

**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**

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Alexion Pharmaceuticals, Inc.



## STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1007-GIGVHD-201

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

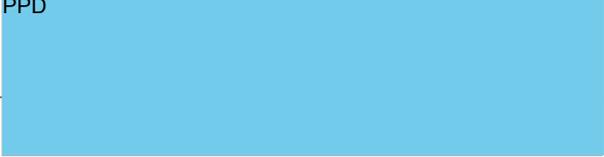
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## 1. APPROVAL SIGNATURES

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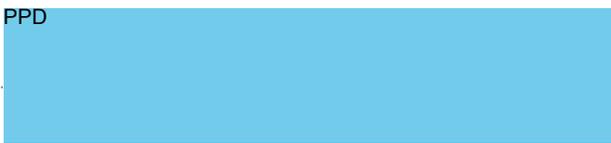
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### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

**Table 1. Abbreviations and acronyms**

<b>Abbreviation or acronym</b>	<b>Explanation</b>
Ab	Antibody
AChR	Acetylcholine receptor
AE	Adverse event
BP	Blood Pressure
C5	Complement protein 5
cm	Centimeters
C <sub>MAX</sub>	Maximal concentration
C <sub>MIN</sub>	Minimal concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HAHA	Human Anti-human Antibody
HR	Heart Rate
IP	Investigational Product
IST	Immunosuppressant Therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
LOCF	Last Observation Carried Forward
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol Population
PT	Preferred Term (MedDRA)
PTAEs	Pre-Treatment Adverse Events
RR	Respiration Rate
SAS®	Statistical Analysis Software®
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class (MedDRA)
TEAEs	Treatment-Emergent Adverse Events
WHODrug	World Health Organization Drug Dictionary
GVHD	Graft Versus Host Disease
GI-GVHD	Gastro-Intestinal Graft Versus Host Disease
CR	Complete Response
PR	Partial Response
NR	No Response
MR	Mixed Response
VGPR	Very Good Partial Response

## **4. Description of the Protocol**

ALXN1007-GIGVHD-201 is a phase 2a proof of concept study of ALXN1007 in subjects with newly diagnosed acute graft-versus-host disease (GVHD) involving the lower gastrointestinal (GI) tract (GI GVHD). This study will investigate whether targeting complement through C5a inhibition with ALXN1007 may improve outcomes for subjects with newly diagnosed acute GI GVHD. Following up to a 3-day screening period, eligible subjects will receive 10 mg/kg ALXN1007 administered intravenously (IV) once a week for 8 weeks (Cohort 1), OR 20 mg/kg once a week for 8 weeks (Cohort 2), OR 20 mg/kg twice a week for 8 weeks (Cohort 3). Subjects will be followed for efficacy and safety through Day 180 and subject survival status will be collected at Day 360. Approximately 30 subjects confirmed by biopsy to have GI GVHD will be evaluated during this study.

The objectives of this trial are to evaluate the safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of IV ALXN1007 in subjects with acute GI GVHD of the lower GI tract.

### **4.1. Changes from Analyses Specified in the Protocol**

Following changes in analyses specified in the protocol are noted:

- Safety analyses will be only performed on safety set as opposed to both safety set and modified safety set as mentioned in the protocol.
- Demographics, baseline characteristics and medical history will be only summarized for safety set as opposed to safety set, modified full analysis set and per-protocol set as mentioned in the protocol.
- The imputation rule has been modified from that described in the protocol for overall acute GVHD response, acute GI-GVHD response and acute GVHD response involving all organs.

In addition due to early termination of the study, an abbreviated CSR will be written and a number of pre-specified analyses will not be performed however by-patient listings will be generated for all data collected for this study.

### **4.2. Changes from Analyses Specified in the Previous Version of the SAP**

See section 4.1.

