Host Disease Involving the Lower Gastrointestinal Tract	
Study Center(s): Approximately 12 study centers in North America and Europe; additional centers and countries may be added on an as-needed basis.	
Studied Period: Estimated date first subject enrolled: November 2014 Estimated date last subject completed: December 2017	Phase of Development: 2a
<p>Objectives: The objectives of this trial are to evaluate the safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of intravenous (IV) ALXN1007 administered over an 8 week treatment period in subjects with acute graft-versus-host disease (GVHD) of the lower gastrointestinal (GI) tract.</p> <p>Primary Efficacy Endpoint:</p> <ul style="list-style-type: none"> Overall acute GVHD response rate at Day 28. <p>Other Efficacy Endpoints</p> <ul style="list-style-type: none"> Proportion of subjects with complete response (CR), partial response (PR), mixed response (MR), no response (NR) and Progression for acute GI GVHD at Day 28. Proportion of subjects with CR, PR, MR, NR and Progression for all organs involved with acute GVHD at Days 14, 28 and 56. Very good partial response (VGPR) will be assessed at Days 14, 28 and 56. Proportion of treatment failures at Days 14, 28 and 56. Incidence of acute GVHD flares through Day 86. Cumulative corticosteroid dose at Days 28, 56, 86 and 180. Proportion of subjects with discontinuation of immunosuppressive medication on Days 56, 86 and 180. Overall survival up to Days 180 and 360. Rate of non-relapse mortality at Days 180 and 360. <p>Safety Endpoints:</p> <ul style="list-style-type: none"> Incidence and severity of adverse events (AEs) and serious AEs (SAEs). Incidence of infections. Incidence of abnormal clinical laboratory values. Change from Baseline in clinical laboratory assessments: chemistry panel, coagulation panel, complete blood cell count (CBC) with differential, thyroid function testing and urinalysis. Change from Baseline in electrocardiogram (ECG) findings. Incidence and titer of antibodies to ALXN1007. <p>PK Endpoints:</p> <p>ALXN1007 PK parameters will be determined including, at a minimum, maximum observed concentration in plasma (C_{max}), time to maximum observed concentration in plasma (t_{max}), and trough concentration in plasma pre-next-dose (C_{trough}). Area under the plasma concentration vs. time curve within the dosing interval (AUC_{τ}), area under the plasma concentration vs. time curve from time 0 to 168 hours (AUC_{0-168}) for twice weekly dosing, accumulation ratio (AR) from the first to the last dose, and apparent linear phase half-life ($t_{1/2}$) may also be</p>	

evaluated if feasible.

PD Endpoints:

Key PD parameters may include, but are not limited to, change from Baseline in the levels of complement proteins C3, C4, C5 and C5a. A limited number of PD samples will be assayed for change from Baseline in sC5b9 levels and terminal complement activity (may include chicken red blood cell [cRBC] hemolytic activity and classical complement pathway [CCP] activity).

Exploratory Biomarker Assessments:

Additional exploratory biomarkers of PD effect may include, but are not limited to, change from Baseline in levels of complement alternative pathway proteins (Ba, Bb) and additional assessments of complement activity or GVHD-associated biomarkers (eg, soluble tumor necrosis factor receptor 1 [sTNFR1], suppressor of tumorigenicity 2 [ST2] and regenerating islet-derived protein 3 alpha [REG3a]). Additional assessments may also include measurement of antibodies to factor H. Samples from consenting subjects may also be evaluated for genetic variability that may affect efficacy or safety endpoints (pharmacogenetics [PGx]).

Methodology: This is a Phase 2a open-label study to evaluate the safety, tolerability, PK/PD, and efficacy of ALXN1007 (a C5a inhibitor) in up to 36 subjects with newly diagnosed acute GVHD of the lower GI tract. The first dosing cohort (Cohort 1, up to 18 subjects) will receive 10 mg/kg ALXN1007 administered IV once weekly (QW) for 8 weeks. With approval of Amendment 6, Cohort 2, 20 mg/kg QW for 8 weeks, will be added to the study. An additional cohort (Cohort 3), 20 mg/kg twice weekly for 8 weeks, is planned after review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2 with the Data Monitoring Committee (DMC). At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

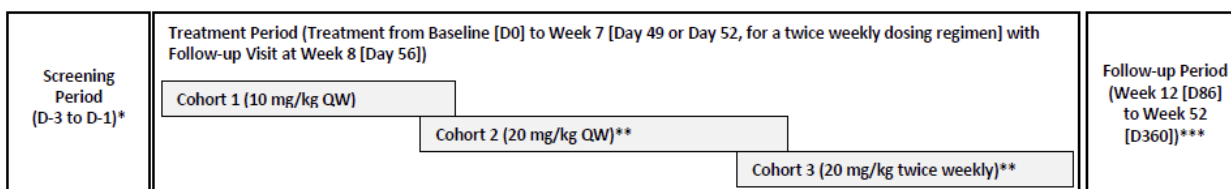
For Cohort 2, the following safety reviews will be performed:

- For the first 2 subjects enrolled, the first ALXN1007 dose may not be administered on the same day. In addition, for the first 2 enrolled subjects, a safety and tolerability review will take place after the second (and prior to the third) ALXN1007 dose for each subject. If the ALXN1007 dose is determined to be sufficiently tolerated by the subject, dosing may continue for that subject. For any other subjects enrolled in the dosing cohort, subjects may not proceed to the third ALXN1007 dose before completion of the safety and tolerability review (of the first 2 doses) for the first 2 subjects.
- After the first 3 subjects have completed the Day 28 procedures and assessments (ie, received all protocol prescribed ALXN1007 doses through Day 28), the DMC will convene to review aggregate safety and tolerability data. Pharmacokinetic and pharmacodynamic data may also be provided for DMC review, if available. After review, the dose of ALXN1007 will be escalated to 20 mg/kg twice weekly for 8 weeks (Cohort 3), unless the DMC recommends a different dose level or dosing regimen, including continuation of 20 mg/kg QW within the cohort (up to a maximum of approximately 6 subjects) or reduction of the dose to the previous dose level or to a dose between planned dose levels. Final dosing decisions will be made by the Sponsor, in consultation with the DMC, based on safety, tolerability and any available PK/PD data.

For Cohort 3 and any additional dosing cohorts exploring a higher dose than Cohort 1 (ie, 10 mg/kg per week), the same safety reviews described above will be performed.

All enrolled subjects will be followed for safety, tolerability, PK/PD, and efficacy over the course of the study, with weekly (or twice weekly, if a twice weekly dosing regimen is evaluated) visits through Day 56 (Week 8), and subsequent follow-up visits at Day 86 (Week 12) and Day 180 (Week 26). Subject survival status will be collected at Day 360 by telephone contact.

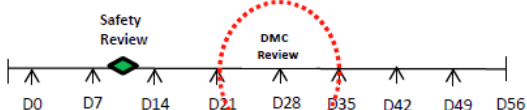
A schematic of the overall study design, including the dose escalation and safety review plan, can be found below.

General Study Design, Including Dose Escalation and Safety Review Plan

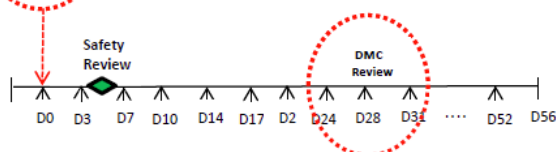
Cohort 1 (n=18 [maximum])
(10 mg/kg QW)



Cohort 2 (n=3 to ~6)
(20 mg/kg QW**)



Cohort 3 (n=3 to ~6)
(20 mg/kg twice weekly**)



* Screening period for the study will be initiated after informed consent form signing (ie, subject enrollment). Acute GI GVHD staging at the time of diagnosis (that can be made up to 7 days prior to the first ALXN1007 dose) will be captured and used for comparison to post-Baseline GVHD staging to assess treatment response.

** With approval of Amendment 6, Cohort 2 (20 mg/kg QW for 8 weeks) will be added to the study. An additional cohort (Cohort 3, 20 mg/kg twice weekly for 8 weeks), is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

*** Follow-up period for the study consists of study visits at Weeks 12 (Day 86) and 26 (Day 180), with telephone contact at Week 52 (Day 360) for survival status only.

Number of Subjects (planned): Up to 36 subjects confirmed by biopsy to have GI GVHD will be enrolled in this study. For the 10 mg/kg QW dosing cohort (Cohort 1), a maximum of 18 subjects will be enrolled. For Cohorts 2 and 3, and any other dosing cohorts that may be added, a minimum of 3 up to a maximum of approximately 6 subjects will be enrolled in each cohort.

Criteria for Inclusion:

Only subjects meeting the following criteria are eligible for study participation.

1. Subjects must be males or females age 18 years or older.
2. Subjects with Stage 1-4 (per the Modified Keystone Grading Schema) acute GVHD of the lower GI tract, without signs of chronic GVHD, at the time of diagnosis, which developed in the first 180 days following allogeneic hematopoietic cell transplantation (HCT) using bone marrow, peripheral blood or cord blood; or after pre-planned donor lymphocyte infusion.
3. Subjects are willing to undergo or must have had an endoscopy of the upper and/or lower GI tract and biopsy to confirm GI GVHD within 7 days of screening. Biopsy results are not needed to initiate treatment; however, if GI GVHD is not confirmed histologically, treatment with ALXN1007 will be discontinued.
4. Subjects must be receiving systemic corticosteroids.
5. Subjects with an absolute neutrophil count (ANC) >500/ μ L at Screening.
6. Subjects and spouse/partner who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least 1 of which must be a barrier method) starting

at Screening and continuing through the entire study (for at least 3 months after the last dose of ALXN1007 if study treatment is stopped early or subject withdraws consent). Highly effective contraception is defined as:

- a. Established use of oral, injected or implanted hormonal methods of contraception.
 - b. Placement of an intrauterine device or intrauterine system.
 - c. Double barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (double barrier method will count as 2 forms of contraception).
7. Male subjects must not donate sperm during the Screening and Treatment Periods, and for at least 3 months after the last dose of ALXN1007.
 8. Subjects are willing and able to give written informed consent and to comply with all study visits and procedures.

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria should not participate in this study.

1. Subjects with a body weight > 140 kg (for Cohorts dosing 20 mg/kg of ALXN1007 and higher only).
2. Subjects with signs and symptoms of chronic GVHD.
3. Subjects with an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection. (Subjects with a controlled infection receiving definitive therapy for 72 hours prior to enrollment [ie, Screening Visit/sign ICF] are eligible.)
4. Subjects who test positive for *Clostridium difficile* from a sample collected up to 3 days prior to Screening/sign ICF.
5. Subjects known to be infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
6. Subjects with relapsed/persistent malignancy requiring rapid immune suppression withdrawal.
7. Subjects who received an unplanned (not part of the original transplant therapy plan) donor lymphocyte infusion.
8. Subjects who received previous systemic treatment for acute GVHD, except for a maximum of 3 days (72 hours) of 2 mg/kg methylprednisolone (or equivalent dose of prednisone).
9. Subjects who received any corticosteroid therapy (for indication other than GVHD) at doses >0.5 mg/kg/day methylprednisolone equivalence within 7 days prior to the onset of GVHD therapy.
10. Subjects with unresolved veno-occlusive disease of the liver defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction (renal, ascites).
11. Subjects known to have an uncontrolled thyroid disorder.
12. Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the duration of the study.
13. Subjects with creatinine clearance (CrCl) <40 mL/minute, as calculated by the Cockcroft-Gault formula (Cockcroft-Gault: $\text{CrCl} = [140 - \text{age}] \times [\text{Wt in kg}] \times [0.85 \text{ if female}] / [72 \times \text{Cr}]$).
14. Subjects participating in any investigational drug trial, or with exposure to any other investigational agent, device and/or procedure, beginning at Screening and throughout the entire trial. Investigational drugs, devices and/or procedures must be discontinued upon enrolling (ie, Screening/sign ICF) into this study.
15. Subjects with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, pose any additional risk for the subject, or confound the assessments of the subject.
16. Subjects with prior exposure to ALXN1007 or known allergies, hypersensitivity or intolerance to ALXN1007 or its excipients.

Investigational Product, Dosage and Mode of Administration: All subjects meeting the inclusion and exclusion

criteria for the study will receive ALXN1007 over an 8 week treatment period. The first dosing cohort (Cohort 1) will receive 10 mg/kg ALXN1007 administered IV QW for 8 weeks. With approval of Amendment 6, Cohort 2, 20 mg/kg QW for 8 weeks, will be added to the study. An additional cohort (Cohort 3), 20 mg/kg twice weekly for 8 weeks, is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available. The planned dosing cohorts in this study are summarized below:

Planned ALXN1007 Dosing Cohorts

Dosing Cohort ¹	Total ALXN1007 Dose per Week	Dosing Regimen	Infusion Duration	Sample Size
1	10 mg/kg	10 mg/kg QW (8 total doses)	1 hour ± 10 minutes	18 (maximum)
2	20 mg/kg	20 mg/kg QW (8 total doses)	2 hours ± 10 minutes	3 to approximately 6 ²
3	40 mg/kg	20 mg/kg twice weekly (16 total doses)	2 hours ± 10 minutes	3 to approximately 6 ²

¹ At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

² For Cohorts 2 and 3 (and any other dosing cohorts that may be added), a minimum of 3 up to a maximum of approximately 6 subjects may be enrolled.

For subjects on a weekly treatment schedule, there should be a minimum of 4 days between ALXN1007 doses. For subjects on a twice weekly treatment schedule, there should be a minimum of 2 days between ALXN1007 doses.

For subjects who are unable to tolerate weekly doses of 20 mg/kg or higher, dose reduction to a minimum of 10 mg/kg per week may be permitted after discussion between the Principal Investigator and the Alexion Medical Monitor.

Duration of Treatment: 8 weeks; duration of each patient's participation is 1 year.

Reference Therapy, Dosage and Mode of Administration: Not applicable.

Criteria for Evaluation:

Primary Efficacy Assessment: Overall Acute GVHD Response

The primary efficacy assessment is overall acute GVHD response at Day 28. Overall acute GVHD response is defined as improvement from diagnosis in any organ by at least 1 stage, without progression in any other organ and with no additional therapy (-ies) being administered. Subjects will be graded according to the Modified Keystone Grading Schema displayed in the table below.

Modified Keystone Grading Schema

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No Rash	Rash <25% BSA	25-50% BSA	>50% BSA	Bullae and desquamation
Lower GI Tract¹	<500 ml/day stool volume	500-1000 ml/day stool volume	1001-1500 ml/day stool volume	>1500 ml/day stool volume	Severe abdominal pain +/- ileus, frank blood or melena
Liver²	≤2 mg/dl	2.1-3 mg/dl	3.1-6 mg/dl	6.1-15 mg/dl	>15 mg/dl

Abbreviations: BSA = body surface area; GI = gastrointestinal (Przepiorka, 1995)

¹ Lower GI tract assessment consists of determination of stool volume over a 24-hour period. Detailed instructions for determining stool volume can be found in the Study Operations Manual (SOM) for the study.

² Values presented for each stage are bilirubin level.

Other Efficacy Assessments:

1. Acute GI GVHD Response Criteria: Proportion of subjects with CR, PR, MR, NR and Progression will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the subject's acute GI GVHD Stage (see lower GI tract row of the Modified Keystone Grading Schema table above) at the time of diagnosis, prior to initiation of treatment with ALXN1007 and corticosteroids for management of acute GI GVHD. Response will be based on the following response definitions:

- **Complete Response (CR):** A Stage of 0 for the GVHD grading in the lower GI tract with no additional intervening therapy for their GVHD.
- **Partial Response (PR):** Improvement by at least 1 Stage in GI GVHD symptoms without progression in others with no additional intervening therapy for their GVHD.
- **Mixed Response (MR):** Improvement in lower GI tract with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- **Progression:** Deterioration in lower GI tract.
- **No Response (NR):** Absence of any improvement or progression as defined above. Subjects receiving secondary therapy (including need to re-escalate steroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5) will be classified as non-responders.

2. Response for All Organs Involved with Acute GVHD: Proportion of subjects with CR, PR, MR, Progression and NR for all organs involved with acute GVHD will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the subject's acute GVHD Stage (see Modified Keystone Grading Schema table above) at the time of diagnosis, prior to initiation of treatment with ALXN1007 and corticosteroids for management of acute GI GVHD. Response will be based on the following response definitions:

- **Complete Response (CR):** A Stage of 0 for the GVHD grading in all evaluable organs with no additional intervening therapy for their GVHD.
- **Partial response (PR):** Improvement by at least 1 Stage in 1 or more organs involved with GVHD symptoms without progression in others with no additional intervening therapy.
- **Mixed response (MR):** Improvement in 1 or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- **Progression:** Deterioration in at least 1 organ without any improvement in others.
- **No response (NR):** Absence of any improvement or progression as defined. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5) will be classified as non-responders.
- **Very Good Partial Response (VGPR)** will also be determined based on the criteria provided by [Martin et al, 2009](#) (see [Appendix 2](#)).

3. Treatment Failure: The proportion of treatment failures will be determined over time. The following will be considered as treatment failures:

- No response
- Progression
- Administration of additional systemic therapy for GVHD (or re-escalation of corticosteroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5)
- Mortality

4. GVHD Flares: Flares are defined as any progression of acute GVHD through Day 86 after an initial response (ie, earlier CR or PR) that require re-escalation of corticosteroid dosing (ie, administration of ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or

after Day 5), or initiation of additional topical or systemic therapy for GVHD.

5. Discontinuation of Immunosuppressive Medications

Discontinuation of immunosuppression will be assessed over time. The date of discontinuation of corticosteroids will be recorded. In addition, dates for discontinuation of all other systemic immunosuppressive medications (including cyclosporine [CSA], tacrolimus, sirolimus, etc) for treatment or prevention of acute GVHD will be captured.

6. Cumulative and Average Corticosteroid Dose

Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each subject will be converted to mg/kg. The cumulative and average corticosteroid doses will be calculated over time.

