

**Single Arm Study of ALXN1210 in Complement Inhibitor
Treatment-naïve Adult and Adolescent Patients With
Atypical Hemolytic Uremic Syndrome (aHUS)**

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Date of Protocol: 07 May 2019

PROTOCOL ALXN1210-aHUS-311
SINGLE ARM STUDY OF ALXN1210 IN COMPLEMENT INHIBITOR
TREATMENT-NAÏVE ADULT AND ADOLESCENT PATIENTS WITH
ATYPICAL HEMOLYTIC UREMIC SYNDROME (aHUS)

Sponsor: Alexion Pharmaceuticals, Inc. (Alexion)
100 College Street
New Haven, CT 06510 USA

Sponsor Contact:

PPD

Alexion Pharmaceuticals, Inc.
121 Seaport Blvd, 7th Floor
Boston, MA 02210 USA
Telephone: PPD
Email: PPD

Medical Monitor:

PPD

Alexion Pharmaceuticals, Inc.
121 Seaport Blvd, 7th Floor
Boston, MA 02210 USA
Telephone: PPD
Email: PPD

IND Number: 128367

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Amendment 2 (Global): 23 Jan 2017

Amendment 3 (Global): 19 Jul 2017

Amendment 4 (Global): 07 May 2019

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SPONSOR SIGNATURE PAGE

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HEMOLYTIC UREMIC SYNDROME (aHUS)**

PROTOCOL NUMBER: ALXN1210-aHUS-311

PPD



Alexion Pharmaceuticals, Inc.

5/8/2018

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ALXN1210. I have read the ALXN1210-aHUS-311 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

STUDY CONTACT INFORMATION

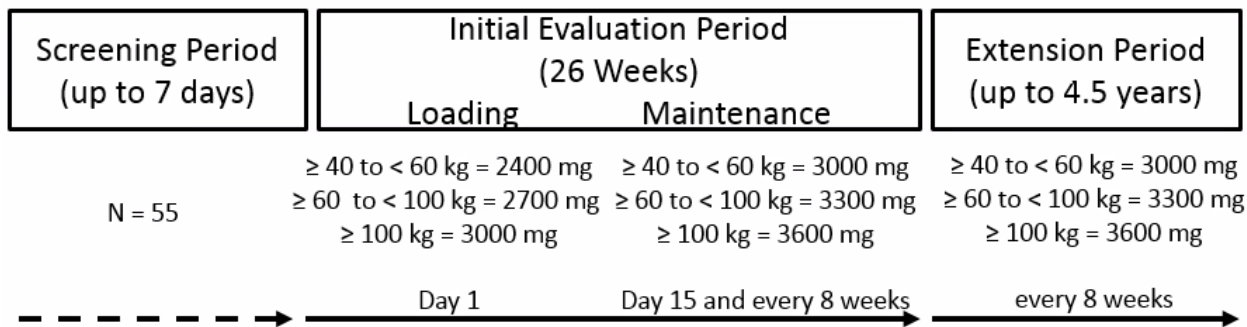
Emergency Contact Information

Study Role	Name	Address and Telephone Number
Clinical Project Leader	PPD [REDACTED]	Alexion Pharmaceuticals, Inc. 121 Seaport Blvd, 7 th Floor Boston, MA 02210 USA Telephone: PPD [REDACTED] Email: PPD [REDACTED]
Medical Monitor	[REDACTED]	Alexion Pharmaceuticals, Inc. 121 Seaport Blvd, 7 th Floor Boston, MA 02210 USA Telephone: PPD [REDACTED] Email: PPD [REDACTED]
24-Hour Emergency Contact Phone Number		PPD [REDACTED]

2. SYNOPSIS

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc.	
Name of Investigational Product: ALXN1210	
Name of Active Ingredient: ALXN1210	
Title of Study: Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)	
Protocol Number: ALXN1210-aHUS-311	EudraCT Number: 2016-002027-29
Study Centers: Approximately 200 investigative sites globally.	
Length of Study: Estimated date first patient treated: Nov 2016 Actual first patient treated: Mar 2017 Estimated date last patient completed (last patient last visit): May 2023	Phase of Development: 3
<p>Primary Objective: The primary objective of the study is to assess the efficacy of ALXN1210 in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis, and renal impairment.</p> <p>Secondary Objectives: The secondary objectives of the study are to assess the following:</p> <ol style="list-style-type: none"> 1. To characterize the safety and tolerability of ALXN1210 in this patient population 2. To evaluate the efficacy of ALXN1210 by the following additional measures: <ol style="list-style-type: none"> a. Dialysis requirement status b. Time to Complete TMA Response c. Complete TMA Response status over time d. Observed value and change from baseline in estimated glomerular filtration rate (eGFR) e. Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline f. Observed value and change from baseline in hematologic parameters (platelets, lactate dehydrogenase [LDH], hemoglobin) g. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between h. Change from baseline in quality of life (QoL), as measured by EuroQol 5 dimensions 3 level (EQ-5D-3L; all patients), Functional Assessment of Chronic Therapy (FACIT) Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires i. TMA parameters in patients who discontinue treatment but remain in the study 3. To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ALXN1210 by the following measures: <ol style="list-style-type: none"> a. Changes in serum ALXN1210 concentration over time b. Changes in free complement component 5 (C5) concentrations over time c. Changes in free C5 and ALXN1210 concentration in patients who discontinue treatment but remain in the study 4. To evaluate the long-term safety and efficacy of ALXN1210 	
<p>Study Design and Methodology: This is a Phase 3, single arm, multicenter study to evaluate the safety and efficacy of ALXN1210 administered by intravenous (IV) infusion to adolescent (12 to < 18 years of age) and adult (≥ 18 years of age) patients with aHUS. All patients must be naïve to complement inhibitor treatment and include at least 6 and up to 10 adolescent (12 to < 18 years of age at Screening) patients and at least 10 and up to 25 patients with prior kidney transplants. A minimum of 30 patients who meet all laboratory criteria for TMA (platelet</p>	