## 5. DEFINITIONS

### 5.1. Efficacy

#### Secondary Therapy

A key factor in several of the efficacy parameters is determination of secondary therapy (re-escalation of steroid and/or additional intervening therapy) which may consist of any of the following changes to background therapy during the study treatment period:

1. Re-escalation: 2.5mg/kg/day prednisone equivalent for 2 consecutive days starting on or after Day 6 (note, the day of 1<sup>st</sup> ALXN1007 is denoted by Day 1 for analysis purpose)
2. Additional systemic therapy for treatment of GVHD (including but not limited Biologics/anti-TNF or Antineoplastic medications administered post-baseline for treatment of GVHD)

#### 5.1.1. Primary Endpoint(s)

The primary efficacy endpoint is the overall acute GVHD response at Day 28. The overall acute GVHD response is defined as improvement from Baseline in any organ (skin, lower GI tract and liver) by at least 1 stage, without progression in any other organ and with no additional therapy being administered. Baseline will be defined as the stage value determined at the diagnosis i.e. the first value recorded prior to 1<sup>st</sup> ALXN1007 infusion. At every visit, patients will be graded according to the Modified Keystone Grading Schema displayed in **Table 2**.

**Table 2. Modified Keystone Grading Schema**

	<b>Stage 0</b>	<b>Stage 1</b>	<b>Stage 2</b>	<b>Stage 3</b>	<b>Stage 4</b>
<b>Skin</b>	No Rash	Rash <25% BSA	Rash 25-50% BSA	Rash >50% BSA	Bullae and desquamation
<b>Lower GI Tract</b>	<500 ml/day stool volume	500-1000 ml/day stool volume OR Severe nausea and vomiting	1001-1500 ml/day stool volume	>1500 ml/day stool volume	Severe abdominal pain +/- ileus, frank blood or melena
<b>Liver</b>	Bilirubin ≤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

## 5.1.2. Other Efficacy Endpoints

### 5.1.2.1. Acute GI GVHD response

Acute GI-GVHD responses will be derived based on the following order (Progression, NR, MR, PR and CR) and these responses are mutually exclusive. The effect of secondary therapy only needs to be applied to 'NR' and no need to apply separately to MR, PR and CR because of inherent ordering.

- **Progression:** deterioration in lower GI tract staging (positive change from baseline).
- **No Response (NR):** no change in lower GI tract staging OR receiving secondary therapy.
- **Mixed Response (MR):** improvement in lower GI tract AND deterioration in another organ.
- **Partial Response (PR):** improvement in lower GI tract (provided lower GI tract staging is not 0) AND no deterioration in another organ.
- **Complete Response (CR):** lower GI tract Stage = 0

### 5.1.2.2. Response for All Organs Involved with Acute GVHD

Acute all organ-GVHD responses will be derived based on the following order (Progression, NR, MR, PR and CR) and these responses are mutually exclusive. Note, the effect of secondary therapy only needs to be applied to 'NR' and no need to apply separately to MR, PR and CR.

- **Progression:** Deterioration in at least 1 organ AND no improvement in other organs
- **No Response (NR):** no change in any organ OR receiving secondary therapy
- **Mixed Response (MR):** Improvement in at least 1 organ AND deterioration in another organ
- **Partial Response (PR):** Improvement in at least 1 organ AND no deterioration in another organ (provided not all stages are 0)
- **Complete Response (CR):** all organ stages are 0

### 5.1.2.3. Very Good Partial Response (VGPR):

- **Skin:** No rash, or residual erythematous rash involving <25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count)
- **Liver:** Total serum bilirubin concentration <2 mg/dL or <25% of baseline at enrollment
- **Gut:**
  - Tolerating food or enteral feeding
  - Predominantly formed stools
  - No overt gastrointestinal bleeding or abdominal cramping

- No more than occasional nausea or vomiting

Note: For abbreviated CSR, this endpoint will not be analyzed.

#### 5.1.2.4. Treatment Failure

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

- No response (all organs)
- Progression (all organs)
- Administration of additional systemic therapy for GVHD (or re-escalation of corticosteroid dose to  $\geq 2.5$  mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day])
- Mortality occurred prior to Day 56

Note: For abbreviated CSR, this endpoint will not be analyzed.