7. Overall Survival: Overall survival will be computed up to Days 180 and 360.

8. Non-Relapse Mortality: At Days 180 and 360, non-relapse mortality due to any cause other than the underlying malignancy, will be assessed.

Safety Assessments:

Safety evaluations will include assessment of the following:

- AEs/SAEs
- Physical exam and vital signs
- ECGs
- Laboratory tests
- Urinalysis
- Thyroid function tests
- Immunogenicity assessments

PK/PD: Blood samples will be collected and plasma assayed for ALXN1007 concentration. The actual blood sampling times will be recorded and used in calculations for PK parameter estimation. The PD effects of ALXN1007 may be determined by assessing plasma concentrations of C3, C4, C5a, C5 and sC5b-9. Serum terminal complement activity may be measured by the cRBC hemolysis and Wieslab™ CCP assays.

Exploratory Biomarker Assessments: Biopsy specimens may be evaluated for complement deposition or for immune cell characterization by immunohistochemistry (IHC). Blood samples will be collected at Baseline, Day 7, 28, 49, 86, 180 and at the Early Termination (ET) visit (if this occurs) and may be used to characterize changes in the levels of biomarkers associated with alternative complement pathways activation or of mechanistic biomarkers thought to be associated with the development of GI GVHD. Pharmacodynamic effects on complement may include, but are not limited to, assessments of plasma Ba and Bb. Additional biomarkers associated with GVHD and downstream effects of complement activation may include, but are not limited to, sTNFR1, ST2 and REG3a. Additional exploratory analyses, including anti-factor H antibody titer, may be performed.

Statistical Methods:

General: All data collected during the study will be presented in summary tables, figures and/or by-subject data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using percentages and frequency distributions. Graphical displays will be presented as appropriate. All analysis tabulations will be presented by dose across the full range of doses actually examined in the study.

A stopping rule for excess mortality at Day 56 will be applied after every 6 subjects are accrued. If a mortality rate of 40% is observed, a 20% increase in mortality over the historical rate, there will be a 71.0% chance of triggering the stopping rule with 30 subjects. Additionally, an informal interim analysis will occur after all subjects have completed Day 56, which is the end of the treatment period. This interim analysis will summarize the primary endpoint and other efficacy endpoints with the exception of overall survival and non-relapse mortality. In terms of safety, all treatment emergent adverse events (TEAEs), infections, neutropenia and infusion reactions will be summarized. The interim analyses will also summarize PK and PD results. Additional informal interim analyses may be conducted based on regulatory requests and/or Sponsor discretion. A final analysis will be conducted at

study completion.

Efficacy: Efficacy analyses will be performed on the modified Full Analysis Set (mFAS) as well as on a Per Protocol (PP) set. The mFAS will include all subjects who receive at least 1 dose of ALXN1007 and for whom GI GVHD is confirmed through biopsy. The PP set is a subset of the mFAS and will include all subjects who have no major protocol deviation(s) that might potentially affect efficacy. The PP set will be fully described in the Statistical Analysis Plan (SAP), and subjects identified prior to database lock.

Safety: Safety analyses will be performed on the Safety Set and on the modified Safety Set, as specified in the SAP. The Safety Set is defined as all subjects who receive at least 1 dose of ALXN1007. The modified Safety Set is defined as all subjects who receive at least 1 dose of ALXN1007 and for whom GI GVHD is confirmed through biopsy. Safety assessments will consist of summarizing all AEs, SAEs, infections, and laboratory values including: chemistry panel, coagulation panel, CBC with differential, thyroid function testing, and urinalysis results. Changes from Baseline in vital signs and laboratory assessments will be summarized. A brief interim safety report summarizing AEs and SAEs will be generated when the first six subjects have completed the Day 86 visit.

PK/PD/Exploratory Biomarkers: Pharmacokinetic and PD analyses will be performed on all subjects who receive at least 1 dose of ALXN1007 and who have evaluable PK and PD data. Graphs of plasma ALXN1007 concentration time profiles for individual subjects and for means will be provided. Non-compartmental PK methods will be used to estimate PK parameters of interest (eg, C_{max} , t_{max} , area under the plasma or serum concentration vs. time curve [AUC], etc). Actual dosing and sampling times will be used for all calculations. Descriptive statistics will be calculated for PK parameters and plasma concentration data at each sampling time, as appropriate. Additional model-based exploratory analyses may be performed.

For PD, summary tabulations of mean, SD, median, minimum and maximum will be presented. The relationship between changes in PD biomarkers, exploratory biomarkers and the effects of ALXN1007 treatment outcome will be evaluated.

For the exploratory biomarker analyses, the relationship between plasma ALXN1007 concentration and key PD and exploratory biomarkers will be assessed by graphical display. Additional model-based exploratory analyses may also be performed.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen presenting cell
AR	accumulation ratio from the first to the last dose (8th dose AUC _τ /1st dose AUC _τ)
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Anti-thymocyte globulin
AUC	area under the plasma (or serum) concentration vs. time curve
AUC ₀₋₁₆₈	area under the plasma concentration vs. time curve from time 0 to 168 hours
AUC _{inf}	area under the plasma or serum concentration vs. time curve between 0 and infinity
AUC _τ	area under the plasma or serum concentration vs. time curve within the dosing interval
BP	blood pressure
Bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
C5aR	C5a receptor
CBC	complete blood cell count
CCP	classical complement pathway
CI(s)	confidence interval(s)
C _{max}	maximum observed concentration in plasma or serum
CMV	cytomegalovirus
CPK	creatine phosphokinase
CR	complete response
cRBC	chicken red blood cell
CrCl	creatinine clearance
CSA	cyclosporine
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	trough concentration in plasma or serum pre-next-dose
DAF	decay-accelerating factor
DC	dendritic cell

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EIU	exposure in utero
EOI	end of infusion
ET	early termination
FT-4	free thyroxine
GCP	Good Clinical Practice
GI	gastrointestinal
GI GVHD	gastrointestinal graft-versus-host disease
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
Hr	hour
IB	Investigator's Brochure
IBW	ideal body weight
IC	inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IFN- γ	interferon gamma
IHC	immunohistochemistry
IL	interleukin
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	intravenous
IVIG	intravenous immunoglobulin
KD	affinity dissociation constant
K _i	inhibitory constant
LPS	lipopolysaccharide
MAD	multiple ascending dose
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MHC	major histocompatibility complex
MiHA	minor histocompatibility antigens

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
MR	mixed response
NK	natural killer
NOAEL	no observed adverse effect level
NR	no response
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PGx	pharmacogenetic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PLE	protein-losing enteropathy
PO	orally (by mouth)
PP	Per Protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QW	once weekly
RBC	red blood cell
REG3a	regenerating islet-derived protein 3 alpha
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SOI	start of infusion
SOM	Study Operations Manual
ST2	suppressor of tumorigenicity 2
sTNFR1	soluble tumor necrosis factor receptor 1
t _{1/2}	apparent linear phase half-life
TBI	total body irradiation
TEAE	treatment-emergent adverse event
TGF	transforming growth factor
Th	T helper
TLR	toll-like receptor
t _{max}	time to maximum observed concentration in plasma or serum
TMA	thrombotic microangiopathy
TNF	tumor necrosis factor

Abbreviation or Specialist Term	Explanation
TNFR1	tumor necrosis factor receptor 1
TPO	thyroid peroxidase antibody
Treg	T regulatory cell
TSH	thyroid-stimulating hormone
QW	every week
USP	United States Pharmacopeia
VGPR	very good partial response
VOD	veno-occlusive disease
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

4. OVERVIEW AND BACKGROUND

4.1. Introduction

The Sponsor, Alexion Pharmaceuticals, Inc. (“Alexion”) is currently developing ALXN1007 for the treatment of newly diagnosed acute graft-versus-host disease (GVHD) in subjects with lower gastrointestinal (GI) tract involvement.

ALXN1007 is a recombinant humanized monoclonal antibody that binds to complement component C5a and its metabolite C5a desArg. In vitro and in vivo nonclinical data and data from the completed Phase 1 clinical studies have demonstrated that ALXN1007 is well tolerated, is highly specific for its epitope, is a potent antagonist of C5a-mediated signaling and depletes C5a/C5a desArg from the circulation.

Preclinical data suggest that complement plays a critical role in the pathophysiology of acute GVHD. Human studies suggest that complement may be particularly important in acute GVHD involving the lower GI tract, a disorder for which current therapy (ie, systemic corticosteroids) is of limited efficacy. For this reason, Alexion plans to determine whether targeting complement through C5a inhibition with ALXN1007 may improve outcomes for subjects with newly diagnosed acute GVHD of the lower GI tract. This Phase 2a, open-label study has been designed to evaluate the safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD), and efficacy of intravenous (IV) ALXN1007 in subjects with acute GVHD involving the lower GI tract following hematopoietic cell transplantation (HCT).

4.2. Function and Activity of ALXN1007

ALXN1007 binds C5a/C5a desArg with an affinity (affinity dissociation constant [K_D] \approx 60 pM) that is approximately 100-fold stronger than its affinity for native full length C5 ($K_D \approx$ 5 nM) and displays no detectable cross reactivity for any other antigens tested. ALXN1007 binding to C5a blocks the association of C5a with its primary receptor (C5aR) with an inhibitory constant (K_i) of 29 pM in vitro. ALXN1007 binding to C5a in vivo is nearly instantaneous, while binding to C5 occurs slowly, reaching saturation at 48-72 hours in normal healthy volunteers. The formation of the ALXN1007:C5 complex is hypothesized to be rate-limited by the exposure of the epitope on C5 recognized by ALXN1007. As the rate of ALXN1007:C5 complex formation is slower than the rate of new C5 synthesis, free C5 reaches equilibrium at approximately 20% of pre-dose levels in healthy volunteers (\sim 20 μ g/mL) dosed with saturating levels of ALXN1007. Thus, ALXN1007 functions as a complete antagonist of C5a and a partial antagonist of C5 in vivo.

4.3. Scientific Rationale

4.3.1. C5a Blockade in Acute GVHD Involving the Lower GI Tract

GVHD remains one of the most challenging obstacles to successful HCT, with significant morbidity and high mortality (Deeg, 2007). More than 20,000 HCT are performed worldwide annually, primarily for malignancy. Acute GVHD typically occurs during the first 3 months following HCT with an incidence ranging from 17%-25% for severe (Stage 3-4) acute GVHD characterized by inflammatory involvement of the skin, GI tract and liver (Karanas, 2008;

[Nguyen, 2010](#)). Patients are often nonresponsive to therapy, with mortality rates of up to 83% in patients with Stage 3-4 acute gastrointestinal GVHD (GI GVHD) ([Irani, 2008](#)).

Acute GI GVHD occurs as a consequence of several biologic mechanisms. First, the endothelial layer of the GI tract is damaged during cytotoxic (myeloablative or nonmyeloablative) conditioning of the host, prior to transplant. The damaged tissues release a cascade of inflammatory cytokines, which activate host dendritic cells (DCs) to upregulate cell surface major histocompatibility complex (MHC) molecules ([Hill, 2000](#)). These cells, in turn, can present additional minor histocompatibility antigens (MiHA) to engrafted donor T cells, exacerbating the immune response through the elaboration of T cell cytokines including interleukin (IL)-2, tumor necrosis factor (TNF)- α , IL-6, IL-18 and others ([Toubai, 2012](#)). Proliferating T cells polarize to a T helper (Th)-1 phenotype, with increasing evidence for Th17 T cells in the development of disease ([Coghill, 2011](#)). Cytotoxic T cells and natural killer (NK) cells participate in further tissue destruction ([Kroemer, 2008](#)). Newly emerging data suggest a role for complement in the development of GI GVHD, presenting a novel approach to managing this toxicity with complement inhibiting agents ([Rubio, 2009](#)).

A role for complement in the development of acute GVHD is implicated by several preclinical studies in mice. First, the conditioning regimens used to deplete host immune cells prior to transplant can be potent activators of complement. Host DCs and myeloid cells isolated just 3-4 hours following total body irradiation (TBI) in mice decrease their cell surface expression of complement negative regulatory proteins (decay-accelerating factor [DAF]) and express up to 40-fold increases in mRNA encoding complement components C3, C5, factor B, and factor D ([Kwan, 2012](#)). Complement proteins regulate DC and antigen presenting cell (APC) activation in mouse GVHD ([Kwan, 2012](#); [Ma, 2013](#)), with host APC derived C5a thought to signal through C5aR expressed on donor T cells to exacerbate disease ([Kwan, 2012](#)). Following TBI, mice also show greater numbers of skin infiltrating T cells and increased C3d staining at sites of infiltration in the skin. This may reflect the enhanced activity of Th17 T cells, which preferentially migrate to skin tissue ([Coghill, 2011](#)). C3-deficient mice have reduced GVHD mediated morbidity and mortality that is associated with a decrease in donor Th1/Th17 polarization and Th1-driven DC activation ([Ma, 2013](#)).

One hypothesis for disease progression is that lipopolysaccharide (LPS) released from damaged gut tissue promotes host DC maturation and induces increased C3/C5 complement production by DCs. Complement production, in turn, amplifies toll-like receptor (TLR) signaling and lowers the threshold for Th17 activation by LPS stimulated DCs in the gut, where they are found in relatively high numbers, and the inflammatory response injures the host ([Kwan, 2012](#)). In support of this hypothesis, co-activation of TLR4 and C5aR pathways in murine macrophages increased Th17-inducing capacity in vitro ([Fang, 2009](#)), and DAF-deficient mice show increased GVHD clinical progression with ~5-fold higher levels of interferon gamma (IFN- γ) producing splenic T cells than normal mice ([Kwan, 2012](#)). Treatment with a C5aR antagonist in vivo ameliorated clinical signs of GVHD when administered 7 days post-transplant and improved signs when administered 14 days post-transplant, suggesting that C5a blockade may be therapeutically effective in preventing or treating disease ([Kwan, 2012](#)). In other studies, local inflammation in non-lymphoid tissues was a prerequisite setting for homing of circulating, activated T cells to a GVHD target tissue and initiation of disease ([Chakraverty, 2006](#)) and increased transplant-related mortality has been shown to be associated with inflammation, as evidenced by neutrophil infiltration in GI GVHD ([Socie, 2004](#)).

Several studies point to a role for complement in the development of GI GVHD in HCT patients. In a study of 34 adult oncology patients allografted with HCT after conventional myeloablative conditioning, 15 (44%) showed complement activation that correlated with development of GI GVHD and poor outcome ([Rubio, 2009](#)). Complement activation (measured by a decrease of C3 and C4 proteins below normal values and of at least 50% of their pre-HCT levels, indicating complement consumption) occurred within the first 8 weeks following transplant in 11/15 subjects and was significantly associated with the development of acute GI GVHD. Eighty percent (80%) of subjects demonstrating activated complement developed acute GI GVHD, while only 5.3% of the subjects without elevated activation developed the disease ($p=0.0028$). Complement activation in this subject cohort did not correlate with skin or hepatic acute GVHD, thrombotic microangiopathy (TMA), veno-occlusive disease (VOD), or chronic GVHD. Subjects with complement activation had a significantly increased incidence of capillary leak syndrome concomitant to the conditioning toxicity or GVHD, with this complication occurring in 66.7% of subjects with activated complement versus 10.5% in subjects without evidence of complement activation ($p=0.019$). Complement activation in this study was also predictive, occurring 1-3 weeks prior to the onset of clinical GI GVHD. Finally, overall subject survival at Day 100 after transplant was significantly reduced in subjects demonstrating complement activation ($p=0.008$) because of increased toxicity-related mortality ($p=0.02$) and relapse ($p=0.01$). Parallel mouse models of complement activation and GI GVHD by the same authors were not predictive. A large follow-up study is currently underway to extend and confirm these results ([Rubio, 2013](#)). Taken together, these data implicate a role for complement/C5a activation in the development of acute GVHD and imply a role for Th17 T cells in the pathogenesis of disease.

One mechanism by which complement activation can influence GVHD development is by a differentiation or polarization to a T helper cell (Th17) phenotype. Th17 cells play a role in the development or exacerbation of several autoimmune and inflammatory diseases, including GVHD. C3 regulates Th1/Th17 differentiation in bone marrow transplantation, and complement activation regulates the alloimmune responses in a murine model of GVHD ([Ma, 2012](#)). One study in HCT subjects supported the hypothesis that Th17 cells are involved in the acute phases of GVHD and concluded that they may represent a novel target for therapeutic strategies ([Dander, 2009](#)). The authors demonstrated increased numbers of Th17 cells producing IL-17 in the circulation of acute and active GVHD subjects compared to healthy donors and a close correlation between numbers of Th17 cells and the clinical course of GVHD.

A role for complement/C5a in the differentiation or polarization of Th17 cells has been shown in several preclinical models of human disease. Complement promotes the development of inflammatory Th17 cells through synergistic interaction with TLR signaling and IL-6 production ([Fang, 2009](#)). Complement activation via lectin, classical or alternative pathways and the resulting generation of C5a potently promotes the differentiation/expansion of self-reactive T cells to Th17 cells that mediate autoimmune arthritis in SKG mice ([Hashimoto, 2010](#)). Complement activation can be triggered by either exogenous or endogenous stimuli to cause Th17-mediated autoimmune disease, with C5a demonstrated as a key mediator of both Th17-mediated autoimmunity as well as microbial immunity ([Hashimoto, 2010](#)).

In other preclinical studies, C5a-mediated increases of CD40 and CD40L molecules on DCs and T cells are critical to Th1/Th17 mediated inflammation in a Gaucher disease model ([Pandey, 2013](#)). In models of experimental allergic asthma, C5aR-deficient mice were shown to possess

increased frequency of myeloid derived suppressor cells, DCs with lower expression levels of CD11b and decreased capacity to produce Th17 promoting cytokines in vitro (Schmudde, 2013). C5aR-deficient DCs also demonstrated impaired ability to drive Th1 and Th17 differentiation and accelerated death of activated CD4 T cells (Schmudde, 2013). Other studies have demonstrated that C5a-C5aR signaling is critical for both T regulatory cell (Treg) and Th17 differentiation through regulation of DC function (Weaver, 2010). Finally, the absence of C5a and C3a signaling in CD4+ T cells resulted in the induction of a high frequency of induced Tregs in an endogenous transforming growth factor (TGF)- β 1 dependent manner, suggesting that regimens designed to inhibit complement, and in particular C5a, could result in both Treg generation and suppression of Th17 inflammatory T cell response (Strainic, 2013).