count of < 150,000 per microliter, LDH $\geq 1.5 \times$ upper limit of normal (ULN), hemoglobin \leq lower limit of normal (LLN), and serum creatinine level \geq ULN) as determined by the central laboratory at Day 1, will be enrolled. The study consists of an up to 7-day Screening Period, a 26-week Initial Evaluation Period and an Extension Period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first. Patients will receive a weight-based loading dose of ALXN1210 IV (≥ 40 to < 60 kg = 2400 mg; ≥ 60 to < 100 kg = 2700 mg; ≥ 100 kg = 3000 mg) on Day 1, followed by weight-based maintenance doses of ALXN1210 IV (≥ 40 to < 60 kg = 3000 mg; ≥ 60 to < 100 kg = 3300 mg; ≥ 100 kg = 3600 mg) on Day 15 and once every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment in the Initial Evaluation Period followed by maintenance doses q8w in the Extension Period. The end of trial is defined as the last patient's last visit. Weight-based dosing is based on the patient's body weight recorded at the last visit or more recently.



Number of Patients (planned): Approximately 55 patients are planned for enrollment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Patients must meet all inclusion and no exclusion criteria. Patients who fail any of the eligibility criteria may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Patients may be rescreened a maximum of 2 times. Evaluation of Inclusion Criteria 2a and 2b may be based on local laboratory results within 28 days prior to the start of the Screening Period or laboratory results obtained during the Screening Period from a local or central laboratory. If a local laboratory is used to define eligibility, additional samples will be collected during the Screening Period for LDH, platelet count, hemoglobin and serum creatinine and tested at the central laboratory. If patients are found to not meet the eligibility criteria for serum creatinine (Inclusion Criterion 2c) based on central laboratory results, they must not be enrolled into the study; if the subject has received the first dose of ALXN1210 the patient must be withdrawn from the study, and may be replaced. All analyses in this study will be based on results from the central laboratory. A central laboratory result for Inclusion Criterion 2c may not be available prior to first dose; results received after the first dose indicating that eligibility is not satisfied could lead to discontinuation and replacement of the patient.

The study will enroll at least 6 and up to 10 adolescent (12 to < 18 years of age at Screening) patients and at least 10 and up to 25 patients with prior kidney transplants. A minimum of 30 patients who meet all laboratory criteria for TMA (platelet count of < 150,000 per microliter, LDH $\geq 1.5 \times$ upper limit of normal (ULN), hemoglobin \leq lower limit of normal (LLN), and serum creatinine level \geq ULN) as determined by the central laboratory at Day 1, will be enrolled.

Inclusion Criteria:

1. Male or female patients ≥ 12 years of age and weighing ≥ 40 kg at the time of consent.
2. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:
 - a. Platelet count < 150,000 per microliter (μ L) during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
 - b. LDH $\geq 1.5 \times$ upper limit of normal (ULN) during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin \leq lower limit of normal (LLN) for age and gender during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
 - c. Serum creatinine level \geq ULN during the Screening Period in adults (≥ 18 years of age), or $\geq 97.5^{\text{th}}$ percentile for age at Screening in adolescents (≥ 12 to < 18 years of age) (patients who require

dialysis for acute kidney injury are also eligible).

3. Among patients with a kidney transplant:
 - a. Known history of aHUS prior to current kidney transplant, **or**
 - b. No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (eg, suspending or reducing the dose) of calcineurin inhibitor ([CNI]; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor ([mTORi]; eg, sirolimus, everolimus).
4. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.
5. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who receive a meningococcal vaccine less than 2 weeks before initiating ALXN1210 treatment must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.
6. Patients < 18 years of age must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines.
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
8. Willing and able to give written informed consent and comply with the study visit schedule. For patients < 18 years of age, patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]).

Exclusion Criteria:

1. Known familial or acquired 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13' (ADAMTS13) deficiency (activity < 5%). Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.
2. Known Shiga toxin-related hemolytic uremic syndrome (ST-HUS) as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin producing bacteria. Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.
3. Positive direct Coombs test. Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.
4. Known Human Immunodeficiency Virus (HIV) infection.
5. Unresolved meningococcal disease.
6. Patients with a confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics.
7. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.
8. Pregnancy or breastfeeding.