#### 5.1.2.5. Acute GVHD Flares

Flares are defined as any progression of acute GVHD through Day 86 after an initial response (i.e., earlier CR or PR) that require re-escalation of corticosteroid dosing, or initiation of additional topical or systemic therapy for GVHD.

Note: For abbreviated CSR, this endpoint will not be analyzed.

#### 5.1.2.6. Discontinuation of Immunosuppressive Medications

Patients are expected to be on immunosuppressive medications at baseline and during the study (on or after 1<sup>st</sup> dose of ALXN1007). For analysis purpose, the immunosuppressive medications used for GVHD will be identified using Standardized Drug Grouping (SDG) classification based on WHO drug dictionary. The time (days) on immunosuppressive medications will be calculated as (last date on immunosuppressive medication – date of 1<sup>st</sup> ALXN1007 dose) + 1.

Note: For abbreviated CSR, this endpoint will not be summarized, however a by-patient listing will be produced.

#### 5.1.2.7. Cumulative and Average Corticosteroid Dose

Cumulative and average corticosteroid dose at Days 28, 56, 86 and 180 will be analyzed. For analysis purpose, the corticosteroids during the study will be identified using Standardized Drug Grouping (SDG) classification based on WHO drug dictionary. The prednisone equivalent of corticosteroid dose in mg will be calculated using the following conversion table using the dosing frequency and numeric dose as captured on the case report form:

**Table 3. Prednisone Equivalence Conversion**

Medication	Prednisone equivalent (mg)
Dexamethasone	6

<b>Medication</b>	<b>Prednisone equivalent (mg)</b>
Hydrocortisone	0.25
Hydrocortisone Sodium Succinate	0.25
Methylprednisolone	1.25
Methylprednisolone Sodium Succinate	1.25
Prednisone	1

Note: For abbreviated CSR, steroid dose will not be summarized, however a by-patient listing will be produced for all concomitant medications.

#### **5.1.2.8. Overall Survival**

Assessment of overall survival at Days 180 and 360 will be measured based on the time (days) since 1<sup>st</sup> ALXN1007 dose to death due to any reason. Patients with incomplete follow-up for other reasons will be censored.

#### **5.1.2.9. Non-Relapse Mortality**

Assessment of non-relapse mortality at days 180 and 360 will be measured based on the time (days) since 1<sup>st</sup> ALXN1007 dose to death due to any reason other than the underlying malignancy relapse. Relapse related deaths will be considered as competing risk. Patients with incomplete follow-up for any other reasons will be censored.

### **5.2. Safety**

The safety of ALXN1007 will be assessed based on incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and changes from baseline through trial completion in vital signs, ECG, routine clinical laboratory tests (chemistry, hematology, urinalysis), incidence and titer of antibodies to ALXN1007, and pregnancy tests for female patients of childbearing potential.

Note: see details in the later sections for which parameters the results will not be summarized.

#### **5.2.1. Adverse Events (AEs)**

Treatment-emergent adverse events (TEAE) will be defined as any adverse event with onset on or after 1<sup>st</sup> ALXN1007 administration.

#### **5.2.2. Vital Signs**

Following vital signs are measured by visit for this study:

<ul style="list-style-type: none"> <li>• Systolic blood pressure (mmHg)</li> <li>• Diastolic blood pressure (mmHg)</li> </ul>	<ul style="list-style-type: none"> <li>• Respiration rate (RR)</li> <li>• Weight (kg)</li> </ul>
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<ul style="list-style-type: none"><li>• Heart Rate (HR) (beats per minute)</li><li>• Temperature (°C)</li></ul>	<ul style="list-style-type: none"><li>• Height (cm), measured at screening only</li></ul>
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### 5.2.3. Laboratory Assessments

Following laboratory parameters are collected for this study by visit:

- Chemistry panel,
- Coagulation panel,
- CBC with differential
- Platelets
- Urinalysis
- Stool test for *C. difficile*
- Blood test for absolute neutrophil count (ANC)
- Creatinine clearance
- Serum pregnancy test
- Urine dipstick pregnancy test
- Creatine phosphokinase (CPK)
- Thyroid function tests (TPO, TSH, FT-4)
- Levels of CSA, tacrolimus and/or sirolimus

### 5.2.4. Physical Examination

Abnormality finding for following body systems is collected for this study:

- General appearance
- Skin
- HEENT (Head, Ear, Eye, Nose, Throat)
- Neck
- Lymph nodes
- Chest
- Heart
- Abdomen
- Extremities
- Neurological
- Musculoskeletal

### 5.2.5. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be conducted to assess the ECG outcome as follows:

- Normal
- Abnormal
  - Clinically significant
  - Not clinically significant.

### **5.2.6. Immunogenicity**

Blood samples will be collected to test for antibodies to ALXN1007 in plasma just prior to dosing, at Baseline and on Days 7, 28, 56, 86 and 180, as well as at the ET visit. Blood samples will be evaluated for anti-drug antibodies (ADA) to describe the presence or absence of an immune response to ALXN1007 and to evaluate, if antibodies are detected, whether the antibodies neutralize the activity of ALXN1007 (ability of ALXN1007 to inhibit C5a). 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 patient.

Note: For abbreviated CSR, no summaries will be performed for antibodies, however all available results will be listed.

### **5.3. Pharmacokinetic and Pharmacodynamic Analysis**

Blood samples for PK/PD will be collected at the time points indicated in the schedule of events (Refer Table 3 in protocol) 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 will be determined by assessing plasma concentrations of biomarkers, which will include C3, C4, C5a, C5 and sC5b-9. Serum terminal complement activity will be measured by the cRBC hemolysis and Wieslab™ CCP assays.

The PK/PD modeling analyses will be detailed in a separate analysis plan.

Note: For abbreviated CSR, no analysis will be performed for PK and PD.

### **5.4. Exploratory Biomarker Assessment**

Blood samples will be collected just prior to dosing at Baseline, Days 7, 28, 49, 86 and 180, as well as the ET visit ; 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. Biomarkers associated to 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, tumor necrosis factor receptor 1 (TNFR1), suppressor of tumorigenicity 2 (ST2) and regenerating islet-derived protein 3 alpha (REG3a). Additional exploratory analyses, including anti-factor H antibody titer, may be performed.

Note: For abbreviated CSR, no analysis will be performed for exploratory biomarkers.

## **6. DATA SETS ANALYZED (STUDY POPULATIONS)**

Study populations are defined as follows:

### **6.1. Safety Set**

The Safety Set includes all patients who receive at least 1 dose of ALXN1007. This set will be used to summarize demographics, baseline characteristics, medical history, prior and concomitant medications, adverse events, laboratory results, vital signs and ECG.

### **6.2. Modified Safety Set**

The modified Safety Set is defined as all patients who receive at least 1 dose of ALXN1007 and for whom GI GVHD is confirmed through biopsy. The modified safety set defined in the protocol has the identical definition as the modified full analysis set defined below. Hence this set will not be used for any pre-specified analyses covered by this statistical analysis plan.

### **6.3. Modified Full Analysis Set (mFAS)**

The mFAS will include all patients who receive at least 1 dose of ALXN1007 and for whom GI GVHD is confirmed through biopsy. This analysis set will be used for efficacy analysis.

### **6.4. Per Protocol Set (PP)**

The Per-Protocol (PP) Set is a subset of the mFAS population, excluding patients with major protocol deviations. This population may be used to summarize efficacy. Protocol deviations will be classified in the following categories:

- Did not fulfill eligibility criteria
- Met discontinuation criteria but continued IP treatment
- Received incorrect IP/dose
- Received prohibited concomitant medication
- Protocol-required procedure not adhered to
- Other

The PP analysis set will be identified prior to database lock.