4.4. Dose Justification

Two Phase I clinical studies of ALXN1007 have been completed to date, including a single ascending dose study (SAD; Study C11-002) in healthy volunteers over a dose range of 0.06 to 20 mg/kg administered by IV infusion and a multiple ascending dose study (MAD; Study ALXN1007-US-HV-102) in healthy volunteers with 3 repeated doses administered as IV infusion at 6 or 10 mg/kg to assess PK/PD and safety. Overall ALXN1007 PK results in the SAD (C11-002) study indicate that ALXN1007 exhibits non-linear (more than proportional increase in exposure with increasing dose) PK at the doses evaluated. The non-linearity was greater at the lower doses (eg, below 6 mg/kg). This behavior may be explained by target mediated drug disposition. Over the studied single dose ranges, ALXN1007 showed concentration dependent inhibitory effects on C5a and C5. Data from the MAD (ALXN1007-US-HV-102) study showed that following administration of 6 mg/kg weekly or 10 mg/kg every other week for a total of 3 doses, the area under the plasma concentration vs. time curve (AUC) values within dosing intervals following the 3rd dose were not predicted by the AUC estimates following the first dose (ie, the AUC values following the third dose were greater than the AUC between 0 and infinity [AUC_{inf}] following the first dose). The accumulation ratios (ARs) from the 1st to the 3rd dose (3rd dose AUC within the dosing interval [AUC_{τ}]/1st dose AUC_{τ}) were 2.3 and 1.6 for 6 mg/kg weekly and 10 mg/kg every other week, respectively. Nearly complete inhibition of plasma C5a was observed over the 3-week dosing phase for the 6 mg/kg once weekly (QW) cohort and the 6-week dosing phase for the 10 mg/kg every other week cohort. The inhibition of plasma C5 reached a plateau of approximately 80% inhibition after the first dose and was sustained for the duration of dosing in both dosing cohorts.

Alexion is conducting this Phase 2a trial in subjects with GI GVHD. This patient population exhibits significant morbidity and mortality and has a narrow window of treatment opportunity. The clinical status of patients with acute GVHD of the lower GI tract deteriorates rapidly, necessitating urgent and aggressive medical intervention (Deeg, 2007; Macmillan, 2002). The standard of care for treatment of GI GVHD is corticosteroids, which have shown beneficial effects in approximately one half of patients (Garnett, 2013). ALXN1007 will be coadministered with corticosteroids in this study. The following factors were considered for ALXN1007 dose selection:

1. It is important that ALXN1007 doses selected for this study are at the higher end of the dose response in order to maximize suppression of C5a to explore potential indicators of

efficacy of ALXN1007 in this small cohort of subjects with debilitating GI GVHD who are receiving concurrent treatment with standard of care.

2. Acute GI GVHD-related protein losing enteropathy (PLE) (Papadopolou, 1996; van der Meij, 2013) is common in this disease population. It is expected that GI GVHD patients may clear ALXN1007 faster than healthy individuals, as patients with PLE have been shown to lose significant amounts (up to 60%) of administered therapeutic proteins (Chaudhury, 2006; Fasanmade, 2010; Ungaro, 2012).

Given the above considerations, an initial dosing regimen of 10 mg/kg administered IV weekly was selected for this study. The available PK/PD data from the healthy volunteer (SAD [C11-002] and MAD [ALXN1007-US-HV-102]) studies indicated that a single dose of 10 mg/kg and 10 mg/kg every other week reduced C5a levels by >95%. Weekly dosing was chosen to potentially compensate for the expected higher clearance in GI GVHD patients due to PLE. The estimated toxicological margins from these studies also supported this dose selection. For a 10 mg/kg weekly dose regimen, the estimated AUC-based toxicological margin was determined to be 1.6, which accounts for the more than dose-proportional increase in AUC from the SAD (C11-002) study (ie, a 2.6 fold increase in AUC_{inf} going from 6 to 10 mg/kg dose); and also the more than proportional accumulation from the first dose to the third dose in the MAD (ALXN1007-US-HV-102) study, with an accumulation index of 2.3 for the 6 mg/kg weekly dosing regimen.

An interim PK/PD analysis was performed for 10 patients receiving the 10 mg/kg weekly dose for 8 weeks in the current study. The interim results indicated:

1. Clearance was approximately 30% higher in GI GVHD patients than in healthy volunteers, most likely due to PLE in GI GVHD patients.
2. C5a was not completely suppressed (ie, >90% inhibition) in most of the patients. Inhibitory concentration (IC)₅₀ and IC₉₀ for C5a suppression was at least 15-fold higher in GI GVHD patients compared to that observed in healthy volunteers, presumably due to a higher C5a formation rate (due to complement activation) and formation of C5a in tissues in GI GVHD patients that may require higher systemic ALXN1007 concentration to suppress C5a.

The above observations suggested that the dose level initially selected for this study (10 mg/kg weekly) may not sufficiently suppress C5a and that higher doses should be explored. Simulation based on a PK/PD model developed using the interim data of 10 GI GVHD patients in the current study indicated that at 20 mg/kg twice weekly or 40 mg/kg weekly, the lower limit of the 90% confidence interval (CI) of the trough concentration of ALXN1007 would be above the IC₉₀ of C5a suppression in these patients. Based on these findings, at least one additional dosing cohort (Cohort 2, 20 mg/kg QW for 8 weeks) will be added. An additional cohort, 20 mg/kg twice weekly for 8 weeks (Cohort 3), is planned for inclusion in this study after Data Monitoring Committee (DMC) review of the safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts may also be explored based on cumulating safety, tolerability and available PK/PD data.

Based on modeling, the predicted mean C_{max} on Day 28 in the 10 GI GVHD patients was 603, 781 and 1180 ug/mL at 20 mg/kg QW, 20 mg/kg twice weekly and 40 mg/kg QW dosing

regimens, respectively; the predicted mean area under the plasma concentration vs. time curve from time 0 to 168 hours (AUC_{0-168}) on Day 28 was 43600, 81300 and 87200 h*ug/mL at 20 mg/kg QW, 20 mg/kg twice weekly and 40 mg/kg QW dosing regimens, respectively. The predicted mean C_{max} on Day 56 in the 10 GI GVHD patients was 636, 851 and 1250 ug/mL at 20 mg/kg QW, 20 mg/kg twice weekly and 40 mg/kg QW dosing regimens, respectively; the predicted mean AUC_{0-168} on Day 56 was 48500, 91400 and 97100 h*ug/mL at 20 mg/kg QW, 20 mg/kg twice weekly and 40 mg/kg QW dosing regimens, respectively. In the 6-month Good Laboratory Practice (GLP) monkey toxicology study, C_{max} and AUC_{0-168} at 10 mg/kg (the no observed adverse effect level [NOAEL]) were 617 ug/mL and 72963 h*ug/mL, respectively. For the 20 mg/kg QW dosing regimen, at Day 28, C_{max} will approach that at the NOAEL, but AUC will be below that at the NOAEL. At 20 mg/kg twice weekly or 40 mg/kg weekly dosing regimens, C_{max} and AUC_{0-168} are expected to exceed the NOAEL exposure from the 6-month GLP monkey toxicology study. However, according to recent feedback received by Alexion from the US Food and Drug Administration's Office of Hematology and Oncology Products, the ALXN1007 program for GI GVHD will be considered under the principles outlined in the International Council for Harmonization (ICH) S9 Guideline for Nonclinical Evaluation for Anticancer Pharmaceuticals, which states that upper dose limits for clinical studies are not limited by the highest dose or exposure tested in nonclinical studies.

A schematic of the study design, including the dose escalation and safety review plan, can be found in [Figure 1](#).

Refer to the current Investigator's Brochure (IB) for ALXN1007 for additional information on available PK/PD and safety data for ALXN1007.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Objectives

The objectives of this trial are to evaluate the safety, tolerability, PK/PD, and efficacy of IV ALXN1007 administered over an 8 week treatment period in subjects with acute GVHD of the lower GI tract.

5.2. Endpoints

5.2.1. Primary Efficacy Endpoint

- Overall acute GVHD response rate at Day 28.

5.2.2. Other Efficacy Endpoints

- Proportion of subjects with complete response (CR), partial response (PR), mixed response (MR), no response (NR) and Progression for acute GI GVHD at Day 28.
- Proportion of subjects with CR, PR, MR, NR and Progression for all organs involved with acute GVHD at Days 14, 28 and 56. Very good partial response (VGPR) will be assessed at Days 14, 28 and 56.
- Proportion of treatment failures at Days 14, 28 and 56.
- Incidence of acute GVHD flares through Day 86.
- Cumulative corticosteroid dose at Days 28, 56, 86 and 180.
- Proportion of subjects with discontinuation of immunosuppressive medication on Days 56, 86 and 180.
- Overall survival up to Days 180 and 360.
- Rate of non-relapse mortality at Days 180 and 360.

5.2.3. Safety Endpoints

- Incidence and severity of adverse events (AEs) and serious AEs (SAEs).
- Incidence of infections.
- Incidence of abnormal clinical laboratory values.
- Change from Baseline in clinical laboratory assessments: chemistry panel, coagulation panel, complete blood cell count (CBC) with differential, thyroid function testing, and urinalysis.
- Change from Baseline in electrocardiogram (ECG) findings.
- Incidence and titer of antibodies to ALXN1007.

5.2.4. Pharmacokinetic Endpoints

ALXN1007 PK parameters will be determined including, at a minimum, maximum observed concentration in plasma (C_{\max}), time to maximum observed concentration in plasma (t_{\max}), and trough concentration in plasma pre-next-dose (C_{trough}). Area under the plasma concentration vs. time curve within the dosing interval (AUC_{τ}), AUC_{0-168} for twice weekly dosing, accumulation ratio (AR) from the first to the last dose, and apparent linear phase half-life ($t_{1/2}$) may also be evaluated if feasible.

5.2.5. Pharmacodynamic Endpoints

Key PD parameters may include, but are not limited to, change from Baseline in the levels of complement proteins C3, C4, C5 and C5a. A limited number of PD samples will be assayed for change from Baseline in sC5b9 levels and terminal complement activity (may include chicken red blood cell [cRBC] hemolytic activity and classical complement pathway [CCP] activity).

5.2.6. Exploratory Biomarker Endpoints

Additional exploratory biomarkers of PD effect may include, but are not limited to, change from Baseline in levels of complement alternative pathway proteins (Ba, Bb) and additional assessments of complement activity or GVHD-associated biomarkers (eg, soluble tumor necrosis factor receptor 1 [sTNFR1], suppressor of tumorigenicity 2 [ST2] and regenerating islet-derived protein 3 alpha [REG3a]). Additional assessments may also include measurement of antibodies to factor H. Samples from consenting subjects may also be evaluated for genetic variability that may affect efficacy or safety endpoints (pharmacogenetics [PGx]).

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 2a open-label study to evaluate the safety, tolerability, PK/PD, and efficacy of ALXN1007 (a C5a inhibitor) in up to 36 subjects with newly diagnosed acute GVHD of the lower GI tract (see [Section 5](#) for further details on study objectives and endpoints).

An endoscopy of the upper and/or lower GI tract and biopsy must be performed within 7 days of screening to confirm the diagnosis of GI GVHD, but the results may not be available prior to initiation of ALXN1007 treatment. If ALXN1007 treatment is initiated, and biopsy results received post initiation of treatment do not confirm a diagnosis of GI GVHD, ALXN1007 treatment must be discontinued and an early termination (ET) visit scheduled.

The first dosing cohort (Cohort 1, up to 18 subjects) will receive 10 mg/kg ALXN1007 administered IV QW for 8 weeks. With approval of Amendment 6, Cohort 2, 20 mg/kg QW for 8 weeks, will be added to the study. An additional cohort (Cohort 3), 20 mg/kg twice weekly for 8 weeks, is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

For Cohort 2, the following safety reviews will be performed:

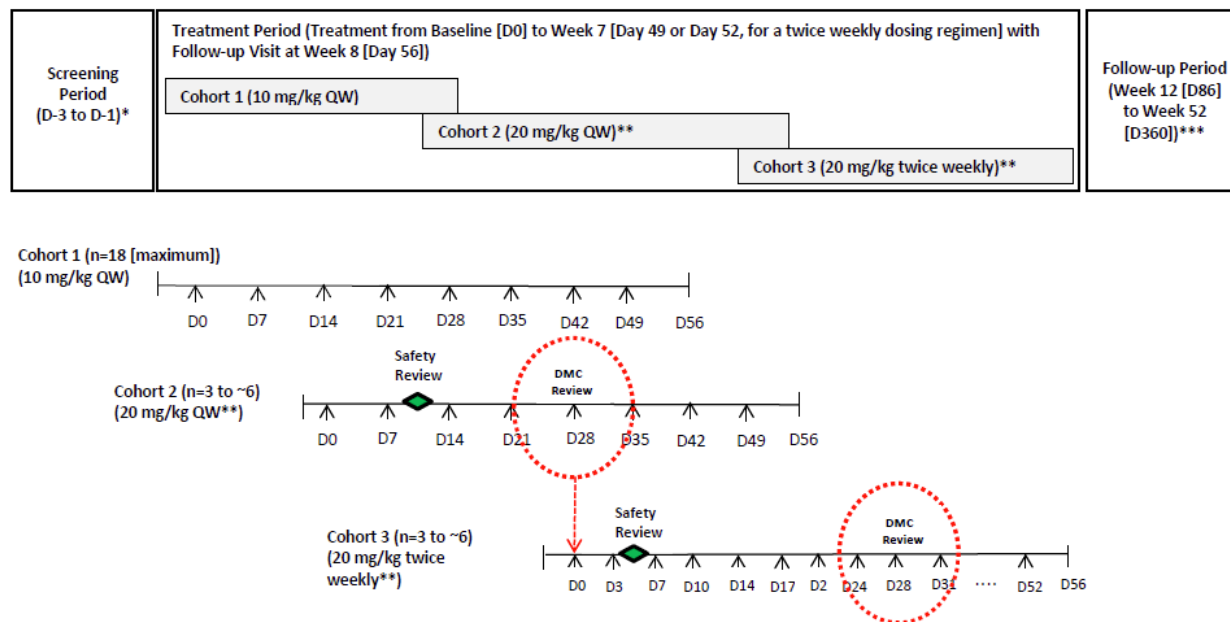
- For the first 2 subjects enrolled, the first ALXN1007 dose may not be administered on the same day. In addition, for the first 2 enrolled subjects, a safety and tolerability review will take place after the second (and prior to the third) ALXN1007 dose for each subject. If the ALXN1007 dose is determined to be sufficiently tolerated by the subject, dosing may continue for that subject. For any other subjects enrolled in the dosing cohort, subjects may not proceed to the third ALXN1007 dose before completion of the safety and tolerability review (of the first 2 doses) for the first 2 subjects.
- After the first 3 subjects have completed the Day 28 procedures and assessments (ie, received all protocol prescribed ALXN1007 doses through Day 28), the DMC will convene to review aggregate safety and tolerability data. Pharmacokinetic and pharmacodynamic data may also be provided for DMC review, if available. After review, the dose of ALXN1007 will be escalated to 20 mg/kg twice weekly for 8 weeks (Cohort 3), unless the DMC recommends a different dose level or dosing regimen, including continuation of 20 mg/kg QW within the cohort (up to a maximum of approximately 6 subjects) or reduction of the dose to the previous dose level or to a dose between planned dose levels. Final dosing decisions will be made by the Sponsor, in consultation with the DMC, based on safety, tolerability and any available PK/PD data.

For Cohort 3 and any additional dosing cohorts exploring a higher dose than Cohort 1 (ie, 10 mg/kg per week), the same safety reviews described above will be performed.

All enrolled subjects will be followed for safety, tolerability, PK/PD, and efficacy over the course of the study, with weekly (or twice weekly, if a twice weekly dosing regimen is evaluated) visits through Day 56 (Week 8), and subsequent follow-up visits at Day 86 (Week 12) and Day 180 (Week 26). Subject survival status will be collected at Day 360 by telephone contact.

A graphical display of the general study design, including the dose escalation and safety review plan, can be found in [Figure 1](#). [Table 3](#) provides a summary tabulation of required study assessments by visit for subjects on a once weekly ALXN1007 dosing schedule (for subjects receiving a total weekly dose of 20 mg/kg or less). [Table 4](#) provides a summary tabulation of required study assessments by visit for subjects on a twice weekly ALXN1007 dosing schedule (for subjects receiving total weekly doses greater than 20 mg/kg). [Table 5](#) summarizes blood sample collection time points for PK and PD assessments for the study based on frequency of ALXN1007 dosing (ie, weekly or twice weekly).

Procedures to be followed when a subject discontinues from ALXN1007 treatment or terminates study participation prior to the Week 26 (Day 180) Visit are discussed in [Section 7.3.2](#).

Figure 1: General Study Design, Including Dose Escalation and Safety Review Plan

* Screening period for the study will be initiated after informed consent form signing (ie, subject enrollment). Acute GI GVHD staging at the time of diagnosis (that can be made up to 7 days prior to the first ALXN1007 dose) will be captured and used for comparison to post-Baseline GVHD staging to assess treatment response.

** With approval of Amendment 6, Cohort 2 (20 mg/kg QW for 8 weeks) will be added to the study. An additional cohort (Cohort 3, 20 mg/kg twice weekly for 8 weeks), is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

*** Follow-up period for the study consists of study visits at Weeks 12 (Day 86) and 26 (Day 180), with telephone contact at Week 52 (Day 360) for survival status only.