9. Heart, lung, small bowel, pancreas, or liver transplant.
10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria.
11. Among patients without a kidney transplant, history of kidney disease other than aHUS, such as:
 - a. Known kidney biopsy finding suggestive of underlying disease other than aHUS
 - b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg small kidneys for age)
 - c. Known family history and/or genetic diagnosis of noncomplement mediated genetic renal disease (eg, focal segmental glomerulosclerosis)
12. Identified drug exposure-related HUS.
13. Receiving plasma exchange/plasma infusion (PE/PI), for 28 days or longer, prior to the start of Screening for the current TMA.
14. History of malignancy within 5 years of Screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
15. Bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) within the last 6 months prior to the start of Screening.
16. HUS related to known genetic defects of cobalamin C metabolism.
17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), or antiphospholipid antibody positivity or syndrome.
18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for end-stage kidney disease [ESKD]).
19. Patients receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening.
20. Patients receiving other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless:
 - a. part of an established post-transplant antirejection regimen, or
 - b. patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or
 - c. steroids are being used for a condition other than aHUS (eg, asthma).
21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.
22. Prior use of eculizumab or other complement inhibitors
23. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
24. Any medical or psychological condition that, in the opinion of the Investigator or Sponsor, could increase the risk to the patient by participating in the study or confound the outcome of the study.
25. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
26. Use of tranexamic acid within 7 days prior to Screening is prohibited.

Investigational Product, Dosage, and Mode of Administration:

ALXN1210 loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter, administered by IV infusion. Dosages are based on the patient's body weight, as shown in the table below:

Body Weight	Loading Dose (Day 1)	Maintenance Doses (Days 15, 71, and 127)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

Planned Duration of Treatment: 26-week Initial Evaluation Period followed by an Extension Period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Endpoints:

Efficacy Assessments

Primary:

Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Secondary:

1. Dialysis requirement status
2. Time to Complete TMA Response
3. Complete TMA Response status over time
4. Observed value and change from baseline in estimated glomerular filtration rate (eGFR)
5. Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
6. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
7. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
8. Change from baseline in quality of life (QoL), as measured by EuroQol 5 dimensions 3 level (EQ-5D-3L; all patients), Functional Assessment of Chronic Therapy (FACIT) Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires
9. TMA parameters in patients who discontinue treatment but remain in the study

Pharmacokinetics/Pharmacodynamics

1. Changes in serum ALXN1210 concentration over time
2. Changes in free C5 concentrations over time
3. Changes in free C5 and ALXN1210 concentration in patients who discontinue treatment but remain in the study

Exploratory

Biomarkers and APC Activity:

Exploratory biomarkers of PD effect may include, but are not limited to, change from baseline in levels of markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptor 1 [sTNFR1]), endothelial activation/damage (eg, soluble vascular adhesion molecule 1 [sVCAM-1], thrombomodulin), coagulation (eg, D-dimer), and renal injury (eg, cystatin C). Additional assessments may include measurements of ALXN1210 excretion in urine, chicken red blood cell (cRBC) hemolysis, total C5, autoantibodies to complement proteins (eg, anti-factor H) and Alternative Pathway of Complement (APC) activity (eg, Modified Ham's test, complement deposition assay).

Genetics:

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ALXN1210. Patients (or legal guardians) may decline from providing a sample for exploratory genetics and still participate in the study.

Additional Signs or Symptoms of aHUS and Resource Utilization:

Resource utilization will be assessed using the Resource Utilization Patient Questionnaire and additional signs or symptoms of aHUS will be assessed using the Patient-reported aHUS Symptoms Questionnaire.

The Investigator will evaluate extra-renal signs or symptoms of aHUS using a composite of clinical laboratory measurements, vital signs, and an organ system review.

Safety

The long-term safety and tolerability of ALXN1210 will be evaluated by physical examinations, vital signs, electrocardiograms (ECG), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADA) will also be assessed.

Sample Size:

Approximately 55 patients will be enrolled in this study in order to yield at least 50 evaluable patients by Day 183. This sample size is deemed appropriate to provide complete safety information and the necessary precision level for the planned estimation. Assuming a proportion of Complete TMA response of 65%, 50 patients would yield a 95% confidence interval (CI) for the proportion of response with a half-width of approximately 15%. The sample size was increased to 55 patients to account for a potential 10% drop-out rate, thus yielding a total planned sample size of 55 patients.

Statistical methods:

General: All data collected will be presented using summary tables, figures, and data listings. All analyses will be performed using SAS[®] release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients.

An interim clinical study report (CSR) will be prepared at the end of the 26-week Initial Evaluation Period, which will include efficacy, safety, and PK/PD analyses. A final CSR to summarize long-term efficacy, safety, and PK/PD will be produced at study completion. Available exploratory data will be summarized after study completion but may not be included in the CSR. All data collected will be presented using summary tables, figures, and data listings.

Efficacy:

Efficacy analyses will be performed on the Full Analysis Set (FAS). The analysis of the FAS will be the primary analysis.

The FAS will be based on a modified intent to treat (mITT) approach where patients that were enrolled and treated based on verification of inclusion and exclusion criteria through local laboratory results and the assumption that all inclusion and exclusion criteria were satisfied will be excluded from the FAS if it is later shown that certain of the inclusion and exclusion criteria were in fact not satisfied once all Screening laboratory results are available. Based on the above, the FAS will include all patients who receive at least 1 dose of ALXN1210, have at least 1 postbaseline efficacy assessment, and meet all of the following criteria:

- Patients who satisfy Inclusion Criterion number 2c
- Patients who satisfy Exclusion Criterion number 1
- Patients who satisfy Exclusion Criterion number 2

The FAS will be determined prior to database lock and prior to the database snapshot for the analysis performed at the end of the 26-week Initial Evaluation Period.

Primary efficacy:

The primary efficacy endpoint is Complete TMA Response during the 26-week Initial Evaluation Period. The primary analysis will consist in estimating the proportion of complete TMA responders among ALXN1210 treated patients. This will be performed by calculating the point estimate and a 95% CI for the proportion of complete TMA responders in ALXN1210 treated patients. The CI will be based on the asymptotic Gaussian approximation method with a continuity correction.