Note: For abbreviated CSR, Per Protocol Set will not be derived.

### **6.5. PK/PD Analysis Set**

PK/PD analyses will be performed on the PK/PD Analysis Set. The PK/PD Analysis Set includes all patients who receive at least 1 dose of ALXN1007 and who have evaluable PK and PD data. Refer to PK/PD analysis plan for details.

Note: For abbreviated CSR, PK analysis Set will not be derived.

## **7. STATISTICAL ANALYSIS**

All statistical calculations will be performed using SAS, unless otherwise specified. All data will be presented in the form of listings sorted by treatment group (cohort) and patient ID. Tabular summaries will be presented based on the following grouping: 10mg/kg once weekly, 20mg/kg once weekly, 20mg/kg twice weekly and overall (all three treatment groups combined).

For continuous variables, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum values. Frequencies and percentages will be calculated for categorical variables. Graphical displays will be produced, as mentioned in this SAP.

### **7.1. Study Subjects**

#### **7.1.1. Disposition of Subjects**

Following summaries will be tabulated:

- Number of patients screened and reasons for screen failure
- Number of patients treated
- Number of patients in safety set and number of patients excluded from this set along with reasons
- Number of patients in modified full analysis set and number of patients excluded from this set along with reasons (Note: For abbreviated CSR, Per Protocol Set will not be derived.)
- Number of patients in per protocol set and number of patients excluded from this set along with reasons
- Number of patients completed and discontinued along with reasons for discontinuation during treatment period, follow-up period as well as overall study
- Survival status at Day 360

#### **7.1.2. Protocol Deviations**

All the protocol deviations will be listed. Number and percentage of patients not meeting inclusion/exclusion criteria will be tabulated for safety set.

Note: tabular summary will not be presented for protocol deviations; by-patient listing will be produced.

#### **7.1.3. Demographics, Disease Characteristics and Medical History**

All demographic and medical history information will be summarized using Safety set.

##### **7.1.3.1. Demographics**

The following demographic variables will be summarized:

- Age (Years)

- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)

### **7.1.3.2. Disease Characteristics**

Following disease characteristics will be tabulated:

#### **7.1.3.2.1. Transplant history**

- Donor type (matched related, matched unrelated, mismatched, other) (n, %)
- Graft source (Bone marrow, peripheral blood, umbilical cord) (n, %)
- Transplant indication (acute myeloid leukemia, mantle cell lymphoma etc.) (n, %); these indications will be identified by review of medical history.

#### **7.1.3.2.2. Endoscopy, Biopsy and GI-GVHD confirmation**

- GI-GVHD onset day categories post-transplant at enrollment (<10, 10-19, 20-29, 30-39, 40-49, 50-59, ≥60) (n, %)
- Confirmation of GI-GVHD through upper GI tract biopsy (yes, no)
- Confirmation of GI-GVHD through lower GI tract biopsy (yes, no)

#### **7.1.3.2.3. Baseline Staging Information, Extent of Rash, Stool Volume**

- Staging score (0, 1, 2, 3 and 4) for each organ (skin, lower GI tract and liver) (n, %)

### **7.1.3.3. Medical History**

Medical history will be tabulated by number (%) of patients in the Safety Set for each system organ class and preferred term.

Note: For abbreviated CSR, no tabular summary will be provided for medical history, however a by-patient listing will be produced.

### **7.1.4. Prior and Concomitant Medications / Therapies**

Prior medications are defined as medications taken or therapies received by patients prior to the first dose of ALXN1007. Concomitant medications are defined as medications taken or therapies received by patients during the study after first dose of ALXN1007. Medications will be coded using the World Health Organization Drug Dictionary version. Summaries will be performed on the Safety set. A medication will be considered conservatively both prior and concomitant if partial start or stop dates are recorded such that its designation as a prior and/or concomitant medication could not be determined with certainty.