Table 3: Schedule of Events for Subjects on a Once Weekly ALXN1007 Dosing Schedule

Procedures and Evaluations	Screening	Treatment (± 2 days)									Follow-up (± 15 days, except for ET)			
		0	1	2	3	4	5	6	7	8	12	26	ET	52
Weeks														
Days	-3 to -1	Baseline	7	14	21	28	35	42	49	56	86	180	ET	360
Informed Consent	X													
Eligibility - Inclusion/Exclusion Criteria	X	X ¹												
Medical History, Demographics	X													
ALXN1007 Administration ²		X	X	X	X	X	X	X	X					
Acute GVHD Staging ³	X	X	X	X	X	X	X	X	X	X	X	X	X	
Antibiotic Prophylaxis Against Meningococcal Infection ⁴	X	X	X	X	X	X	X	X	X	X	X ⁴		X ⁴	
Physical Exam ⁵	X					X				X		X	X	
ECG		X ⁶				X ⁶				X		X	X	
Vital Signs ⁷	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	
Stool <i>Clostridium difficile</i> Testing (Local lab)	X													
CSA, Tacrolimus, and/or Sirolimus Levels (if needed) ⁸		X	X		X		X		X				X	
CMV-PCR		X	X	X	X	X	X	X	X	X			X	
Routine Laboratory Test ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine Clearance (local lab)	X													
ANC (local lab)	X													
Endoscopy of Upper and/or Lower GI Tract / Biopsy ¹	X													
CPK, Thyroid Function Tests (Central lab)		X	X			X				X	X	X	X	

Table 3: Schedule of Events (Continued)

Procedures and Evaluations	Screening	Treatment (± 2 days)									Follow-up (± 15 days, except for ET)			
Days	-3 to -1	Baseline	7	14	21	28	35	42	49	56	86	180	ET	360
Weeks		0	1	2	3	4	5	6	7	8	12	26		52
Pregnancy Test (if applicable; Local lab) ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis ⁹	X	X				X				X		X	X	
PK and PD ¹¹		X	X	X	X	X	X	X	X	X	X	X	X	
Antibodies to ALXN1007 ¹²		X	X			X				X	X	X	X	
Exploratory Biomarkers ¹³		X	X			X			X		X	X	X	
PGx ¹⁴		X												
AEs ¹⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	
HCT Information (including conditioning regimen)	X													
Survival Status														X

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; BP = blood pressure; CMV-PCR = cytomegalovirus-polymerase chain reaction; CPK = creatine phosphokinase; CSA = cyclosporine; ECG = electrocardiogram; EOI = end of infusion; ET = early termination; GI = gastrointestinal; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; hr = hour; ICF = informed consent form; IV=intravenous; PD = pharmacodynamic; PGx = pharmacogenetics; PK = pharmacokinetic; SAEs = serious adverse events; SOI = start of infusion; SOM = study operations manual.

¹ Endoscopy of upper and/or lower GI tract/biopsy to be performed unless performed within 7 days prior to screening. Biopsy results to be reviewed when available. If biopsy results do not confirm GI GVHD, study treatment will be discontinued, and an ET visit will be performed. Biopsy tissue from patients confirmed to have GI GVHD may be evaluated by immunohistochemistry (at MD Anderson) for evidence of complement deposition or immune cell characterization.

² ALXN1007 dose (depending upon the dosing cohort to which subjects are assigned; refer to [Section 6.3](#)) will be administered by continuous IV infusion. There should be a minimum of 4 days between ALXN1007 doses. Additional details on infusion preparation and administration for ALXN1007 doses being investigated in this study can be found in the Pharmacy Manual. Because anaphylaxis might occur at any time during an infusion, subjects will be monitored closely prior to and through 2 hours following the end of the infusion.

³ Acute GVHD staging includes skin, liver and GI assessments, which will be performed using the Modified Keystone Grading Schema. Lower GI tract assessment consists of determination of stool volume over a 24-hour period. Detailed instructions for determining stool volume can be found in the study operations manual (SOM) for the study. Staging will be collected at all time points indicated in the Schedule of Events (including at Screening and Baseline). In addition, the stage at the time of diagnosis, that can occur up to 7 days prior of the first dose of ALXN1007, will also be recorded and will be used 1) to determine study eligibility and 2) for comparison to post-Baseline GVHD staging to assess treatment response to ALXN1007 in combination with corticosteroids.

⁴ Subjects must continue or begin antibiotic prophylaxis active against meningococcal infection prior to receiving the first dose of ALXN1007. Subjects already receiving empirical antibiotic prophylaxis for bacterial infections or therapeutic antibiotic treatment must be receiving an antibiotic throughout the treatment period and for 6 weeks after the last dose of ALXN1007 that is active against encapsulated organisms (including *Neisseria meningitidis*) based on institutional guidelines. If patients are receiving

prophylactic, empirical or therapeutic antibiotic treatment with drugs that have activity against meningococcus (and pneumococcus) no additional antibiotic prophylaxis will be required during that treatment period.

⁵ Height measurement at Screening only.

⁶ ECG to be performed pre-dose and at end of infusion (EOI).

⁷ Vital Signs: BP, pulse, temperature and respiratory rate. Vital signs will be obtained after the subject has been supine or seated for at least 5 minutes.

⁸ The timing of sample collection (eg, trough) should be appropriate for the drug being monitored and not coupled with the timing of administration of ALXN1007.

⁹ Screening labs should be done at local lab; Baseline through end of study assessments are to be done at central lab.

¹⁰ Serum pregnancy test at Screening only (local lab); serum or urine dipstick pregnancy tests thereafter (local lab). For women of childbearing potential only. If Baseline is within 24 hours of the Screening pregnancy test, it does not need to be repeated.

¹¹ Refer to [Table 5](#) for required time points for PK/PD sample collection time points by visit.

¹² On all dosing days, samples will be collected within 4 hours prior to the start of infusion (SOI). If positive for antibodies to ALXN1007 on Day 180 or the ET visit, the subject may be followed every 3 months until negative or stabilized, based on the measured titer and the safety assessments in that specific subject.

¹³ On all dosing days, samples will be collected within 4 hours prior to the SOI.

¹⁴ To participate in this optional PGx portion of the study, subjects must also sign the pharmacogenetic informed consent document.

¹⁵ All AEs will be recorded from the signing of informed consent until 30 days after the last dose of ALXN1007. All SAEs will be recorded from signing of informed consent through the Day 180 visit. In addition, any notifications of death as a result of the Day 360 survival follow-up will also be recorded; the cause of death or event leading to death should be reported as an SAE. Note: There is no time limit for reporting SAEs that are considered causally related.

Table 4: Schedule of Events for Subjects on Twice Weekly ALXN1007 Dosing Schedule

Procedures and Evaluations	Screening	Treatment Period (± 1 day)																Follow-up (± 15 days, except for ET)				
Weeks		0		1		2		3		4		5		6		7		8	12	26		52
Days	-3 to -1	Baseline	3	7	10	14	17	21	24	28	31	35	38	42	45	49	52	56	86	180	ET	360
Informed Consent	X																					
Eligibility - Inclusion/Exclusion Criteria	X	X ¹																				
Medical History, Demographics	X																					
ALXN1007 Administration ²		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Acute GVHD Staging ³	X	X		X		X		X		X		X		X		X		X	X	X	X	
Antibiotic Prophylaxis Against Meningococcal Infection ⁴	X	X		X		X		X		X		X		X		X		X	X ⁴		X ⁴	
Physical Exam ⁵	X									X								X		X	X	
ECG		X ⁶								X ⁶								X		X	X	
Vital Signs ⁷	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X		X		X		X		X		X		X		X		X	X	X	X	
Stool <i>Clostridium difficile</i> Testing (Local lab)	X																					
CSA, Tacrolimus, and/or Sirolimus Levels (if needed) ⁸		X		X				X				X				X					X	
CMV-PCR		X		X		X		X		X		X		X		X		X			X	
Routine Laboratory Test ⁹	X	X		X		X		X		X		X		X			X		X	X	X	
Creatinine Clearance (local lab)	X																					
ANC (local lab)	X																					
Endoscopy of Upper and/or Lower GI Tract / Biopsy ¹	X																					
CPK, Thyroid Function Tests (Central lab)		X		X						X								X	X	X	X	

Table 4: Schedule of Events for Subjects on Twice Weekly ALXN1007 Dosing Schedule (Continued)

Procedures and Evaluations	Screening	Treatment Period (± 1 day)																Follow-up (± 15 days, except for ET)				
Weeks		0		1		2		3		4		5		6		7		8	12	26		52
Days	-3 to -1	Baseline	3	7	10	14	17	21	24	28	31	35	38	42	45	49	52	56	86	180	ET	360
Pregnancy Test (if applicable; Local lab) ¹⁰	X	X		X		X		X		X		X		X		X		X	X	X	X	
Urinalysis ⁹	X	X								X								X		X	X	
PK and PD ¹¹		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Antibodies to ALXN1007 ¹²		X		X						X								X	X	X	X	
Exploratory Biomarkers ¹³		X		X						X						X			X	X	X	
PGx ¹⁴		X																				
AEs ¹⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HCT Information (including conditioning regimen)	X																					
Survival Status																						X

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; BP = blood pressure; CMV-PCR = cytomegalovirus-polymerase chain reaction; CPK = creatine phosphokinase; CSA = cyclosporine; ECG = electrocardiogram; EOI = end of infusion; ET = early termination; GI = gastrointestinal; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; hr = hour; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PGx = pharmacogenetics; PK = pharmacokinetic; SAEs = serious adverse events; SOI = start of infusion; SOM = study operations manual.

¹ Endoscopy of upper and/or lower GI tract/biopsy to be performed unless performed within 7 days prior to screening. Biopsy results to be reviewed when available. If biopsy results do not confirm GI GVHD, study treatment will be discontinued, and an ET visit will be performed. Biopsy tissue from patients confirmed to have GI GVHD may be evaluated by immunohistochemistry (at MD Anderson) for evidence of complement deposition or immune cell characterization.

² ALXN1007 dose (depending upon the dosing cohort to which subjects are assigned; refer to [Section 6.3](#)) will be administered by continuous IV infusion. There should be a minimum of 2 days between ALXN1007 doses. Additional details on infusion preparation and administration for ALXN1007 doses being investigated in this study can be found in the Pharmacy Manual. Because anaphylaxis might occur at any time during an infusion, subjects will be monitored closely prior to and through 2 hours following the end of the infusion.

³ Acute GVHD staging includes skin, liver and GI assessments, which will be performed using the Modified Keystone Grading Schema. Lower GI tract assessment consists of determination of stool volume over a 24-hour period. Detailed instructions for determining stool volume can be found in the study operations manual (SOM) for the study. Staging will be collected at all time points indicated in the Schedule of Events (including at Screening and Baseline). In addition, the stage at the time of diagnosis, that can occur up to 7 days prior of the first dose of ALXN1007, will also be recorded and will be used 1) to determine study eligibility and 2) for comparison to post-Baseline GVHD staging to assess treatment response to ALXN1007 in combination with corticosteroids.

⁴ Subjects must continue or begin antibiotic prophylaxis active against meningococcal infection prior to receiving the first dose of ALXN1007. Subjects already receiving empirical antibiotic prophylaxis for bacterial infections or therapeutic antibiotic treatment must be receiving an antibiotic throughout the treatment period and for 6 weeks after the last dose of ALXN1007 that is active against encapsulated organisms (including *Neisseria meningitidis*) based on institutional guidelines. If patients are receiving prophylactic, empirical or therapeutic antibiotic treatment with drugs that have activity against meningococcus (and pneumococcus) no additional antibiotic prophylaxis will be required during that treatment period.

- ⁵ Height measurement at Screening only.
- ⁶ ECG to be performed pre-dose and at end of infusion (EOI).
- ⁷ Vital Signs: BP, pulse, temperature and respiratory rate. Vital signs will be obtained after the subject has been supine or seated for at least 5 minutes.
- ⁸ The timing of sample collection (eg, trough) should be appropriate for the drug being monitored and not coupled with the timing of administration of ALXN1007.
- ⁹ Screening labs should be done at local lab; Baseline through end of study assessments are to be done at central lab.
- ¹⁰ Serum pregnancy test at Screening only (local lab); serum or urine dipstick pregnancy tests thereafter (local lab). For women of childbearing potential only. If Baseline is within 24 hours of the Screening pregnancy test, it does not need to be repeated.
- ¹¹ Refer to [Table 5](#) for required time points for PK/PD sample collection time points by visit.
- ¹² On all dosing days, samples will be collected within 4 hours prior to the start of infusion (SOI). If positive for antibodies to ALXN1007 on Day 180 or the ET visit, the subject may be followed every 3 months until negative or stabilized, based on the measured titer and the safety assessments in that specific subject.
- ¹³ On all dosing days, samples will be collected within 4 hours prior to the SOI.
- ¹⁴ To participate in this optional PGx portion of the study, subjects must also sign the pharmacogenetic informed consent document.
- ¹⁵ All AEs will be recorded from the signing of informed consent until 30 days after the last dose of ALXN1007. All SAEs will be recorded from signing of informed consent through the Day 180 visit. In addition, any notifications of death as a result of the Day 360 survival follow-up will also be recorded; the cause of death or event leading to death should be reported as an SAE. Note: There is no time limit for reporting SAEs that are considered causally related.

Table 5: Blood Sample Collection Time Points for Pharmacokinetics and Pharmacodynamic Assessments

Study Week / Day	Blood Sample Collection Time Point(s) ¹	ALXN1007 Dosing Schedule	
		Weekly	Twice Weekly
Week 0 / Baseline	Within 4 hours prior to infusion	X	X
	End of infusion	X	X
	3 hours post SOI	X ²	X ³
Week 0 / Day 3	Within 4 hours prior to infusion	---	X
	End of infusion	---	X
	3 hours post SOI	---	X
Week 1 / Day 7	Within 4 hours prior to infusion	X	X
Week 1 / Day 10	Within 4 hours prior to infusion	---	X
Week 2 / Day 14	Within 4 hours prior to infusion	X	X
Week 2 / Day 17	Within 4 hours prior to infusion	---	X
Week 3 / Day 21	Within 4 hours prior to infusion	X	X
Week 3 / Day 24	Within 4 hours prior to infusion	---	X
Week 4 / Day 28	Within 4 hours prior to infusion	X	X
	End of infusion	X	X
	3 hours post SOI	X ²	X ³
Week 4 / Day 31	Within 4 hours prior to infusion	---	X
	End of infusion	---	X
	3 hours post SOI	---	X
Week 5 / Day 35	Within 4 hours prior to infusion	X	X
Week 5 / Day 38	Within 4 hours prior to infusion	---	X
Week 6 / Day 42	Within 4 hours prior to infusion	X	X
Week 6 / Day 45	Within 4 hours prior to infusion	---	X
Week 7 / Day 49	Within 4 hours prior to infusion	X	X
	End of infusion	X	X
	3 hours post SOI	X ²	X ³
Week 7 / Day 52	Within 4 hours prior to infusion	---	X
	End of infusion	---	X
	3 hours post SOI	---	X
Week 8 / Day 56	Any time during the study visit	X	X
Week 12 / Day 86	Any time during the study visit	X	X
Week 26 / Day 180	Any time during the study visit	X	X
ET visit (if applicable)	Any time during the study visit	X	X

Abbreviations: ET = early termination; SOI = start of infusion

¹ End of infusion time point has a collection window of ± 5 minutes; 3 and 5 hour post SOI time points have a window for collection of ± 15 minutes; and 24, 48 and 72 hour time points have a window for collection of ± 2 hours.

² For subjects who are hospitalized, sample should also be collected 5, 24, 48, and 72 hours post SOI.

³ For subjects who are hospitalized, sample should also be collected 5, 24, and 48 hours post SOI.

6.1.1. Screening Period

Once informed consent has been obtained, subjects will be screened over a period of 3 days prior to Baseline for study eligibility determination, medical history review and demographic data collection. Every attempt will be made to minimize this 3 day period, and subjects may have their Screening and Baseline visits on the same date. Assessments required for Screening and/or eligibility determination will also include the following: acute GVHD staging (at the Screening visit; staging at the time of diagnosis, that can occur up to 7 days prior of the first dose of ALXN1007, will also be recorded), physical exam (including height), vital signs, weight, *C. difficile* stool test, laboratory tests, endoscopy of upper and/or lower GI tract with biopsy, pregnancy test (for women of childbearing potential), and recording of AEs (see [Section 11.2](#)), prior and concomitant medications and therapies, and information on HCT performed, including conditioning regimen and post-transplant GVHD prophylaxis regimen (see [Section 8.2](#)). Results of evaluations performed as part of “standard of care” prior to informed consent are allowed for *C. difficile* testing and endoscopic biopsy.

6.1.1.1. Biopsy

A biopsy of the upper and/or lower GI tract performed within 7 days of screening can be used to determine eligibility. Biopsy results may not be available until after the first treatment visit. If GI GVHD is not confirmed histologically, study treatment will be discontinued and an ET visit should be completed 6 weeks after the last dose of ALXN1007 was received. Subjects should continue antibiotic prophylaxis for 6 weeks after the last dose of ALXN1007 (see [Section 6.1.1.3](#)).

All biopsy specimens will be reviewed by both the Investigator's local pathology lab, as well as The University of Texas MD Anderson Cancer Center laboratory, which will serve as the central pathology laboratory for this study. Any discrepancies in biopsy interpretation between the central pathology laboratory and the Investigator's local pathology laboratory will be resolved by the Alexion Medical Monitor and the Investigator to determine if study treatment should continue.

6.1.1.2. GVHD Staging

Staging will be collected at all time points indicated in the Schedule of Events (including at Screening and Baseline; refer to [Table 3](#) and [Table 4](#)). In addition, the stage at the time of diagnosis, that can occur up to 7 days prior of the first dose of ALXN1007, will also be recorded and will be used 1) to determine study eligibility and 2) for comparison to post-Baseline GVHD staging to assess treatment response to ALXN1007 in combination with corticosteroids. Acute GVHD staging will be performed using the Modified Keystone Grading Schema ([Table 10](#) and [Appendix 1](#)), which includes skin, liver and lower GI assessments. Lower GI assessment consists of determination of stool volume over a 24-hour period. Detailed instructions for determining stool volume can be found in the study operations manual (SOM) for the study.