Secondary efficacy:

For the secondary efficacy endpoint of time to Complete TMA Response, a Kaplan-Meier cumulative distribution curve will be generated along with a 2-sided 95% CI. The corresponding summary table will present the cumulative distribution function (CDF) estimate, the number of patients at risk, the number of patients responding, and the number of patients censored at each postbaseline time point. The table will also present first quartile,

median, and third quartile, along with corresponding 2-sided 95% CI, of time to complete response.

Complete TMA response will also be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point. A similar approach will be used to summarize the number and proportion of patients with an increase from baseline in hemoglobin ≥ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Kidney function (dialysis requirement status, eGFR, CKD stage) as well as hematologic parameters (platelets, LDH, hemoglobin) will be summarized at baseline and each postbaseline time point. Descriptive statistics for continuous variables (eGFR, platelets, LDH, hemoglobin) will be used to summarize the observed value as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may be fit to test whether changes differ from zero at each time point. Dialysis requirement status and CKD stage will be summarized over time. Dialysis requirement status will be summarized among patients receiving dialysis within 5 days prior to ALXN1210 treatment initiation by presenting the number and proportion of those patients receiving and not receiving dialysis at each time point. A 2-sided 95% CI for the proportion receiving dialysis will be provided. CKD stage will be summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 will be considered the worst category, while Stage 1 will be considered the best category. A 2-sided 95% CI for the proportion will be provided for each category.

Quality of life will be evaluated using EQ-5D-3L (all patients), FACIT Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires. These measures will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may be fit to test whether changes differ from zero at each time point.

Safety:

Safety analyses will be performed on the Safety Set defined as all patients who received at least 1 dose of ALXN1210. The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized by system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to treatment.

Observed values and changes from baseline (last assessment prior to ALXN1210) in ECGs, vital signs, and laboratory assessments, as well as presence of ADA will be summarized. Shifts from baseline in laboratory assessments will be summarized for all study visits.

Pharmacokinetics/Pharmacodynamics:

Sparse PK and PD (free C5) samples will be collected over the course of the study. Individual serum concentration data for all patients who receive at least 1 infusion of ALXN1210 and who have evaluable PK data will be used to derive the PK parameters for ALXN1210.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

The PD effects of ALXN1210 administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of PK/PD relationships may be explored using data from this study or in combination with data from other studies. Pharmacodynamic analyses will be performed for all patients who receive at least 1 infusion of study drug and who have evaluable PD data. For PD parameters, summary tabulations of mean, SD, median, minimum, and maximum values will be presented for actual, change and percentage change from baseline. The relationship between changes in PD parameters, exploratory biomarkers, and the effects of treatment outcome may be evaluated.

Exploratory:

Biomarkers and APC Activity:

Exploratory analyses will evaluate changes from baseline in biomarkers which may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, sTNFR1), endothelial activation/damage (eg, sVCAM-1, thrombomodulin) coagulation (eg, D-dimer), and renal injury (eg, cystatin C). Additional analysis may include evaluation of ALXN1210 excretion in urine, cRBC hemolysis, total C5, autoantibodies to complement proteins (eg, anti-factor H) and APC activation (eg, Modified Ham's test, complement deposition assays).

Genetics:

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ALXN1210. Patients (or legal guardians) may decline from providing a sample for exploratory genetics and still participate in the study.

Additional Signs or Symptoms of aHUS and Resource Utilization:

Resource utilization will be assessed using the Resource Utilization Patient Questionnaire (caregiver-reported for all patients) and additional signs or symptoms of aHUS will be assessed using the Patient-reported aHUS Symptoms Questionnaire (patient-reported for patients ≥ 12 years of age; caregiver-reported for patients < 12 years of age). Resource Utilization Questionnaire data and Patient-reported aHUS Symptoms Questionnaire data will be summarized at baseline and each postbaseline assessment using discrete data summary statistics.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibodies
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADL	activities of daily living
AEs	adverse events
aHUS	atypical hemolytic uremic syndrome
AMR	antibody-mediated rejection
APC	alternative pathway of complement
BMT	bone marrow transplant
BP	blood pressure
C5	complement component 5
CDF	cumulative distribution function
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CNI	calcineurin inhibitor
cRBC	chicken red blood cell
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOI	end of infusion
ESKD	end-stage kidney disease
EQ-5D-3L	EuroQol 5 dimensions 3 level
ET	early termination
FACIT	functional assessment of chronic illness therapy
FAS	full analysis set
FSH	Follicle-stimulating hormone
GCP	good clinical practice
GPV	Global Pharmacovigilance
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
HUS	hemolytic uremic syndrome
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional (or Independent) Ethics Committee
IRB	Institutional Review Board

Abbreviation	Definition
IV	Intravenous
IVIg	intravenous immunoglobulin
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLT	lowest level term
MedDRA [®]	Medical Dictionary for Regulatory Activities
mITT	modified Intent to Treat
MMRM	mixed model for repeated measures
mTORi	mammalian target of rapamycin inhibitor
PD	pharmacodynamic
PEF	peak expiratory flow
PE/PI	plasma exchange/plasma infusion
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
PO	orally
PT	preferred term
QoL	quality of life
q8w	once every 8 weeks
SAEs	serious adverse events
SAP	Statistical Analysis Plan
SD	standard deviation
SLE	systemic lupus erythematosus
SOC	system organ class
SOPs	standard operating procedures
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
sTNFR1	soluble tumor necrosis factor receptor 1
SUSAR	suspected unexpected serious adverse reactions
sVCAM-1	soluble vascular adhesion molecule 1
TEAEs	treatment-emergent adverse events
TMA	thrombotic microangiopathy
ULN	upper limit of normal

5. INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated thrombotic microangiopathy (TMA), most often caused by mutations in genes encoding proteins involved in the alternative pathway of complement (APC) or by autoantibodies against APC regulatory proteins (Noris, 2010). Patients with aHUS are at risk for life-threatening manifestations of disease resulting from endothelial damage, including thrombocytopenia, intravascular hemolysis, acute renal failure, and extra-renal tissue damage. Importantly, approximately 20% of patients experience extra-renal manifestations of disease, including central nervous system, cardiac, gastrointestinal, distal extremity, and severe systemic organ involvement (Loirat, 2011; Brodsky, 2015). Before the availability of eculizumab, mortality rates among patients with aHUS were as high as 15% during the acute progressing phase of the disease (Noris, 2010; Sellier-Leclerc, 2007). Up to 50% of patients progressed to end-stage kidney disease (ESKD), often within a year of disease onset, and required dialysis or kidney transplant to sustain life.

Chronic, uncontrolled terminal complement activation, specifically, activation of complement component 5 (C5) and dysregulation of complement activity, is central to the pathogenesis of aHUS and the devastating manifestations of this disease. As a result, the targeted blockade of C5, with selective inhibition of generation of C5a and C5b-9, represents an important therapeutic mechanism of treatment.

Eculizumab (Soliris[®]) is the standard of care for aHUS patients. Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein C5 with high affinity. Eculizumab has no known off-target interactions with other proteins in vitro or in vivo. In addition, eculizumab is predicted to be effectorless, having no detectable binding to complement C1q or most Fcγ receptors (FcγR I, IIb/c IIIa, IIIb) and more than 10-fold weaker binding than an IgG1 isotype to FcγR IIa. Upon binding to the complement protein C5, eculizumab blocks cleavage to C5a and C5b by C5 convertase; which prevents generation of the terminal complement complex C5b-9. These attributes underlie the established safety and therapeutic efficacy profile of eculizumab as demonstrated in the 3 pivotal Phase 2 clinical studies (C10-003, C10-004, and C08-002A/B) and supported by subsequent postmarketing experiences.

ALXN1210 and eculizumab are both recombinant, humanized monoclonal antibodies against human complement protein C5 sharing over 99% amino acid sequence homology. The goal of treatment with these complement inhibitors is to achieve immediate, complete, and sustained blockade of terminal complement activity. ALXN1210 is produced in Chinese hamster cells and was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain to extend antibody half-life. These changes are designed to increase the half-life of ALXN1210 relative to eculizumab, increasing the duration of complete terminal complement inhibition, while preserving both the high degree of specificity for binding to C5 and the effectorless nature of the antibody.

Two studies of ALXN1210 are ongoing in patients with paroxysmal nocturnal hemoglobinuria (PNH) who are naïve to treatment with complement inhibitors. Study ALXN1210-PNH-103 is a Phase 1b, open-label, multiple dose study, and Study ALXN1210-PNH-201 is a Phase 2, open-label, multiple dose study. ALXN1210-PNH-103 is designed to assess dose ranging over a 2-fold range of trough exposure levels, while Study ALXN1210-PNH-201 is designed to assess

dose intervals of 4, 6, 8, and 12 weeks. Each study in patients with PNH also includes a 2-year extension phase. In addition, Study ALXN1210-HV-104 is being conducted to assess the pharmacokinetic (PK) profile of ALXN1210 in healthy Japanese subjects.

Preliminary data from ALXN1210-PNH-103, indicate ALXN1210 treatment resulted in rapid reductions in lactate dehydrogenase (LDH) levels in 100% of patients, which were sustained through 2 to 4 monthly dosing intervals, consistent with the extended half-life ($t_{1/2}$) of ALXN1210 (Lee, 2016). There was a notable decrease in the need for blood transfusions. These preliminary LDH data suggest that rapid, complete, and sustained complement inhibition with ALXN1210 results in highly effective blockade of intravascular hemolysis.

More information about the PK, mechanism of action, known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ALXN1210 may be found in the current edition of the Investigator's Brochure (IB).

5.1. Benefits and Risks Assessment

5.1.1. Potential Benefits

ALXN1210 and eculizumab are recombinant, humanized monoclonal antibodies that bind the same epitope on complement protein C5 and deliver rapid, sustained, and specific inhibition of C5 activation and the terminal complement cascade through identical mechanisms of action. Due to its close pharmacological relationship to eculizumab and specificity for C5, ALXN1210 is anticipated to allow longer dosing intervals while having a safety and efficacy profile similar to eculizumab. While eculizumab is an effective therapy for the treatment of aHUS, chronic administration of the eculizumab regimen may pose an important burden to patients, many of whom have to miss days of work or school to accommodate once-every-2-week treatment. In some cases, patients may refuse treatment or are not compliant due to the frequency of treatment. Practice survey research supports the assumption that less frequent once-every-8-week infusions associated with ALXN1210 will have a positive impact on daily life for patients and their caregivers.