The number (%) of patients taking prior and concomitant medications will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 1 and generic name. In addition, by-patient listings will be provided for the following:

- Prior investigational agents
- Secondary therapies (during the study)

## **7.2. Efficacy Analyses**

Efficacy analyses will be performed on the modified Full Analysis Set (mFAS). For efficacy, Baseline is defined as the first available assessment prior to first dose of ALXN1007, this value is supposed to be representative of value at diagnosis of GI-GVHD.

### **7.2.1. Primary Efficacy Analysis**

Overall GVHD response rate along with 95% confidence intervals (CIs) will be calculated at Day 28. The confidence interval will be calculated using Clopper-Pearson exact method.

#### **7.2.1.1. Handling of Dropouts or Missing Data**

- Imputations will be performed up to Day 180 visit (maximum visit for stage data)
- If a patient has been administered with secondary therapy or died before the next missing visit, all subsequent missing values will be imputed as NR (non-responder), otherwise, last non-missing response will be carried forward.

#### **7.2.1.2. Subgroup Analysis**

No subgroup analysis is planned for primary endpoint.

#### **7.2.1.3. Multicenter Studies**

No center-specific summary will be produced. Data from all centers will be pooled together.

#### **7.2.1.4. Hypothesis Testing and Significance Level**

No formal hypothesis testing will be performed.

#### **7.2.1.5. Sensitivity Analyses**

Observed response rates (without any imputation) at Day 28 will be tabulated along with 95% Clopper-Pearson exact confidence intervals. In addition, both imputed and observed results will be presented at all study visits.

### **7.2.2. Other Efficacy Analyses**

#### **7.2.2.1. Acute GI-GVHD response, acute GVHD response (all organ), Very Good Partial Response, Treatment Failure**

Number (%) of responders according to the following response criteria will be calculated at for all visits along with 95% Clopper-Pearson exact confidence intervals (CIs) for both observed and imputed summaries:

- Acute GI GVHD Response Criteria (complete response, partial response, mixed response, no response and progression)
- Acute GVHD Response Criteria involving all organs (complete response, partial response, mixed response, no response and progression)

### **Imputation technique for missing acute GI-GVHD and all organ-GVHD response**

- There could be two types of missing data
  - Missing data at intermediate visits (for example, patient may miss Day 28 visit but still has data on Day 21 and 35).
  - Missing data due to discontinuation or deaths.
- Imputations will be performed up to Day 180 visit (maximum visit for stage data)
- For missing visits due to death, all subsequent visits will be imputed as “progression” (irrespective of secondary therapy); note, the protocol defined visit windows can be either  $\pm 2$  or  $\pm 15$  days depending on whether they fall in the treatment-period vs. follow-up period. However, the analysis windows are wider than protocol defined visit windows; if death occurs within a pre-specified analysis window for a particular visit (even if the target day for that visit is less than the day of death), missing values will be considered as ‘progression’.
  - Example: non-missing responses on Day 7, secondary therapy starting on Day 9, death on day 10, Day 14 onward – impute as progression.
- If all post-baseline responses are missing due to an early death, then missing responses will be imputed as “progression”.
- For other missing visits, following imputation rules will be implemented:
  - If the previous observed response is “Progression”, then subsequent missing visits will be imputed as “Progression” irrespective of secondary therapy
  - If response is not “progression” at the previous visit and a patient has been administered with secondary therapy since then, all subsequent missing visits will be imputed as NR
    - Example: Day 14 is CR, Day 28 and Day 35 visits are missing
      - If no secondary therapy flag before Day 28, then Day 28 response will be imputed as CR
      - If secondary therapy administered before Day 28, both Day 28 and 35 missing responses will be imputed as NR
  - Otherwise, carry forward the last non-missing response. Only post-baseline responses are carried forward. If first post-baseline response is missing and the patient did not die, no response can be carried forward.

#### **7.2.2.1.1. Individual Staging Score, Skin Rash BSA and Stool volume**

A by-patient listing for these parameters will be produced. No tabular summaries will be generated.