6.1.1.3. Antibiotic Prophylaxis

Subjects must continue or begin antibiotic prophylaxis active against meningococcal infection prior to receiving the first dose of ALXN1007. Subjects already receiving empirical antibiotic prophylaxis for bacterial infections or therapeutic antibiotic treatment must be receiving an

antibiotic throughout the treatment period and for 6 weeks after the last dose of ALXN1007 that is active against encapsulated organisms (including *Neisseria meningitidis*) based on institutional guidelines. If patients are receiving prophylactic, empirical or therapeutic antibiotic treatment with drugs that have activity against meningococcus (and pneumococcus), no additional antibiotic prophylaxis will be required during that treatment period.

6.1.2. Treatment Period (Baseline - Day 56)

The first dosing cohort (Cohort 1) will receive 10 mg/kg ALXN1007 administered IV QW for 8 weeks. With approval of Amendment 6, Cohort 2, 20 mg/kg QW for 8 weeks, will be added to the study. An additional cohort, 20 mg/kg twice weekly for 8 weeks (Cohort 3), is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week for 8 weeks) may also be explored as described in [Section 6.3](#).

Review of biopsy histology for confirmation of GI GVHD will occur when biopsy results are available. For subjects without histologically confirmed GI GVHD, refer to [Section 6.1.5](#) for guidance on discontinuing ALXN1007 treatment and conducting an ET visit.

The first ALXN1007 dose will be administered at Baseline. Following this, subjects will receive once weekly dosing until Day 49, or twice weekly dosing until Day 52 (if twice weekly dosing schedule is being administered). On Day 56, subjects will undergo follow-up evaluations but will not receive ALXN1007 treatment.

Each visit during the Treatment Period (including Day 56) should occur at the day indicated ± 2 days (if the subject is on a weekly dosing schedule) or ± 1 day (if the subject is on a twice weekly dosing schedule). For subjects on a weekly dosing schedule, there should be a minimum of 4 days between ALXN1007 doses. For subjects on a twice weekly dosing schedule, there should be a minimum of 2 days between ALXN1007 doses. If the recommended acceptable windows cannot be observed, the Sponsor or its representative must be contacted prior to scheduling a visit.

All doses of ALXN1007 will be administered as a continuous IV infusion. Subjects will remain under observation for 2 hours after the infusion. Refer to [Sections 9.4](#) and [9.5](#), as well as the Pharmacy Manual, for procedures pertaining to the preparation and administration of ALXN1007.

6.1.2.1. Baseline

Prior to Infusion of ALXN1007

Baseline evaluations will include the following: acute GVHD staging, ECG, vital signs, weight, laboratory tests, including any monitoring of anti-rejection drugs, if applicable, pregnancy test (for women of childbearing potential) (note: if the Baseline visit is within 24 hours of Screening, the pregnancy test does not need to be repeated), PK/PD (collected within 4 hours prior to the start of infusion [SOI]), antibodies to ALXN1007, exploratory biomarkers, optional PGx (if consent has been provided), recording of AEs (see [Section 11.2](#)) and concomitant medications and therapies (see [Section 8.2](#)).

The Investigator or designee must confirm that the subject is receiving antibiotic prophylaxis active against meningococcal infection prior to receiving the first dose of ALXN1007.

Administration of ALXN1007

All doses of ALXN1007 will be administered as a continuous IV infusion. Subjects will remain under observation during and for 2 hours after the infusion. Refer to [Sections 9.4](#) and [9.5](#) and the Pharmacy Manual for procedures pertaining to the preparation and administration of ALXN1007.

Post Infusion of ALXN1007

Blood samples for PK/PD will be collected at the end of infusion (EOI) plus 3 hours post-SOI. If the subject is hospitalized, then PK/PD samples will also be collected 5 hr, 24 hr, 48 hr and 72 hr post-SOI (for subjects on a weekly ALXN1007 dosing schedule) or 5 hr, 24 hr and 48 hr post-SOI (for subjects on a twice weekly ALXN1007 dosing schedule). End of infusion time point has a collection window of ± 5 minutes; 3 and 5 hour post SOI time points have a window for collection of ± 15 minutes; and 24, 48 and 72 hour time points have a window for collection of ± 2 hours.

An ECG will also be done at EOI.

Subjects will remain under observation for 2 hours after the infusion.

6.1.2.2. Days 3-56

The evaluations that will occur during the remainder of the Treatment Period include the following: acute GVHD staging (Days 7, 14, 21, 28, 35, 42, 49, and 56), physical exam (Days 28 and 56 only), ECG (pre and post dose on Day 28, and once on Day 56), vital signs (all visits), weight (Days 7, 14, 21, 28, 35, 42, 49, and 56), laboratory tests (Days 7, 14, 21, 28, 35, 42, 49 [for subjects on a weekly dosing schedule] or 52 [for subjects on a twice weekly dosing schedule], and 56 [for subjects on a weekly dosing schedule]), pregnancy test (urine or serum, for women of childbearing potential) (Days 7, 14, 21, 28, 35, 42, 49, and 56), antibodies to ALXN1007 (Days 7, 28 and 56), exploratory biomarkers (Days 7, 28 and 49), and recording of AEs (see [Section 11.2](#)) and concomitant medications and therapies (see [Section 8.2](#)).

Samples for PK/PD assessment will also be collected during this same time period. A summary of study visits (and time points) for PK/PD sample collection can be found in [Table 5](#) (see also [Table 3](#) and [Table 4](#)).

6.1.3. Follow-up Period (Day 86 - Day 180)

Subjects will return to the site for follow-up visits on Days 86 and 180 following Baseline. Each follow-up visit should occur within ± 15 days of the planned date.

The evaluations that will occur during the Follow-up Period (Days 86 and 180) include the following: acute GVHD staging, physical exam (Day 180 only), ECG (Day 180 only), vital signs, weight, laboratory tests, pregnancy test (for women of childbearing potential), PK/PD (see [Table 5](#)), antibodies to ALXN1007, exploratory biomarkers, and recording of AEs (see [Section 11.2](#)) and concomitant medications and therapies (see [Section 8.2](#)).

6.1.4. Survival Status on Day 360

Subjects and/or their caregivers will be contacted by the site on Day 360 (± 15 days) following Baseline. Questions regarding the subject's survival status will be asked of the subject and/or the caregiver by telephone call.

6.1.5. Early Termination Visit

An ET visit will be conducted when the following occur:

- In the event that the biopsy results do not confirm GI GVHD, study treatment will be discontinued, and an ET visit will be performed 6 weeks after the last dose of ALXN1007 was received.
- If the subject discontinues for any reason after receiving at least 1 dose of ALXN1007 and before the Day 180 visit, the ET visit should be performed (within 5 days) if possible.

The ET visit assessments will include acute GVHD staging, physical exam, ECG, vital signs, weight, various laboratory tests, PK/PD, antibodies to ALXN1007, exploratory biomarkers, and recording of AEs (see [Section 11.2](#)) and concomitant medications and therapies (see [Section 8.2](#)).

Note: Subjects must continue antibiotic prophylaxis active against meningococcal infection for 6 weeks after the last dose of ALXN1007.

6.1.6. Missing Visits

Subjects who are unable to complete a scheduled visit must be contacted by the site study staff to determine the reason. For subjects who miss a dose, the Investigator is responsible for discussing the status and future treatment of these subjects with the Alexion Medical Monitor. Every effort must be made to undertake the protocol-specified evaluations through Day 180.

Follow-up due diligence and documentation are discussed in [Section 7.3.2](#).

6.2. Number of Subjects

Up to 36 subjects confirmed by biopsy to have GI GVHD will be enrolled in this study. For the 10 mg/kg QW dosing cohort (Cohort 1), a maximum of 18 subjects will be enrolled. For Cohorts 2 and 3, and any other dosing cohorts that may be added, a minimum of 3 up to a maximum of approximately 6 subjects will be enrolled in each cohort.

6.3. Treatment Assignment

All subjects meeting the inclusion and exclusion criteria for the study will receive ALXN1007 over an 8 week treatment period. The first dosing cohort (Cohort 1) will receive 10 mg/kg ALXN1007 administered IV QW for 8 weeks. With approval of Amendment 6, Cohort 2, 20 mg/kg QW for 8 weeks, will be added to the study. An additional cohort, 20 mg/kg twice weekly for 8 weeks (Cohort 3), is planned after DMC review of safety and tolerability data at Day 28 on the first 3 patients in Cohort 2. The planned dosing cohorts in this study are summarized in [Table 6](#).

Table 6: Planned ALXN1007 Dosing Cohorts

Dosing Cohort ¹	Total ALXN1007 Dose per Week	Dosing Regimen	Infusion Duration	Sample Size
1	10 mg/kg	10 mg/kg QW (8 total doses)	1 hour ± 10 minutes	18 (maximum)
2	20 mg/kg	20 mg/kg QW (8 total doses)	2 hours ± 10 minutes	3 to approximately 6 ²
3	40 mg/kg	20 mg/kg twice weekly (16 total doses)	2 hours ± 10 minutes	3 to approximately 6 ²

¹ At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg per week) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

² For Cohorts 2 and 3 (and any other dosing cohorts that may be added), a minimum of 3 up to a maximum of approximately 6 subjects may be enrolled.

Details on allowance for dose adjustments, as well as stopping rule criteria for ALXN1007 dosing, can be found in [Section 6.4](#).

6.4. Dose Adjustment and Stopping Criteria

6.4.1. Dose Adjustment Criteria

For subjects who are unable to tolerate weekly doses of 20 mg/kg or higher, dose reduction to a minimum of 10 mg/kg weekly may be permitted after discussion between the Principal Investigator and the Alexion Medical Monitor. For subjects unable to tolerate the minimum weekly dose of 10 mg/kg QW, ALXN1007 treatment will be discontinued.

If ALXN1007 treatment is prematurely discontinued, procedures for continued follow-up outlined in [Section 7.3.2](#) must be followed.

6.4.2. Safety Criteria for Stopping Doses

For all subjects (irrespective of ALXN1007 dose), if an adverse reaction occurs during the administration of ALXN1007, the infusion may be slowed or stopped at the discretion of the Principal Investigator (PI). If the infusion is slowed or temporarily stopped, **the total infusion time should not exceed 3 hours**. The adverse reaction must be recorded on the AE page of the electronic case report form (eCRF).

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. For this reason, subjects will be carefully observed during each infusion. Subjects will remain under observation for 2 hours after the infusion. Advice on management and prevention of infusion reactions is included in [Section 9.5.1](#).

If a subject experiences a **Grade 4 AE related** to study treatment, ALXN1007 treatment should be permanently discontinued (see [Section 7.3](#)).

Treatment with ALXN1007 should be held if any of the following occurs:

- If a subject experiences a **Grade 3 AE related** to study treatment; or

- If a subject experiences a **Grade 4 AE unrelated** to study treatment; or
- If a subject experiences an acute infection that is either not identified or controlled by the next scheduled infusion.

The PI should discuss the AE/acute infection as soon as possible with the Sponsor before resuming ALXN1007 treatment. Treatment with ALXN1007 may be resumed once the AE/acute infection has resolved, stabilized or returned to baseline. There should be a minimum of 4 days between ALXN1007 doses for subjects receiving weekly treatment. For subjects receiving twice weekly treatment, there should be a minimum of 2 days between ALXN1007 doses. If the recommended acceptable visit windows cannot be observed (see [Section 6.1.2](#)), the Sponsor Medical Monitor or designee must be contacted.

6.5. Criteria for Study Termination

6.5.1. End of Study for an Individual Patient

Study participation will end for each individual subject at Day 360. The last clinic visit will be at the Day 180 Visit, and the subject's survival status will be collected on Day 360 via telephone contact.

6.5.2. End of Study for All Patients

The study will end when all treated subjects have either completed the Day 360 data collection, the ET visit, or are documented as lost to follow-up.

6.5.3. Study Termination by Sponsor

The Sponsor may terminate this study at any time for any reason including, for example, clinical or administrative reasons.

6.5.4. Stopping Guidelines for Excessive Mortality

Mortality of 40% at Day 56 would be considered unexpected and an unacceptable number of excess deaths compared to the anticipated and historical rate of approximately 20% (data on file). Therefore, a stopping rule for Day 56 mortality will be applied after every 6 subjects are accrued. The study will be stopped at interim evaluation (t) if the number of deaths is $\geq X_t$, eg, if 4 or more deaths in the first 6 subjects or 6 or more deaths in the first 12 subjects, etc, as detailed in [Table 7](#) below. A 20% mortality rate, which is anticipated based on historical data, will have a 2.6% chance of triggering the stopping rule for mortality. If a mortality rate of 40% is observed, a 20% increase in mortality over the historical rate, there will be a 71.0% chance of triggering the stopping rule with 30 subjects.

Table 7: Cumulative Stopping Probabilities for Mortality Rates at Day 56

Evaluation (t)	Total N	X _t	Cumulative Probabilities of Stopping at Evaluation (t) with Observed Mortality Rates	
			0.20	0.40
1	6	4	1.7%	17.9%
2	12	6	1.9%	33.5%
3	18	8	1.6%	43.7%
4	24	10	1.3%	51.0%

Evaluation (t)	Total N	Xt	Cumulative Probabilities of Stopping at Evaluation (t) with Observed Mortality Rates	
			0.20	0.40
5	30	11	2.6%	71.0%

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Only subjects meeting the following criteria are eligible for study participation.

1. Subjects must be males or females age 18 years or older.
2. Subjects with Stage 1-4 (per the Modified Keystone Grading Schema) acute GVHD of the lower GI tract, without signs of chronic GVHD, at the time of diagnosis, which developed in the first 180 days following allogeneic hematopoietic cell transplantation (HCT) using bone marrow, peripheral blood or cord blood; or after pre-planned donor lymphocyte infusion.
3. Subjects are willing to undergo or must have had an endoscopy of the upper and/or lower GI tract and biopsy to confirm GI GVHD within 7 days of screening. Biopsy results are not needed to initiate treatment; however, if GI GVHD is not confirmed histologically, treatment with ALXN1007 will be discontinued.
4. Subjects must be receiving systemic corticosteroids.
5. Subjects with an absolute neutrophil count (ANC) $>500/\mu\text{L}$ at Screening.
6. Subjects and spouse/partner who are of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least 1 of which must be a barrier method) starting at Screening and continuing through the entire study (for at least 3 months after the last dose of ALXN1007 if study treatment is stopped early or subject withdraws consent). Highly effective contraception is defined as:
 - a. Established use of oral, injected or implanted hormonal methods of contraception.
 - b. Placement of an intrauterine device or intrauterine system.
 - c. Double barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (double barrier method will count as 2 forms of contraception).
7. Male subjects must not donate sperm during the Screening and Treatment Periods, and for at least 3 months after the last dose of ALXN1007.
8. Subjects are willing and able to give written informed consent and to comply with all study visits and procedures.

7.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria should not participate in this study.

1. Subjects with a body weight > 140 kg (for Cohorts dosing 20 mg/kg of ALXN1007 and higher only).
2. Subjects with signs and symptoms of chronic GVHD.
3. Subjects with an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening

physical signs or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection. (Subjects with a controlled infection receiving definitive therapy for 72 hours prior to enrollment [ie, Screening Visit/sign ICF] are eligible.)

4. Subjects who test positive for *C. difficile* from a sample collected up to 3 days prior to Screening/sign ICF.
5. Subjects known to be infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
6. Subjects with relapsed/persistent malignancy requiring rapid immune suppression withdrawal.
7. Subjects who received an unplanned (not part of the original transplant therapy plan) donor lymphocyte infusion.
8. Subjects who received previous systemic treatment for acute GVHD, except for a maximum of 3 days (72 hours) of 2 mg/kg methylprednisolone (or equivalent dose of prednisone).
9. Subjects who received any corticosteroid therapy (for indication other than GVHD) at doses >0.5 mg/kg/day methylprednisolone equivalence within 7 days prior to the onset of GVHD therapy.
10. Subjects with unresolved veno-occlusive disease of the liver defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction (renal, ascites).
11. Subjects known to have an uncontrolled thyroid disorder.
12. Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control for the duration of the study.
13. Subjects with creatinine clearance (CrCl) <40 mL/minute, as calculated by the Cockcroft-Gault formula (Cockcroft-Gault CrCl = $[140 - \text{age}] \times [\text{Wt in kg}] \times [0.85 \text{ if female}] / [72 \times \text{Cr}]$).
14. Subjects participating in any investigational drug trial, or with exposure to any other investigational agent, device and/or procedure, beginning at Screening and throughout the entire trial. Investigational drugs, devices and/or procedures must be discontinued upon enrolling (ie, Screening/sign ICF) into this study.
15. Subjects with any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, pose any additional risk for the subject, or confounds the assessments of the subject.
16. Subjects with prior exposure to ALXN1007 or known allergies, hypersensitivity or intolerance to ALXN1007 or its excipients.

7.3. Subject Withdrawal Criteria

The Investigator should notify the Sponsor and their site monitor of all study withdrawals as soon as possible.

Subjects may withdraw consent at any time. Every effort should be made to ensure subjects are willing to comply with study participation prior to conducting the screening procedures and the subject should be fully informed of the restrictions related to the change of concomitant medications during the study.

Investigators may choose to discontinue a subject's treatment because of an AE as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the subject's safety or well-being (safety, behavioral or administrative reasons).

Subjects should be permanently discontinued from ALXN1007 treatment if any of the following occur during the study:

- Serious infusion reaction (such as bronchospasm with wheezing or requiring ventilatory support or symptomatic hypotension, refer to [Section 9.5.1](#)) or serum sickness-like reactions manifesting 1 to 14 days after drug administration;
- A Grade 4 AE related to study treatment;
- Severe uncontrolled infection;
- Malignancy other than non-melanoma skin cancer or relapse of the disease for which the bone marrow transplant was performed;
- Meningococcal infection;
- Initiation of protocol prohibited medications;
- Pregnancy or planned pregnancy; or
- If the Alexion Medical Monitor and/or the Investigator deem it is in the best interest of the subject (eg, the subject is unable to tolerate the minimum ALXN1007 dose for the study; see [Section 6.4.1](#)).