5.1.2. Identified and Potential Risks

5.1.2.1. Infections (N. Meningitidis and Other Encapsulated Organisms)

Increased susceptibility to infection with encapsulated bacteria, particularly *N. meningitidis*, is a known risk associated with complement inhibition. Similar to eculizumab, the main risk associated with ALXN1210 is the risk of meningococcal infections. Specific risk mitigation measures are in place to address this risk, as described in [Section 9.8](#).

5.1.2.2. Immunogenicity

Therapeutic proteins, including humanized mAbs like ALXN1210, may be associated with immunogenicity reactions. Consequently, monitoring of immunogenicity is in place for this study, as described in [Section 7.3](#) and [Section 11.6](#). No immunogenicity reactions have been observed to date in clinical studies with ALXN1210.

5.1.2.3. Pregnancy Exposure

No studies of ALXN1210 have been conducted in pregnant women. Pregnant or nursing female patients are excluded from the clinical trial. Patients enrolled in the study, and their spouse/partner, will use a highly effective or acceptable method of contraception as required in [Section 9.10](#).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective of the study is to assess the efficacy of ALXN1210 in complement inhibitor treatment naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA as characterized by thrombocytopenia, hemolysis, and renal impairment.

6.1.2. Secondary Objectives

The secondary objectives of the study are to assess the following:

1. To characterize the safety and tolerability of ALXN1210 in this patient population
2. To evaluate the efficacy of ALXN1210 by the following additional measures:
 - a. Dialysis requirement status
 - b. Time to Complete TMA Response
 - c. Complete TMA Response status over time
 - d. Observed value and change from baseline in estimated glomerular filtration rate (eGFR)
 - e. Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
 - f. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
 - g. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
 - h. Change from baseline in quality of life (QoL), as measured by EuroQol 5 dimensions 3 level (EQ-5D-3L; all patients), Functional Assessment of Chronic Therapy (FACIT) Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires
 - i. TMA parameters in patients who discontinue treatment but remain in the study
3. To characterize the PK/pharmacodynamics (PD) of ALXN1210 by the following measures:
 - a. Changes in serum ALXN1210 concentration over time
 - b. Changes in free C5 concentrations over time
 - c. Changes in free C5 and ALXN1210 concentration in patients who discontinue treatment but remain in the study
4. To evaluate the long-term safety and efficacy of ALXN1210

6.2. Endpoints

6.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

6.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study are the following and will be measured through 26 weeks and over the entire study period:

1. Dialysis requirement status
2. Time to Complete TMA Response
3. Complete TMA Response status over time
4. Observed value and change from baseline in eGFR
5. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
6. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
7. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
8. Change from baseline in QoL, as measured by EQ-5D-3L (all patients), FACIT Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires
9. TMA parameters in patients who discontinue treatment but remain in the study

6.2.3. Pharmacokinetic and Pharmacodynamic Endpoints

The PK and PD endpoints of this study are the following:

1. Changes in serum ALXN1210 concentration over time
2. Changes in free C5 concentrations over time
3. Changes in free C5 and ALXN1210 concentration in patients who discontinue treatment but remain in the study

6.2.4. Safety Endpoints

The safety and tolerability of ALXN1210 will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of AEs and SAEs. The proportion of patients who develop antidrug antibodies (ADA) will also be assessed.

6.2.5. Exploratory Endpoints

6.2.5.1. Biomarkers and APC Activity Endpoints

Exploratory biomarkers of PD effect may include, but are not limited to, change from baseline in levels of markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptor 1 [sTNFR1]), endothelial activation/damage (eg, soluble vascular adhesion molecule 1 [sVCAM-1], thrombomodulin), coagulation (eg, D-dimer), and renal injury (eg, cystatin C). Additional assessments may include measurements of ALXN1210 excretion in urine, chicken red blood cell (cRBC) hemolysis, total C5, autoantibodies to complement proteins (eg, anti-factor H) and APC activity (eg, Modified Ham's test, complement deposition assays).

6.2.5.2. Genetics Endpoints

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ALXN1210. Patients (or legal guardians) may decline from providing a sample for exploratory genetics and still participate in the study.

6.2.5.3. Additional Signs or Symptoms of aHUS and Resource Utilization

Resource utilization will be assessed using the Resource Utilization Patient Questionnaire ([Appendix H](#)) and additional signs or symptoms of aHUS will be assessed using the Patient-reported aHUS Symptoms Questionnaire ([Appendix I](#)).

The Investigator will evaluate extra-renal signs or symptoms of aHUS using a composite of clinical laboratory measurements, vital signs, and an organ system review.