#### **7.2.2.2. Overall Survival**

Kaplan-Meier estimate of survival rate at Day 180 and 360 along with 95% CI (using loglog transformation) will be summarized. Patients who are still alive as of the last known follow-up will be right censored as of the time point of analyses. Estimated time (days) of death based on KM method will be provided for 25<sup>th</sup>, 50<sup>th</sup> (i.e. median) and 75<sup>th</sup> percentile along with 95% CI.

#### **7.2.2.8. 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 related death as competing risk.

#### **7.2.3. Pharmacokinetic and Pharmacodynamic Analyses**

No analyses on PK and PD parameters will be produced for the abbreviated CSR.

#### **7.2.4. Exploratory Biomarker Analyses**

No analyses on exploratory biomarkers will be produced for the abbreviated CSR.

### **7.3. Safety Analyses**

All safety analyses will be conducted on the Safety Set. No formal hypothesis testing is planned. Baseline is defined as the last available assessment prior to the first dose of ALXN1007.

#### **7.3.1. Study Duration, Treatment Compliance, and Exposure**

For each dosing visit, number (%) of patients with study treatment administered, total dose (mg) will be summarized by descriptive statistics. The study dose (mg) will be calculated as 5×mL administered when incomplete dose is administered, note that per pharmacy manual, the final conc. is 5mg/ml.

#### **7.3.2. Adverse Events (AEs)**

Treatment-Emergent Adverse Events (TEAEs) will be tabulated and presented separately. AEs will be coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

##### **7.3.2.1. Overall Summary of Adverse Events**

An overall summary of TEAEs and non-fatal serious TEAEs and non-serious TEAEs will be presented. The number of events (n) and number (%) of patients with events will be shown for the following event subcategories:

**Table 4. Subcategories For Treatment-Emergent Adverse Events (TEAEs)**

<b>Relationship:</b> Related AEs (possibly, probably, or definitely related), Not Related AEs (not related or unlikely)
<b>Severity:</b> Grade 1,2,3,4,5
<b>Leading to withdrawal</b>

**7.3.2.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)**

The number of TEAEs and the number (%) of patients with events will be presented by SOC and PT. Patients are counted once in each SOC and PT. The ordering of SOC and PT is to be done by the most prevalent SOC in the overall ALXN1007 group reporting any AEs in that SOC, then by most prevalent PT reporting any AEs in that SOC. For SOC/PT with same number of patients (e.g., to break ties) they should be further sorted by number of events (when applicable) and then alphabetically. Similar tabulations will be done for SAEs and non-SAEs separately. Additionally tabulations by PT only will be produced for TEAEs and SAEs where PTs will be sorted by the most prevalent AEs in that PT in the overall ALXN1007 group.

**7.3.2.3. AEs and SAEs by SOC, PT, and Relationship**

Summaries of TEAEs and TESAEs by grouped relationship (related/not related) to treatment will be provided by SOC and PT.

**7.3.2.4. AEs and SAEs by SOC, PT, and Toxicity Grade**

Summaries of TEAEs and TESAEs by SOC, PT and CTC toxicity grades will be provided.

**7.3.2.5. Deaths, Other SAEs and Other Significant Adverse Events**

Summaries of TEAEs leading to death will be provided by SOC and PT. Summaries of TEAEs leading to study treatment discontinuation will be provided by SOC and PT.

**7.3.3. Other Safety**

Baseline for safety assessment (i.e. laboratory values, vital signs) will be defined as last non-missing value prior to 1<sup>st</sup> ALXN-1007 infusion.

**7.3.3.1. Analyses for Laboratory Tests**

Descriptive statistics by visit will be presented for each laboratory parameter (as mentioned in Section 5.2.3). Changes from Baseline as well as shift tables for laboratory parameters will be presented. All laboratory values will be classified as normal, below normal (low), or above normal (high) based on normal ranges supplied by the central laboratory. Frequencies of abnormal values will be presented in tabular form. Similar tabulations will be provided based on CTC toxicity grades. For purposes of analyses, laboratory results based upon standardized units will be used.