Subjects who withdraw, or are withdrawn, from the study will not be replaced with a newly enrolled subject, with the exception of subjects who do not have biopsy confirmation of GI GVHD (see [Sections 6.1.5](#) and [7.3.2](#)).

7.3.1. Pregnancy and Breast Feeding

Reproduction and development studies with ALXN1007 have not been performed. ALXN1007 should not be administered to women who are pregnant or breast feeding (please refer to [Section 11.2.8](#) for additional information).

7.3.2. Handling of Withdrawals and Discontinuation from Study Treatment

The following procedures will be followed when a subject withdraws or is withdrawn from study participation:

- If the subject withdraws consent prior to the Day 180 visit, the ET visit should be performed for safety at the time of consent withdrawal (within 5 days), if subject allows.
- Subjects must continue antibiotic prophylaxis active against meningococcal infection for 6 weeks after the last dose of ALXN1007.

- The reason(s) for withdrawal will be recorded in the subject's source documents and the eCRF.

The following procedures will be followed when an investigator discontinues a subject from study treatment:

- In the event of early discontinuation from study treatment, subjects will be requested to return for the remainder of the scheduled study visits through the Day 180 visit.
- In the event that the biopsy results do not confirm GI GVHD, study treatment will be discontinued and an ET visit will be performed 6 weeks (+/- 5 days) after the last dose of ALXN1007 was received.
- If a subject discontinues study treatment due to an AE, the event will be followed until it is resolved or, in the opinion of the PI, the subject is determined to be medically stable. Subjects will be requested to return for the remainder of the scheduled study visits through the Day 180 visit.

For female subjects who become pregnant, please refer to [Section 7.3.1](#).

Subjects who fail to return for final assessments will be contacted by the site study staff members in an attempt to have the subjects comply with the protocol. As it is vital to obtain follow-up data, every effort must be made to undertake protocol-specified follow-up procedures. Follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the subject's last known address. Refer to the SOM for additional information.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

ALXN1007 is a humanized, anti C5a monoclonal antibody formulated to 10 mg/mL. ALXN1007 will be diluted with 0.9% sodium chloride for injection, United States Pharmacopeia (USP).

Further details on study drug description and preparation and administration instructions are provided in the current version of the ALXN1007 IB and the Pharmacy Manual.

8.2. Prior and Concomitant Medications and Therapies

Prior and concomitant medications and therapies will be recorded on the eCRF as follows:

- All medications and therapies from 7 days prior to signing the ICF through 30 days after the last dose of ALXN1007.
- All medications and therapies used to treat SAEs occurring through the Day 180 visit.

8.2.1. Hematopoietic Cell Transplantation Information (Including Conditioning Regimen)

Details on HCT performed will also be recorded on the eCRF as follows:

- All medications or treatments including, but not limited to, anti-thymocyte globulin (ATG), alemtuzumab, irradiation, and chemotherapy, received as part of the conditioning regimen in preparation for HCT.
- Additional information related to HCT including, but not limited to, transplant date, donor sex, donor cytomegalovirus (CMV) serostatus, donor type (eg, matched related, matched unrelated, mismatched), graft source (eg, bone marrow, peripheral blood, cord blood), manipulation of graft source (eg, T cell depletion), and post-transplant GVHD prophylaxis regimen.

8.2.2. Immunosuppressive Medications

GVHD prophylaxis should be based on institutional practice. Subjects developing acute GVHD during GVHD prophylaxis (ie, while on calcineurin inhibitors, sirolimus, etc) should have their prophylaxis medication continued during the study period unless discontinuation is clinically indicated (eg, for management of toxicity). Medications such as cyclosporine (CSA), tacrolimus or sirolimus (if used as GVHD prophylaxis when acute GVHD developed) should be continued at therapeutic doses and adjusted as necessary for renal, central nervous system or other toxicity using conventional management guidelines. The recommended therapeutic trough level of CSA is 200-400 ng/mL measured by whole blood high-performance liquid chromatography (HPLC), and institutional levels for other assays. The recommended therapeutic trough level is 5-15 ng/mL for tacrolimus and 3-12 ng/mL for sirolimus.

Subjects may be switched to an alternate immunosuppressive regimen as clinically indicated or based on side effects at the discretion of the Investigator. Dose adjustments for CSA should be

made based on serum bilirubin and creatinine. As applicable, drug levels of CSA, tacrolimus and sirolimus should be obtained at Baseline and on dosing on Days 7, 21, 35 and 49, as well as the ET visit. The timing of sample collection (eg, trough) should be appropriate for the drug being monitored and not coupled with the timing of administration of ALXN1007. This will be done for monitoring and dose adjustment per standard of care, or more frequently as needed. These immunosuppressants may result in a variety of drug interactions, which may require dose adjustments:

- **Cyclosporine (CSA):** Dosing should follow institutional practice with typical regimens consisting of initial IV CSA dose followed by tapering and then oral dosing with tapering.
- **Tacrolimus:** Dosing should follow institutional practice with typical regimens consisting of initial IV tacrolimus dose followed by tapering and then oral dosing with tapering.
- **Sirolimus:** Dosing should follow institutional practice with typical regimens consisting of an oral loading dose followed by tapering.
- **Mycophenolate mofetil:** Dosing should follow institutional practice with typical regimens consisting of oral dosing.
- **Intravenous immunoglobulin (IVIG):** Dosing should follow institutional practice.

8.2.3. Corticosteroids

All subjects treated in this trial will receive corticosteroids at a suggested dose equivalent to prednisone 2 mg/kg/day PO (orally) (or methylprednisolone 1.6 mg/kg/day IV) as therapy for acute GVHD with maximal doses determined per institutional guidelines and adjusted per ideal body weight (IBW) as suggested below. Corticosteroids may be given in divided doses. Subjects unable to tolerate oral prednisone (or equivalent) due to nausea, or for whom absorption is a concern, should be prescribed IV methylprednisolone. Corticosteroid tapering may follow local institutional practice. The corticosteroid dose should not be tapered to less than 0.25 mg/kg/day prednisone (or equivalent) (or 0.2 mg/kg/day methylprednisolone) prior to 28 days following corticosteroid initiation.

Suggested IBW Dosing Guidelines

- If subject weighs less than 100% of IBW, dosing is based on actual body weight.
- If subject weighs 100% to 120% of IBW, dosing is based on IBW.
- If subject weighs more than 120% of IBW, dosing is based on adjusted body weight per institutional guidelines.
- Maximum weight for dosing is 100 kg.

Corticosteroid dose should be rounded based on pill strength (for example, 5 or 10 mg for prednisone; 4 or 8 mg for methylprednisolone).

The following is a *suggested* prednisone taper for responders. Variations from the regimen suggested below are allowed based on the discretion of the Investigator.

Suggested Prednisone Taper for Responders:

- Days 1-5: 2 mg/kg/day of prednisone PO (or 1.6 mg/kg/day of methylprednisolone IV) divided once or twice/day.
- Days 6-10: 1.5 mg/kg/day of prednisone once daily.
- Days 11-15: 1 mg/kg/day of prednisone once daily.
- Days 16-20: 0.5 mg/kg/day of prednisone once daily.
- Days 21-28: 0.25 mg/kg/day of prednisone once daily.

Subjects should be tapered as tolerated to no less than 0.25 mg/kg/day (methylprednisolone 0.2 mg/kg/day) prior to 28 days following corticosteroid initiation; then tapered according to institutional guidelines with a goal to reach <0.2 mg/per/kg per day PO of prednisone or <0.16 mg/per/kg IV per day of methylprednisolone by Day 56.

8.2.4. Prevention of Infection and Prophylactic Antibiotics

Prophylactic antimicrobials to prevent bacterial, fungal and viral infections will be administered based on each institution's practice but must include agents directed against Herpes simplex virus, *Pneumocystis jiroveci*, and bacterial and fungal infections. A pre-emptive monitoring and treatment strategy for CMV is required.

Subjects must continue or begin antibiotic prophylaxis active against meningococcal infection prior to receiving the first dose of ALXN1007. Subjects already receiving empirical antibiotic prophylaxis for bacterial infections or therapeutic antibiotic treatment must be receiving an antibiotic throughout the treatment period and for 6 weeks after the last dose of ALXN1007 that is active against encapsulated organisms (including *N. meningitidis*) based on institutional guidelines. If subjects are receiving prophylactic, empirical or therapeutic antibiotic treatment with drugs that have activity against meningococcus (and pneumococcus), no additional antibiotic prophylaxis will be required during that treatment period.

8.2.5. Supportive Care

Subjects will receive treatment based on each center's standard of care practice with respect to supportive care. Nutritional practices with respect to diet and total parenteral nutrition will be instituted by each center's standard practice and recorded on the eCRF. Blood transfusion support and growth factors may be provided based on institutional practices and should be clearly recorded in the eCRF.

8.2.6. Cytotoxic, Biologic and Investigational Agents

Upon enrolling into this study, ie, Screening Visit/sign ICF, any investigational drugs, devices and/or procedures the subject may be receiving (or using) must be discontinued. Cytotoxic, biologic or investigational agents are not permitted throughout the study. These include, but are not limited to, ATG, Alemtuzumab, Rituximab, photopheresis, and Thalidomide.

8.3. Treatment Compliance

All instances of noncompliance and all significant protocol violations will be reported to the appropriate ethics committee per local regulations and reported to the Sponsor or representative.

The infusion of ALXN1007 into subjects will be under the supervision of the PI or designee to ensure that the subject receives the appropriate dose at the appropriate time points during the study and that adequate safety monitoring (both during and up to 2 hours after the infusion) occurs (see [Section 9.5.1](#)).

Subjects who fail to return for a scheduled visit within the accepted intervals must be contacted by the site study staff to determine the reason for missing the appointment. Instructions for handling of missing visits are provided in [Section 6.1.6](#).

8.4. Randomization and Blinding

This is an open-label non-randomized study.

Dosing cohort assignment must be documented in the subject's source documents at the investigational site and in the eCRF for the study. The Sponsor or designee will also maintain documentation of dosing cohort assignment for subjects enrolled in the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

ALXN1007 is a humanized, anti-C5a monoclonal antibody formulated at 10 mg/mL. The sterile formulation is supplied by the Sponsor in a single use 20 mL vial. Each vial contains a total extractable dose of 150 mg per vial. Refer to [Table 8](#) and the current IB for additional information.

Table 8: Study Drug

	Study Drug
Product Name	ALXN1007
Dosage Form	Concentrated solution for infusion
Unit Dose	150 mg
Nominal Fill Volume	15 mL
Route of Administration	Intravenous (IV) infusion
Physical Description	Clear, colorless solution practically free from particles in a 20 mL vial
Manufacturer	Alexion Pharmaceuticals, Inc.

9.2. Study Drug Packaging and Labeling

ALXN1007 is packaged in Type 1 borosilicate glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. The study drug will be supplied in a one vial per kit configuration.

Each kit will have a label describing the contents and a place for the pharmacist to record the subject study number and initials. Please refer to the ALXN1007 Pharmacy Manual to see an example kit label.

ALXN1007 will be released to each site upon receipt of all required essential documents based upon federal, state and local regulations.

9.3. Study Drug Storage

Upon arrival at the study site, the pharmacist should promptly remove ALXN1007 from the shipping cooler and store in refrigerated conditions at 2°C to 8°C (35 to 47°F) and protected from light. ALXN1007 must be stored in a secure, limited-access storage area and the temperature must be monitored daily.

The ALXN1007 drug product should be allowed to warm to room temperature prior to administration. The material must not be heated (for example, by using a microwave or other heat source) other than by ambient air temperature.

Please consult the ALXN1007 Pharmacy Manual for further information regarding the storage conditions and administration of reconstituted ALXN1007.

9.4. Study Drug Preparation

ALXN1007 is dosed on a mg/kg basis. The subject's dose of ALXN1007 will be further diluted into 0.9% sodium chloride solution for injection USP at the volume specified in the ALXN1007 Pharmacy Manual. Doses of ALXN1007 must only be prepared and dispensed by a Pharmacist or a medically qualified staff member. ALXN1007 is to be dispensed only to subjects enrolled (ie, signed ICF) and who are confirmed eligible for participation in this study. Once ALXN1007 is prepared for a subject, it can only be administered to that subject. ALXN1007 vials are for one time use only and any drug product remaining in the vial should not be used for another subject. Any drug remaining in the infusion tubing or sodium chloride 0.9% bag should not be used for another subject.

9.5. Administration

ALXN1007 should NOT be administered as an IV Push.

ALXN1007 solution in sodium chloride 0.9% will be administered to the subject using an IV tubing administration set via an infusion pump. Use of an in-line filter for infusion is recommended. For subjects receiving a 10 mg/kg ALXN1007 dose, IV infusions must be administered over 1 hour \pm 10 minutes. For subjects receiving a 20 mg/kg ALXN1007 dose, IV infusions must be administered over 2 hours \pm 10 minutes.

For subjects on a weekly dosing schedule, there should be a minimum of 4 days between ALXN1007 doses. For subjects on a twice weekly dosing schedule, there should be a minimum of 2 days between ALXN1007 doses. If the recommended acceptable windows cannot be observed, the Sponsor or its representative must be contacted prior to scheduling a visit.

Further details on ALXN1007 preparation and administration for doses being investigated in this study can be found in the Pharmacy Manual.

9.5.1. Management of Potential Drug Infusion Reactions

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. For this reason, subjects will be carefully observed during each infusion. Subjects will remain under observation for 2 hours after the infusion.

Subjects who develop AEs of rash, hives, itching and/or dysphagia of mild to moderate severity during their infusion of ALXN1007 may continue to be infused if deemed to be medically appropriate by the Investigator. Medical intervention may include, but is not limited to, slowing of the infusion rate (with or without treatment) or stopping the infusion, with a total infusion time not to exceed 3 hours. Any acute reaction should be treated according to standard medical practice depending upon clinical signs and symptoms. The AE and any associated concomitant medications must be captured in the subject's source document and eCRF.

Some subjects treated with IV infusions of monoclonal antibodies have experienced concurrent infusion-related reactions with signs or symptoms that can be classified as acute allergic reactions/hypersensitivity reactions or cytokine release syndrome. The signs and symptoms include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness,

hypotension, palpitations and somnolence. Anaphylaxis might occur at any time during an infusion and subjects will be monitored closely prior to and through 2 hours following the end of the infusion. In addition, the re-administration of some monoclonal antibodies has been associated with serum sickness-like reactions manifesting 1 to 14 days after drug administration. All AEs which may indicate an infusion related response will be graded according to criteria from the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Before any infusion is started, the treating physician and other appropriate personnel must make certain medication (adrenaline, inhaled beta agonists, antihistamines and corticosteroids) and other requirements to treat anaphylaxis are readily available. The infusion must be stopped immediately if \geq Grade 2 allergic/hypersensitivity reactions (including drug fever) or \geq Grade 3 cytokine release syndrome/acute infusion reaction occurs. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption of study drug.

Subjects experiencing a reaction during the administration of study drug should be treated according to institutional guidelines. For a Grade 1 or Grade 2 infusion-related reaction, the infusion should be stopped and medication with antihistamine (eg, with diphenhydramine 25 mg to 50 mg PO or equivalent), and acetaminophen (650 mg PO or equivalent) may be considered. If the signs and symptoms have resolved with the above medication(s), the infusion may be restarted. However, the subjects should be infused at a slower rate and be monitored closely for any signs and symptoms of infusion-related reactions during the remainder of the infusion. The study drug should be stopped if the infusion reaction recurs and subsequent doses may not be given. Subjects experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until the PI determines the subject is no longer at risk.

If an event of anaphylaxis occurs, according to the criteria in [Table 9](#), then subcutaneous epinephrine (1/1000, 0.3 to 0.5 mL or equivalent) should be considered. In the case of bronchospasm, inhaled beta agonist also should be considered. Subjects administered antihistamine for the treatment or prevention of infusion reactions should be given appropriate warnings about drowsiness and impairment of driving ability prior to discharge.

In the event of anaphylaxis no further doses of ALXN1007 will be given.

Table 9: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:	
1.	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), <u>AND</u> at least one of the following: <ol style="list-style-type: none"> Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2.	Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours): <ol style="list-style-type: none"> Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) Persistent GI symptoms (eg, crampy abdominal pain, vomiting)
3.	Reduced BP after exposure to known allergen for that subject (minutes to several hours): <ol style="list-style-type: none"> Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow ([Sampson, 2006](#))

Subjects who experience a severe reaction during administration of study drug resulting in discontinuation of study drug will have blood drawn for determination of drug concentration, antibodies to ALXN1007 and complement proteins (ie, C5, C5a, C5b9). Samples should be obtained within 3 hours of the onset of the reaction and 1 week following disappearance of all symptoms. Such subjects should undergo all scheduled safety evaluations required by the protocol.

9.6. Study Drug Accountability

When a drug shipment is received at the site, the pharmacist should verify the contents, sign and date the packing invoice provided with the shipment, and maintain the original for review by the study monitor. Accountability logs will be provided to assist the pharmacist in maintaining current and accurate inventory records covering receipt, dispensing and disposition of ALXN1007. During the study, the following information must be noted in the accountability log: batch number, patient number, assigned dosing cohort, dispensing information, and, if applicable, destruction and returns information. Sites should keep a running total of their drug supply. Empty vials and vials with residual materials should be kept for inspection and accountability by the study monitor prior to their destruction, or handled per local site pharmacy standard operating procedures for clinical investigational products. Refer to the Pharmacy Manual for detailed instructions on general receipt, storage, destruction, and return of study drug.

The study monitor will examine the inventory during the study. Additionally, the inventory records must be readily available and may be subject to regulatory authorities, the local regulatory agency or an independent auditor's inspection at any time.