7. INVESTIGATIONAL PLAN

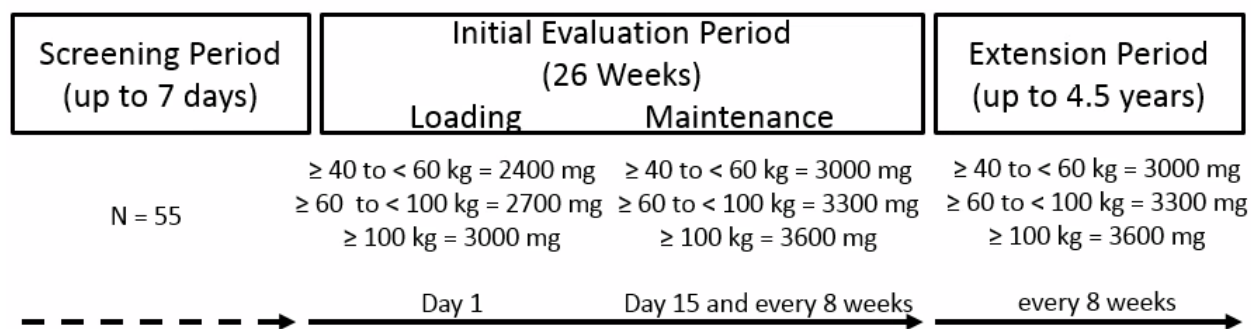
7.1. Summary of Study Design

Study ALXN1210-aHUS-311 is a Phase 3, open-label, single arm, multicenter study to evaluate the safety and efficacy of ALXN1210 administered by intravenous (IV) infusion to adolescent (12 to < 18 years of age) and adult (≥ 18 years of age) patients with aHUS. The study will enroll approximately 55 patients to receive ALXN1210. All patients must be naïve to complement inhibitor treatment and include at least 6 and up to 10 adolescent (12 to < 18 years of age at Screening) patients and at least 10 and up to 25 patients with prior kidney transplants. A minimum of 30 patients who meet all laboratory criteria for TMA (platelet count of < 150,000 per microliter, LDH $\geq 1.5 \times$ upper limit of normal (ULN), hemoglobin \leq lower limit of normal (LLN), and serum creatinine level \geq ULN) as determined by the central laboratory at Day 1, will be enrolled.

The study consists of an up to 7 day Screening Period, a 26-week Initial Evaluation Period, and an Extension Period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first. Dosages are based on the patient's body weight recorded at the last visit or more recently (Table 6). Patients will receive a loading dose of ALXN1210 IV (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg) on Day 1, followed by maintenance doses of ALXN1210 IV (3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg) on Day 15 and once every 8 weeks (q8w) thereafter for a total of 26 weeks of treatment in the Initial Evaluation Period followed by maintenance doses q8w in the Extension Period (Figure 1). The end of trial is defined as the last patient's last visit.

Figure 1 illustrates the study design.

Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-aHUS-311



7.2. Discussion of Design

This Phase 3, open-label, single arm study will evaluate the safety and efficacy of treatment with ALXN1210. Although no formal comparison analyses are planned for this study, results from ALXN1210-treated patients will be evaluated in the context of results reported in eculizumab

studies such as C10-004 trial, for which study design and conduct were similar to the current study.

7.3. Schedule of Assessments

The Schedule of Assessments for Screening and the Initial Evaluation Period is shown in [Table 1](#). The Schedule of Assessments for the Extension Period is shown in [Table 2](#).

Refer to the Laboratory Manual for details on the number of samples and volumes for all sampling and tests during the study.

Additional (unscheduled) visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments will be performed at the discretion of the Investigator. Any tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the electronic Case Report Forms (eCRFs). Local laboratory or central laboratory analysis may be used for Unscheduled Visit tests. However, if local laboratory tests are to be used, duplicate samples will be collected at the Unscheduled Visit for central laboratory testing.

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Initial Evaluation Period

Period	Screening	Initial Evaluation Period																
		-7 to -1	1	8	15	22	29	43	57	71	85	99	113	127	141	155	169	183 ^v /ET
Study Day	-7 to -1																	
Window (day)	N/A		±2	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±2
Informed consent	X																	
Confirmation or administration of meningococcal vaccination ^a	X																	
Medical history and demographics	X																	
ADAMTS13	X																	
ST-HUS screen ^b	X																	
Direct Coombs test	X																	
Height	X																	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^c	X	X		X					X				X					X
FACIT-Fatigue questionnaire /Pediatric FACIT-Fatigue questionnaire ^{d,e}		X	X			X			X				X					X
EQ-5D-3L questionnaire ^e		X	X			X			X				X					X
Patient-reported aHUS symptoms questionnaire ^e		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Resource utilization patient questionnaire ^e		X				X			X				X					X
Physical examination	X																	X
Abbreviated physical examination ^f		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of extra-renal signs or symptoms of aHUS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG ^h	X							X										X
Chemistry ⁱ	X ^w	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LDH isozymes ^j		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation ^k	X ^w	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry	X	X		X		X		X		X		X		X				X
PK/PD sampling ^l		X ^l		X ^l		X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l
Exploratory APC activity ^m		X		X			X		X		X		X		X			X
Exploratory serum and plasma biomarkers ⁿ		X		X					X				X					X
Exploratory urine biomarkers ^o		X		X					X				X					X
Exploratory urine ALXN1210 ^p		X		X		X			X									
Exploratory autoantibody ^q		X							X									
Exploratory genetic sample ^r		X																
Immunogenicity (ADA) ^s		X							X				X					X
Review safety card ^t		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ^u																		
Adverse events																		
ALXN1210 administration ^v		X		X					X				X					

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Initial Evaluation Period (Continued)

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; APC = alternative pathway of complement; ECG = electrocardiogram; EOI = end of infusion; EQ-5D-3L = EuroQol 5 dimensions 3 level; ET = early termination; FACIT = functional assessment of chronic illness therapy; HUS = hemolytic uremic syndrome; LDH = lactate dehydrogenase; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life; ST-HUS = Shiga toxin-related hemolytic uremic syndrome