**7.3.3.2. Vital Signs**

Changes from baseline in vital signs will be summarized by visit.

### 7.3.3.3. Physical Examination

A by-patient listing will be produced for physical examination; no tabular summaries will be generated.

### 7.3.3.4. Electrocardiograms (ECG)

A by-patient listing will be produced for ECG; no tabular summaries will be generated.

### 7.3.3.5. Immunogenicity

A by-patient listing will be produced for anti-bodies to ALXN1007; no tabular summaries will be generated.

## 7.4. Interim Analyses

The following interim data analyses will be performed during the study.

- This study has a stopping guideline for excessive mortality (refer protocol Section 7.5.2). A stopping rule for Day 56 mortality will be applied after every 6 patients are accrued. The study will be stopped at interim evaluation (t) if the number of deaths is  $\geq X_t$ , e.g., if 4 or more deaths in the first 6 patients or 6 or more deaths in the first 12 patients, etc., as detailed in Table 4 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 patients.

At every interim evaluation (t); a listing for patients who died including the cause of death will be produced along with any other data points deemed required.

**Table 5. Cumulative Stopping Probabilities for Mortality Rates at Day 56**

Evaluation (t)	Total N	X <sub>t</sub>	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%
5	30	11	2.6%	71.0%

- A brief interim safety report summarizing AEs and SAEs will be generated when the first six patients have completed the day 86 visit. This will include all the AE and SAE summary tables and listings mentioned in this SAP. Note: This report will be generated after the 6<sup>th</sup> patient completes the day 86 visit. This report will include the first 6 patients only with all the safety data available at the time of data cut.
- Additionally, an informal interim analysis will occur after all patients have completed Day 56, which is the end of the treatment period. This interim analysis will

summarize the primary endpoint and other efficacy endpoints, up to day 56 assessment, with the exception of overall survival and non-relapse mortality. In terms of safety, treatment emergent AEs and SAEs will be summarized with all safety data available. The interim analyses will also summarize PK and PD results. Summary tables and listings will be produced for the following parameters as mentioned in this SAP: Enrollment Status, Patient Disposition (Treatment Period), Demographics, Primary Endpoint, Other Efficacy Endpoints (except overall survival and non-relapse mortality), Concomitant medications, treatment emergent AEs and SAEs.

## **7.5. Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) will conduct interim monitoring of safety data throughout the treatment period of the study. Refer to the study DMC Charter for all DMC procedures, processes and analysis for the study.

## 7 REFERENCES

Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Med.* 2007; 26:2389–2430

Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis; *Clin Cancer Res* 2007; 559 13(2) January 15, 2007; Haesook T. Kim

## 8 APPENDICES

### 9.1 Protocol Schedule of events

For the schedule of events/assessment, this SAP refers to the protocol version 8 dated 12 February 2016.

### 9.2 Changes from Analyses Specified in the Previous Version of the SAP

Not applicable

### 9.3 Sample Size, Power, and Randomization

Up to 36 patients 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.

### 9.4 Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

#### Age

Age will be presented as the number of years between date of birth and the reference date. The following age will be computed, with reference dates indicated:

**Table 6. Age and reference date**

AGE	REFERENCE DATE
• Age at Enrollment	• Date of Signing ICF

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

#### Definition of Baseline Values

Baseline for efficacy is defined as the first available pre-first study dose assessment for all patients. For other analyses, Baseline is defined as the last non-missing value prior to 1<sup>st</sup> dose of ALXN1007.

#### Change from Baseline

Change from baseline will be calculated as

Change of Baseline = Assessment Value – Baseline Assessment Value.

#### Adverse Events

If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
  - the start month is missing, then the AE is treatment emergent; else if
  - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else.
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered Pre-Treatment Adverse Events (PTAEs).

Patient percentages are based on the total number of treated patients.

Related AEs are defined as possible, probable or definitely related. Unrelated AEs are defined as unlikely or not related.