9.7. Study Drug Handling and Disposal

At the completion of the study, in order to satisfy regulatory requirements regarding drug accountability, all remaining ALXN1007 inventory will be reconciled and retained or destroyed according to applicable provincial and federal regulations.

Please refer to the ALXN1007 Pharmacy Manual for further information.

10. EFFICACY ASSESSMENTS

10.1. Primary Efficacy Assessment: Overall Acute GVHD Response

The primary efficacy assessment is overall acute GVHD response at Day 28. Overall acute GVHD response is defined as improvement from diagnosis in any organ by at least 1 stage, without progression in any other organ and with no additional therapy (-ies) being administered. At every visit, subjects will be graded according to the Modified Keystone Grading Schema displayed in [Table 10](#) and [Appendix 1](#).

Table 10: Modified Keystone Grading Schema

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No Rash	Rash <25% BSA	25-50% BSA	>50% BSA	Bullae and desquamation
Lower GI Tract¹	<500 ml/day stool volume	500-1000 ml/day stool volume	1001-1500 ml/day stool volume	>1500 ml/day stool volume	Severe abdominal pain +/- ileus, frank blood or melena
Liver²	≤2 mg/dl	2.1-3 mg/dl	3.1-6 mg/dl	6.1-15 mg/dl	>15 mg/dl

10.2. Other Efficacy Assessments

The following additional efficacy assessments will also be performed.

10.2.1. Acute GI GVHD Response Criteria

Acute GI GVHD response will be assessed at every visit. The proportion of subjects with CR, PR, MR, NR and Progression will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the subject's acute GI GVHD Stage (see lower GI tract row of [Table 10](#)) at the time of diagnosis, prior to initiation of treatment with ALXN1007 and corticosteroids for management of acute GI GVHD. Response will be based on the following response definitions:

- **Complete Response (CR):** A Stage of 0 for the GVHD grading in the lower GI tract with no additional intervening therapy for their GVHD.
- **Partial Response (PR):** Improvement by at least 1 Stage in GI GVHD symptoms without progression in others with no additional intervening therapy for their GVHD.
- **Mixed Response (MR):** Improvement in lower GI tract with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- **Progression:** Deterioration in lower GI tract.
- **No Response (NR):** Absence of any improvement or progression as defined above. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5) will be classified as non-responders.

10.2.2. Response for All Organs Involved with Acute GVHD

Acute GVHD response will be assessed at every visit. The proportion of subjects with CR, PR, MR, Progression and NR for all organs involved with acute GVHD will be determined over time. Scoring of CR, PR, MR, Progression and NR will be in comparison to the subject's acute GVHD Stage (see [Table 10](#)) at the time of diagnosis, prior to initiation of treatment with ALXN1007 and corticosteroids for management of acute GI GVHD. Response will be based on the following response definitions:

- **Complete Response (CR):** A Stage of 0 for the GVHD grading in all evaluable organs with no additional intervening therapy for their GVHD.
- **Partial response (PR):** Improvement by at least 1 Stage in 1 or more organs involved with GVHD symptoms without progression in others with no additional intervening therapy.
- **Mixed response (MR):** Improvement in 1 or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- **Progression:** Deterioration in at least 1 organ without any improvement in others.
- **No response (NR):** Absence of any improvement or progression as defined. Subjects receiving secondary therapy (including need to re-escalate corticosteroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5) will be classified as non-responders.
- **Very Good Partial Response (VGPR)** will also be determined based on the criteria provided in [Appendix 2 \(Martin, 2009\)](#).

10.2.3. Treatment Failure

The proportion of treatment failures will be determined over time. The following will be considered as treatment failures:

- No response
- Progression
- Administration of additional systemic therapy for GVHD (or re-escalation of corticosteroid dose to ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5)
- Mortality

10.2.4. GVHD Flares

Flares are defined as any progression of acute GVHD through Day 86 after an initial response (ie, earlier CR or PR) that require re-escalation of corticosteroid dosing (ie, administration of ≥ 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] for at least 2 consecutive days starting on or after Day 5), or initiation of additional topical or systemic therapy for GVHD.

10.2.5. Discontinuation of Immunosuppressive Medications

Use of immunosuppressive medication will be recorded at every visit. Discontinuation of immunosuppression will be assessed over time. The date of discontinuation of corticosteroids will be recorded. In addition, dates for discontinuation of all other systemic immunosuppressive medications (including CSA, tacrolimus, sirolimus, etc) for treatment or prevention of acute GVHD will be captured.

10.2.6. Cumulative and Average Corticosteroid Dose

Use of corticosteroid medication will be recorded at every visit. Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each subject will be converted to mg/kg. The cumulative and average corticosteroid doses will be calculated over time.

10.2.7. Overall Survival

Overall survival will be computed up to Days 180 and 360.

10.2.8. Non-Relapse Mortality

At Days 180 and 360, non-relapse mortality due to any cause other than the underlying malignancy will be assessed.

Statistical analyses of the efficacy endpoints are summarized in [Section 13](#) and described in more detail in the Statistical Analysis Plan (SAP).

11. SAFETY ASSESSMENT

11.1. Safety Parameters

11.1.1. Demographics

At Screening, once the subject has provided informed consent, the following demographic data will be reviewed and recorded: subjects' initials, date of birth, race or ethnic origin, and sex.

11.1.2. Medical History

The subject's medical history will be recorded at Screening and will include, but not be limited to, the diagnosis for which HCT was performed, disease status at transplantation, CMV serostatus, date of acute GVHD onset, and organ involvement (eg, skin, visceral organs). Subjects will undergo a complete physical exam, vital sign measurements, 12-lead ECG, routine lab tests, and their AEs and concomitant medications and therapies will be reviewed.

An endoscopy of the upper and/or lower GI tract and biopsy will be done to confirm the diagnosis of GI GVHD (results are not needed to initiate treatment), and acute GVHD Stage will be determined based on the Modified Keystone Grading Schema ([Table 10](#) and [Appendix 1](#)).

11.1.3. Physical Examination

The subject will undergo a complete physical examination during Screening, Days 28, 56, 180 and the ET visit if a subject prematurely discontinues or is withdrawn from the study. The complete physical examination will include assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, musculoskeletal and general neurologic examination. For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at these visits.

11.1.4. Vital Signs

The subject's vital signs are to be measured at every visit. Vital signs will include assessments of systolic and diastolic blood pressure (BP), pulse, temperature and respiratory rate. Vital signs will be obtained after the subject has been supine or seated for at least 5 minutes. Ideally, each subject's BP should be measured using the same arm. Systolic and diastolic BPs will be documented in mmHg; temperature in degrees Celsius or degrees Fahrenheit; and heart rate in beats per minute (bpm).

11.1.5. Weight and Height

The subject's height will be measured at Screening only, but weight will be measured at Screening then at periodic study visits through Day 180, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study. [Table 3](#) provides a summary of required assessments by visit for subjects on a once weekly ALXN1007 dosing schedule (for subjects receiving a total weekly dose of 20 mg/kg or less). [Table 4](#) provides a summary of required assessments by visit for subjects on a twice weekly ALXN1007 dosing schedule (for subjects receiving total weekly doses greater than 20 mg/kg). Body weight will be measured in kilograms or pounds. Height will be measured in centimeters or inches.

11.1.6. Electrocardiogram

A 12-lead ECG single measurement will be conducted at Baseline, Days 28, 56 and 180, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study. The ECGs performed at Baseline and Day 28 are to be performed pre-dose and at the end of the infusion.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the eCRF. For any clinically significant abnormal ECG results, the Investigator must contact the Sponsor's Medical Monitor to discuss the subject's continued eligibility to participate in this protocol.

11.1.7. Laboratory Assessments

Subjects will have blood samples collected for routine laboratory tests that include: analysis of chemistry panel, coagulation panel, and CBC with differential and platelets at every study visit ([Appendix 3](#)).

Urinalysis will be conducted at Screening, Baseline, Days 28, 56 and 180, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study.

Local labs may be used to assess ANC, *C. difficile*, serum (or urine) pregnancy, and CrCl.

For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at Baseline (if more than 24 hours from the Screening pregnancy test) and Days 7, 14, 21, 28, 35, 42, 49, 56, 86 and 180, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study. At the Investigator's discretion, serum pregnancy tests may be done in place of urine pregnancy tests.

Blood samples for creatine phosphokinase (CPK) and thyroid function tests (thyroid peroxidase antibody [TPO], thyroid-stimulating hormone [TSH], and free thyroxine [FT-4]) will be collected at Baseline and on Days 7, 28, 56, 86 and 180, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study.

As applicable, levels of CSA, tacrolimus and/or sirolimus will be determined at Baseline and on Days 7, 21, 35 and 49, as well as at the ET visit if a subject prematurely discontinues or is withdrawn from the study. The timing of sample collection (eg, trough) should be appropriate for the drug being monitored and not coupled with the timing of administration of ALXN1007.

11.1.8. Immunogenicity Assessments

Blood samples will be collected to test for both binding and neutralizing antibodies to ALXN1007 in plasma prior to dosing at Baseline, Days 7 and 28; and at Days 56, 86 and 180 or the ET visit if a subject prematurely discontinues or is withdrawn from the study. If tested positive on Day 180 or the ET visit, the test may be repeated on a 3-month basis until it is negative or stabilizes, based on the measured titer and the safety assessments in that specific subject. Further characterization of antibody responses may be conducted as appropriate, including those associated with binding and neutralizing antibodies, to PK/PD, safety and activity of ALXN1007.

Refer to the Laboratory Manual for more information.

11.2. Adverse Event Management

The Investigator is responsible for detecting, assessing, documenting and reporting all AEs.

All AEs will be recorded from the signing of informed consent until 30 days after the last dose of ALXN1007. All SAEs will be recorded from signing of informed consent through the Day 180 visit. In addition, any notifications of death as a result of the Day 360 survival follow-up will also be recorded; the cause of death or event leading to death should be reported as an SAE.

(Note: There is no time limit for reporting SAEs that are considered causally related.)

All observed or volunteered AEs, regardless of causal relationship, must be reported and recorded in the eCRF. AEs reported by the subject, legal guardian, and/or identified in response to an open-ended question from study personnel, or revealed by observation, physical examination or other study procedures must be collected and recorded.

11.2.1. Definition of an Adverse Event

An AE is defined as any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the medicinal product or procedure that occurs during the course of the clinical trial.

Exacerbations of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition are all to be considered AEs.

Abnormal test findings may be considered AEs or SAEs. If an abnormal laboratory value is identified, Investigators are strongly encouraged to report a diagnosis, or a sign or symptom rather than an isolated abnormal laboratory value. An abnormal test finding should be documented as an AE if **any one of the following conditions** is met:

- Is associated with a sign or symptom;
- Requires additional diagnostic testing (repeat tests are not considered additional testing);
- Requires a medical or surgical intervention;
- Leads to a change in study dosing outside of the protocol defined dosing or discontinuation from the trial;
- Requires significant additional treatment;
- Does not meet any of the conditions above; however, the Investigator or Sponsor considers the result as clinically significant or meeting the definition of an AE.

This definition also includes the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;

- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

An AE does not necessarily include the following:

- Medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion, etc); the condition that leads to the procedure is the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder);
- Pre-existing diseases or conditions present or detected prior to the screening evaluation that do not worsen;
- Pre-existing comorbid conditions or progression of the disease being investigated requiring additional testing or treatment (however, if the outcome is fatal it should be reported as an SAE);
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery if planned prior to the start of the study, social and/or convenience admissions, etc).

11.2.2. Definition of a Serious Adverse Event

Any AE that fulfills any one of the criteria listed below must be recorded as a serious adverse event (SAE).

An SAE (experience) or reaction is described as any untoward medical occurrence that at any dose:

1. Results in death
2. Is life-threatening (*The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*)
3. Requires hospitalization or prolongation of hospitalization (*Hospitalization requires inpatient or prolongation of an existing hospitalization. AEs that are associated with hospitalization or prolongation of hospitalization are considered SAEs*). Hospitalization does not necessarily include the following:
 - Rehabilitation/hospice/nursing facility
 - Emergency Room visit less than 24 hours
 - Elective or pre-planned admission/surgery
 - Protocol-specified admission
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect

6. Is an Important Medical Event (*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. 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 dependency or drug abuse.*)

Severity and seriousness must be differentiated. Severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE as described above.

11.2.3. Severity Assessment

An assessment of grading (severity) scale will be made by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. If the AE term is not described in the scales, the AE severity shall be reported according to the following:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life threatening
- Grade 5: Death due to an AE

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode if the severity of the intermittent event changes.

11.2.4. Causality Assessment

An Investigator causality assessment must be provided for all AEs (both non-serious and serious). This assessment must be recorded on the eCRF and any additional forms as appropriate. The definitions for the causality assessments are as follows:

- Not related (unrelated): This relationship suggests that there is no association between the Investigational Product and the reported event.
- Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than the Investigational Product but attribution cannot be made with absolute certainty and a relationship between the Investigational Product and AE cannot be excluded with complete confidence.
- Possibly related: This relationship suggests that treatment with the Investigational Product may have caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the Investigational Product, but could also have been produced by other factors.

- Probably related: This relationship suggests that a reasonable temporal sequence of the event with the Investigational Product administration exists and the likely association of the event with the Investigational Product. This will be based upon the known pharmacological action of the Investigational Product, known or previously reported adverse reactions to the Investigational Product or class of drugs, or judgment based on the PI's clinical experience.
- Definitely related: Temporal relationship to the Investigational Product. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain event, corresponds with the known pharmaceutical profile, improvement on discontinuation, re-appearance on re-challenge.

11.2.5. Outcome

For all AEs, regardless of casual relationship, the Investigator must follow-up on the outcome of the event until the event or sequelae either resolve or stabilize.

If a subject experiences an SAE with an outcome of death:

- The SAE resulting in death should have an outcome documented as death/fatal with an end date being the date of death.
- If the subject had additional AE/SAEs that were ongoing at the time of death, these events would be documented as ongoing with no end date.
- Only 1 event should have an outcome of death/fatal unless an autopsy report or Investigator states otherwise.

11.2.6. Recording of Adverse Events

All observed or volunteered AEs, regardless of causal relationship, must be reported as described in [Section 11.2.4](#).

For all AEs the Investigator must obtain adequate information for the following:

1. Determine the outcome of the AE;
2. Determine if the event meets criteria for an SAE;
3. Assess the severity of the AE; and
4. Determine the causality of the AE.

AEs must be documented in clear, unambiguous medical terminology. Study personnel are advised not to use abbreviations or acronyms.

For each AE, record only the diagnosis on the AE page of the eCRF; do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available, record each sign and symptom as an AE; when a diagnosis becomes available, study personnel are to update the source document and the AE page of the eCRF with the relevant diagnosis only.

For medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion, etc); the condition/diagnosis that leads to the procedure should be recorded as the AE (eg, laparoscopic cholecystectomy is the procedure or treatment for an SAE of necrotic gall bladder).

All AEs that later increase in frequency and or severity (medical and scientific judgment should be exercised by the Investigator) will be considered new AEs and will be recorded on a new line in the source and the eCRF.

Withdrawal due to an AE or SAE event must be clearly differentiated from withdrawal due to other reasons.

11.2.7. Reporting of Serious Adverse Event(s) to Sponsor

All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. All SAEs must be reported to the Sponsor or its representative immediately or within 24 hours of the Investigator or their staff becoming aware of the event regardless of the presumed relationship to the study drug.

The Investigator must verify the accuracy of the information recorded on the SAE pages of the SAE report with the corresponding source documents, and submit the SAE report electronically via the Rave Safety Gateway as applicable. If the eCRF is not available, the Investigator must complete the Contingency SAE paper report, sign and date SAE pages and send a copy via e-mail or fax to the contact information provided below:

Email: PPD [REDACTED]

Fax: PPD [REDACTED]

When further information becomes available, the SAE report should be updated with the new information and reported immediately via the same method as the initial report. Additional follow-up information, if required or available, should be entered into the eCRF and sent to the Sponsor or designee within 24 hours of the Investigator or study site staff becoming aware of this additional information. These reporting timelines should be followed for all initial and follow-up SAEs.

For all SAEs the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious event(s)
- Outcome of the serious event(s)
- Medical records and laboratory/diagnostic information

11.2.8. Exposure During Pregnancy and Lactation

Pregnancy data will be collected during this trial for all subjects.

For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and followed. Exposure during pregnancy, also called exposure *in utero* (EIU), can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

If a subject within this trial or a subject's partner becomes or is found pregnant while treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/ Breast Feeding Form" to the Sponsor or its delegate via the same method as SAE reporting.

The subject should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the subject discontinued study drug or discontinued from the trial. When the outcome of the pregnancy becomes known, the form should be updated and returned to the Sponsor or its delegate. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the Investigational Product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death or congenital anomaly would meet criteria of an SAE and thus, should be reported as an SAE. Elective abortions without complications should not be handled as AEs.

Exposure of an infant to an Alexion product during breast feeding should also be reported on the "Pregnancy Reporting and Outcome / Breast Feeding Form", and any AEs an infant may experience following breast feeding must be reported to the Sponsor or its delegate.

11.2.9. Reporting Requirements

This protocol will use the current Investigators Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor from the Reference Safety Document.

11.2.9.1. Sponsor

The Sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria as per regional and local regulations.

11.2.9.2. Investigator

Investigator must fulfill all local regulatory obligations required for study investigators. It is the PI's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC (if local) of these additional SAEs according to local regulations.

12. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

12.1. Blood Sample Collection

Table 5 summarizes blood sample collection time points for PK and PD assessments for the study based on frequency of ALXN1007 dosing (ie, weekly or twice weekly). At the time of sample collection, actual blood sampling dates and times must be recorded.

The central laboratory will supply established or generally acknowledged methods and shipping instructions.

12.2. Pharmacokinetic and Pharmacodynamic Sample Analysis

Blood samples will be collected and plasma assayed for ALXN1007 concentration. The actual blood sampling times will be used in calculations for PK parameter estimation.

For those patients entering this study less than 4 weeks after receiving another investigational drug, baseline plasma concentrations of the other investigational drug may be assayed. No additional samples will be collected; aliquots from the baseline ALXN1007 PK samples will be used for this assessment if performed.

The PD effects of ALXN1007 will be determined by assessing plasma concentrations of biomarkers, which may include C3, C4, C5a, C5 and sC5b-9. Serum terminal complement activity may be measured by the cRBC hemolysis and Wieslab™ CCP assays.

12.3. Exploratory Biomarker Assessments

Biopsy specimens may be evaluated for complement deposition or for immune cell characterization by immunohistochemistry (IHC).

Blood samples will be collected prior to dosing at Baseline, Days 7, 28 and 49; and at Day 86 and Day 180 (or at the ET visit, if a subject prematurely discontinues or is withdrawn from the study). These samples may be used to characterize changes from Baseline in the levels of biomarkers associated with alternative complement pathways activation or of mechanistic biomarkers thought to be associated with the development of GI GVHD. Pharmacodynamic effects on complement may include, but are not limited to, assessments of plasma Ba and Bb. Additional biomarkers associated with GVHD and downstream effects of complement activation may include, but are not limited to, TNFR1, ST2 and REG3a. Additional exploratory analyses, including anti-factor H antibody titer, may be performed.

Detailed instructions for sample collection, preparation and handling will be supplied in a Laboratory Manual.

12.4. Optional Pharmacogenetic Assessment

For subjects who sign an additional optional consent, a blood sample will be drawn at Baseline for pharmacogenetic (PGx) research to better characterize genetic variability that may affect efficacy or safety endpoints, or the GI GVHD disease process, such as mutations in genes that

regulate the complement pathway. These samples may be used for future exploratory bioanalytical or PGx tests to better understand potential complement-associated genetic mutations as well as the pathogenesis, course, and outcome of GI GVHD.

If permitted, according to local regulations, blood may be used for additional GI GVHD or complement associated genetic analysis from subjects who have consented to this optional component of the clinical study. Refusal to participate will not result in ineligibility for the main part of the clinical study. Blood or DNA samples may be used for analysis of candidate genes believed to be associated with GI GVHD or complement pathways in order to develop improved diagnostic or therapeutic methods. Blood or DNA samples may also be stored for future testing of additional genes that, at a later date, are discovered or found to be associated with GI GVHD, complement signaling pathways, or with the PK or PD of ALXN1007. Additional genotyping will only be performed if it is believed or hypothesized by the Sponsor that such genetic analysis might help clarify issues with the clinical data. No other genetic analysis will be performed and the stored samples will not be used for any other purpose.

Additional information regarding the stored samples is outlined in [Section 17.2](#).

The IRB/IEC and, where required, the applicable regulatory agency, must approve the PGx assessments before these can be conducted at the study site. The approval(s) must be in writing and clearly specify approval of the PGx assessments. In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate that approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When the optional PGx assessments are not approved, this will be clearly indicated in the approval for the clinical study.

13. STATISTICS

This section provides a summary of the statistical analyses that will be completed for this study. Additional details for the statistical analyses will be described in detail in the SAP.

13.1. General Considerations

All data collected during the study will be presented in summary tables, figures and/or by-subject data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using percentages and frequency distributions. Graphical displays will be presented as appropriate.

A stopping rule for excess mortality at Day 56 will be applied after every 6 subjects are accrued. The stopping guidelines for excess mortality will be applied as described in [Section 6.5.4](#).

A brief interim safety report summarizing AEs and SAEs will be generated when the first six subjects have completed the day 86 visit. Additionally, an informal interim analysis will occur after all subjects have completed Day 56, which is the end of the treatment period. This interim analysis will summarize the primary endpoint and other efficacy endpoints with the exception of overall survival and non-relapse mortality. In terms of safety, all treatment emergent adverse events (TEAEs), infections, neutropenia and infusion reactions will be summarized. The interim analyses will also summarize PK and PD results. Additional informal interim analyses may be conducted based on regulatory requests and/or Sponsor discretion. A final analysis will be conducted at study completion.

Efficacy and safety analyses will be performed using SAS for Windows, Version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

No formal hypothesis testing will be performed. Efficacy data will be analyzed using descriptive statistics. All analysis tabulations will be presented by dose across the full range of doses actually examined in the study.

13.2. Determination of Sample Size

Up to 36 subjects confirmed by biopsy to have acute GI GVHD will be enrolled in this study. This sample size is felt to be sufficient for assessment of safety, tolerability, PK/PD, and efficacy of ALXN1007 at doses ranging from 10 mg/kg per week up to 40 mg/kg per week in patients with acute GI GVHD.

13.3. Analysis Population

Safety analyses will be performed on the Safety Set and on the modified Safety Set, as specified in the SAP. The Safety Set is defined as all subjects who receive at least 1 dose of ALXN1007. The modified Safety Set is defined as all subjects who receive at least 1 dose of ALXN1007 and for whom GI GVHD is confirmed through biopsy. PK and PD analyses will be performed on all subjects who receive at least 1 dose of ALXN1007 and who have evaluable PK and PD data.

Efficacy analyses will be performed on the modified Full Analysis Set (mFAS) as well as on a Per Protocol (PP) set. The mFAS will include all subjects who receive at least 1 dose of

ALXN1007 and for whom GI GVHD is confirmed through biopsy. The PP set is a subset of the mFAS and will include all subjects who have no major protocol deviation(s) that might potentially affect efficacy. The PP set will be fully described in the SAP, and subjects identified prior to database lock.

13.4. Demographics and Baseline Characteristics

All demographic, baseline characteristics and medical history data will be summarized using the following sets: mFAS, PP and Safety Populations. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (mean, median, SD, and minimum and maximum).

13.5. Subject Disposition and Treatment Compliance

The number of subjects screened, treated and included in the safety and efficacy analysis sets will be tabulated by counts and percentage of subjects. Reasons for any subject withdrawals will be provided.

Treatment compliance with ALXN1007 will be presented for all subjects.

13.6. Prior and Concomitant Medications and Therapies and Hematopoietic Cell Transplantation Information

Prior and concomitant medications and therapies will be summarized using the Safety Set and the modified Safety Set. Prior medications are defined as medications taken prior to the first dose of ALXN1007. Concomitant medications are defined as medications taken after the first dose of ALXN1007.

Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. Prednisone doses for each subject will be converted to mg/kg. The cumulative and average corticosteroid doses will be calculated through Days 28, 56, 86 and 180.

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug). Medication summaries will be presented by WHODrug Anatomical Therapeutic Chemical (ATC) and by WHODrug generic name.

All HCT information collected, including the conditioning regimen received in preparation for HCT and post-transplant GVHD prophylaxis regimen, will also be summarized and listings provided.

13.7. Efficacy Analyses

Efficacy will be performed on the mFAS and the PP sets, as described in the SAP.

13.7.1. Overall Acute GVHD Response Rate

The proportion of subjects with overall response will be summarized by visit and 95% CIs will be calculated. Subjects who discontinue from the study early will be imputed as having no response.

13.7.2. Acute GI GVHD Response Criteria

Acute GI GVHD response criteria will be based on the proportion of subjects with CR, PR, MR, NR and Progression and will be summarized by visit along with 95% CIs.

Subjects who discontinue from the study early will be imputed as having no response.

13.7.3. Acute GVHD Response Criteria (All Organs)

Response for all organs involved with acute GVHD will be based on the proportion of subjects with CR, PR, MR, NR and Progression and will be summarized at Days 14, 28 and 56. The proportion of subjects with VGPR will be summarized at Days 14, 28 and 56, and 95% CIs will be calculated.

Subjects who discontinue from the study early will be imputed as having no response.

13.7.4. Treatment Failures

The proportion of subjects who meet the treatment failure criteria will be summarized at Days 14, 28 and 56 along with 95% CIs. Subjects who discontinue from the study early will be considered treatment failures.

13.7.5. Overall Survival

Overall survival will be summarized using date of first study treatment with ALXN1007 up to Days 180 and 360 via the use of the Kaplan-Meier method, and 95% CIs will be calculated.

Subjects who are still alive as of the last known follow-up will be right censored as of the date of last subject contact.

13.7.6. Acute GVHD Flares

Cumulative incidence of acute GVHD flares using date of first study treatment with ALXN1007 (Baseline) through Day 86 will be estimated using competing risk survival analysis methods to account for death as a competing risk. Point estimates and 95% CIs will be provided. Subjects who do not experience acute GVHD flares will be right censored as of the date of last subject contact.

13.7.7. Discontinuation of Immunosuppressive Medication

Cumulative incidence of discontinuation of all immunosuppression by Days 28, 56, 86 and 180 post-first study treatment with ALXN1007 will be analyzed using similar methods as described above for acute GVHD flares with death as a competing risk.

13.7.8. Non-Relapse Mortality

Cumulative incidence of non-relapse mortality at Days 180 and 360 post-first study treatment with ALXN1007 will be analyzed using similar methods as described above for acute GVHD flares with relapse as a competing risk.

13.8. Safety Analyses

Safety assessments will consist of summarizing all AEs, SAEs, infections and laboratory values including: chemistry panel, coagulation panel, CBC with differential, thyroid function testing and urinalysis results. Changes from Baseline in vital signs and laboratory assessments will be summarized. Shifts from Baseline in laboratory assessments, as well as physical examination findings, will be summarized for the different time points. All safety analyses will be performed on the Safety Set and the modified Safety Set.

13.8.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.1 or higher).

AEs occurring from the signing of informed consent and prior to the initiation of ALXN1007 treatment (pre-treatment AEs) will be summarized.

Treatment-emergent AEs are AEs with onset after the start of ALXN1007 treatment. TEAEs will be summarized by incidence, Preferred Term, System Organ Class (SOC), seriousness, severity and relationship to treatment.

All AEs, including infections, will be summarized by both event counts and subject counts. For subject counts, if a subject has more than 1 occurrence of an AE for a specific preferred term or SOC, the subject will be counted only once for that preferred term or SOC. The most severe occurrence of an AE as well as the most extreme relationship of the AE will be indicated in cases of multiple occurrences of the same AE.

13.8.2. Laboratory Parameters

Laboratory assessments (chemistry panel, coagulation panel, CBC with differential, thyroid function testing [TPO, TSH, FT-4] and urinalysis) will be summarized by visit. Frequency distribution of abnormal clinical laboratory values will be provided by visit.

13.8.3. Vital Signs, Electrocardiograms, Antibodies to ALXN1007

Vital signs (systolic and diastolic BP, temperature, heart rate, and respiratory rate) and changes from Baseline in vital signs will be summarized by visit. The number and percentage of subjects with ECG findings will be summarized by visit. If a sufficient number of subjects show positive antibody results, the proportion of subjects with antibodies to ALXN1007 post-treatment will be summarized.

13.9. Pharmacokinetic Analyses

PK samples will be assayed for ALXN1007 concentration at Baseline and at the study visits (and time points) outlined in [Table 5](#).

Graphs of plasma ALXN1007 concentration time profiles for individual subjects and for means will be provided. Non-compartmental PK methods will be used to estimate PK parameters of interest (eg, C_{max} , t_{max} , AUC, etc). Actual dosing and sampling times will be used for all calculations. Descriptive statistics will be calculated for PK parameters and plasma concentration data at each sampling time, as appropriate.

Additional model-based exploratory analyses may be performed:

- To explore ALXN1007 PK in healthy (SAD [C11-002] and MAD [ALXN1007-US-HV-102]) and GI GVHD subjects.
- To develop a preliminary population PK model of ALXN1007 in healthy and GI GVHD subjects.
- To explore subject demographics and characteristics predictive of the PK variability of ALXN1007.

13.10. Pharmacodynamic and Exploratory Biomarker Analyses

Summary tabulations of mean, SD, median, minimum and maximum biomarker values will be presented. The relationship between changes in PD biomarkers, exploratory biomarkers and the effects of ALXN1007 treatment outcome will be evaluated.

13.10.1. Exploratory Exposure-Response Analyses

The relationship between plasma ALXN1007 concentration and the key PD and exploratory biomarkers will be assessed by graphical display. Additional model-based exploratory analyses may be performed:

- To explore the PD effects of ALXN1007 on C5a, C5 and terminal complement activity.
- To develop preliminary population PK/PD models of ALXN1007 in humans.
- To conduct an exploratory graphical evaluation to characterize the PK/PD relationships between ALXN1007 exposure and other biomarkers.

Development of these preliminary models may allow simulation based exploration of dose regimens for future studies, as well as determination of the concentration needed to provide target inhibition in the subject population. Development of these models may also provide exposure metrics for correlation of ALXN1007 exposure with safety events (if any). Early development of a PK/PD model can also facilitate optimization of sampling schedule in future studies, potentially reducing sampling load.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor or representative and the Investigator.

During the study, a monitor from the Sponsor or its representatives will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs and that ALXN1007 accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subjects' medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor or its delegate and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Alexion audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board/Independent Ethics Committee

The PI or Sponsor designee, depending on the country requirements, must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials that have been submitted and approved by the IRB/IEC for this study, including the subject informed consent form (ICF) and recruitment materials, must be maintained by the Investigator and made available for inspection.

14.4. Data Monitoring Committee

An independent DMC will be established for the study. The DMC will be responsible for conducting interim monitoring of safety data throughout the treatment period of the study. In addition, for Cohort 2 (the 20 mg/kg QW dosing regimen), Cohort 3 (the 20 mg/kg twice weekly dosing regimen) and any additional dosing cohorts exploring a higher dose than Cohort 1 (ie, 10 mg/kg per week), after the first 3 subjects have completed the Day 28 procedures and assessments (ie, received all protocol prescribed ALXN1007 doses through Day 28), the DMC will convene to review aggregate safety and tolerability (as well as any available PK/PD) data and recommend that the dose be escalated (as applicable), continued within the cohort, or decreased to the previous dose level or to a dose between the planned dose levels. Final dosing decisions will be made by the Sponsor, in consultation with the DMC, based on safety, tolerability and any available PK/PD data.

At the discretion of the Sponsor, and in consultation with the DMC, other dosing cohorts (not to exceed a total dose of 40 mg/kg/per week for 8 weeks) may also be explored based on cumulating safety and tolerability data as well as any PK/PD data that may be available.

The DMC will include at least 1 physician who is an expert in transplant infectious diseases, one physician who is a hematologist/oncologist with expertise in management of GVHD and one statistician, none of whom is affiliated with the Sponsor.

A separate DMC Charter will document all DMC procedures and processes for the study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please refer to [Section 14.2](#) for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit a copy of the written approval to the Sponsor or its designee before he or she can enroll any subject into the study.

The PI, or Sponsor/designee depending on the country requirements, is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with ALXN1007. The Sponsor or its designee will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

16.3. Written Informed Consent

The PI(s) at each study site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, ALXN1007 stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Pharmacodynamic, Pharmacogenetic and Exploratory Biomarker Biological Samples

If a subject has provided consent for long-term storage of biological samples, and if permitted by local regulatory authorities, any remaining biological samples will be stored at a central location or Alexion laboratory for a maximum of 15 years after the last subject's last study visit or longer, if permitted by regulatory authorities. The stored samples will not be used for any purpose other than as outlined in this protocol. The biological samples and other clinical study data for analysis in this study will be single coded for de-identification. The link between the subject enrollment number and any bioanalytical or genetic results (if authorized) will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant samples for analysis, facilitate correlation of biochemical or genetic results with clinical data, allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analyzed.

17.3. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor, its designee or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records. The PI must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

18. PUBLICATION POLICY

The terms for publication are outlined in the Clinical Study Agreement, Statement of Agreement or the Master Clinical Study Agreement. Refer to these documents for further details and information.

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APPENDIX 1. MODIFIED KEYSTONE GRADING SCHEMA

Modified Keystone Grading Schema

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No Rash	Rash <25% BSA	25-50% BSA	>50% BSA	Bullae and desquamation
Lower GI Tract ¹	<500 ml/day stool volume	500- 1000 ml/day stool volume	1001- 1500 ml/day stool volume	>1500 ml/ day stool volume	Severe abdominal pain +/- ileus, frank blood or melena
Liver ²	≤2 mg/dl	2.1-3 mg/dl	3.1-6 mg/dl	6.1-15 mg/dl	>15 mg/dl

Abbreviations: BSA = body surface area; GI = gastrointestinal ([Przepiorka, 1995](#))

¹ Lower GI tract assessment consists of determination of stool volume over a 24-hour period. Detailed instructions for determining stool volume can be found in the Study Operations Manual (SOM) for the study.

² Values presented for each stage are bilirubin level.

APPENDIX 2. VERY GOOD PARTIAL RESPONSE (VGPR) CRITERIA FOR ACUTE GVHD (MARTIN, 2009)

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 the value at diagnosis

Gut

- Tolerating food or enteral feeding
- Predominantly formed stools
- No overt gastrointestinal bleeding or abdominal cramping
- No more than occasional nausea or vomiting

APPENDIX 3. CLINICAL LABORATORY TESTS

<p>Chemistry Panel</p> <ul style="list-style-type: none"> Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Total bilirubin Albumin Total protein Uric acid <p>Complete Blood Count (CBC) with Differential</p> <ul style="list-style-type: none"> White blood cell (WBC) count WBC differential Red blood cell (RBC) count RBC mean corpuscular volume (MCV) RBC distribution width Hemoglobin Hematocrit Platelet count 	<p>Urinalysis</p> <ul style="list-style-type: none"> Appearance Specific gravity pH Protein Blood Glucose Ketone Bilirubin Urobilinogen Nitrite <p>Coagulation Panel</p> <ul style="list-style-type: none"> Prothrombin time (PT) Partial thromboplastin time (PTT) <p>Thyroid Function Tests</p> <ul style="list-style-type: none"> Thyroid-stimulating hormone (TSH) Free Thyroxine (FT-4) Thyroid Peroxidase Antibody (TPO) <p>Creatine Phosphokinase (CPK)</p> <p>Pregnancy test (Human Chorionic Gonadotropin)</p> <p><i>Clostridium difficile</i> culture (stool sample)</p>
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