- ^a All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.
- ^b Stool sample.
- ^c Female patients of childbearing potential only. Serum pregnancy test at Screening and Day 183/ET; urine or serum pregnancy test at all other required time points. A negative pregnancy test result is required prior to administering study drug to female patients of childbearing potential at the indicated study visits.
- ^d FACIT Fatigue version 4 will be used for patients ≥ 18 years of age at Screening. Pediatric FACIT Fatigue will be used for patients < 18 years of age at Screening.
- ^e On dosing days, patient-reported assessments will be performed prior to dosing.
- ^f Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated examination.
- ^g Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (millimeters of mercury [mm Hg]), pulse oximetry, heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [$^{\circ}$ C] or degrees Fahrenheit [$^{\circ}$ F]). On dosing days, vital signs will be taken predose.
- ^h Single 12-lead ECG will be collected at Screening, Day 57, and predose on Day 183 and any time on the ET visit day. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- ⁱ Clinical safety laboratory measurements will be collected predose on dosing days. LDH for eligibility will be determined from the chemistry assessment. Follicle-stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.
- ^j Serum sample for LDH isozyme testing will only be collected at selected sites at any/all timepoints prior to ALXN1210 dosing, dependent on sample testing availability.
- ^k Assessment for safety, as well as the primary and secondary endpoints.
- ^l Serum samples for PK/PD analyses will be collected at the indicated visits. For indicated visits falling on dosing days, samples will be collected predose (within 0.5 hours prior to the start of infusion) and at end of infusion (EOI) (within 0.5 hours after the EOI from the patient's opposite, noninfused arm). In order to minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. For indicated visits not falling on dosing days, samples may be collected at any time that visit day. All collection times will be recorded in the eCRF.
- ^m Collection will be predose on days of dosing and for days without dosing, at any time that visit day. All collection times will be recorded in the eCRF.
- ⁿ Collection will be predose. All collection times will be recorded in the eCRF.
- ^o Collection will be predose and combined with urine stabilizing buffer. All collection times will be recorded in the eCRF.
- ^p Urine sample for drug measurement will be collected at end of infusion (EOI) (within 0.5 hours after the EOI) on Days 1, 15, and 71; and at any time on Day 29.
- ^q Collection will be predose.
- ^r A single whole blood collection from those patients who consent to genetic testing can be collected anytime during the study.
- ^s ADA serum samples will be collected predose on Days 1, 71, and 127. Day 183 collection will occur prior to first dose in the Extension Period. Early termination collection will occur at any time on the ET visit day. All collection times will be recorded in the eCRF.
- ^t Review the Clinical Trial Participant Safety Information Card with the patient and discuss the importance of carrying the safety card at all times, and the risks ALXN1210 treatment, including the risk of meningococcal infection.
- ^u Concomitant medications must be collected at all study visits and checked against the prohibited medication listed in [Section 9.7](#).

Table 1: Schedule of Study Visits and Assessments: Screening Through End of Initial Evaluation Period (Continued)

^v The dose of ALXN1210 is based on the patient's last recorded study visit body weight (Day 1 dosing is based on the body weight at Screening).

^w If a local laboratory is used to define eligibility, additional samples will be collected during the Screening Period for LDH, platelet count, hemoglobin and serum creatinine and tested at the central laboratory.

^x The primary efficacy endpoint assessment is before dosing on Day 183. Dosing on Day 183 is the start of the Extension Period. Please refer to additional Day 183 postdose assessments in [Table 2](#).

Table 2: Schedule of Study Visits and Assessments: Extension Period Day 183 to Day 911

Period	Extension Period													
	183 ^p	239	295	351	407	463	519	575	631	687	743	799	855	911
Study Day	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Window (day)	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-Fatigue questionnaire /Pediatric FACIT-Fatigue questionnaire ^{b,c}				X				X			X			X
EQ-5D-3L questionnaire ^c				X				X			X			X
Patient-reported aHUS symptoms questionnaire ^c		X	X	X	X	X	X	X	X	X	X	X	X	X
Resource utilization patient questionnaire ^c		X	X	X	X	X	X	X	X	X	X	X	X	X
Abbreviated physical examination ^d		X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of extra-renal signs or symptoms of aHUS		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^e		X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X
LDH isozymes ^f		X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and coagulation ^g		X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD sampling ^h	X ^h			X ^h				X ^h			X ^h			X ^h
Exploratory APC activity ⁱ		X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory serum and plasma biomarkers ^j		X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory urine biomarkers ^k		X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA) ^l				X ^l				X ^l			X ^l			X ^l
Review safety card ^m		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ⁿ	←Monitor continuously→													
Adverse events	←Monitor continuously→													
ALXN1210 administration ^o	X ^o	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; APC = alternative pathway of complement; aHUS = atypical hemolytic uremic syndrome; BP = blood pressure; eCRF = electronic case report form; EOI = end of infusion; EQ-5D-3L = EuroQol five dimensions 3 level; ET = early termination; FACIT = functional assessment of chronic illness therapy; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life

Note: For patients who terminate the study early, information on the assessments to be conducted on the ET visit day and further follow-up is provided in [Table 3](#).

Patients who discontinue ALXN1210 treatment, but remain in the study without treatment, should continue attending their scheduled protocol visits until Day 1863 ([Section 8.3.2](#)).

For patients who discontinue ALXN1210 treatment, remain in the study, and further receive retreatment should undergo assessments as described in [Section 8.3.2.1](#).

^a Female patients of childbearing potential only; urine or serum pregnancy test at all required time points. A negative pregnancy test result is required prior to administering ALXN1210 at the indicated study visits.

^b FACIT Fatigue version 4 will be used for patients ≥ 18 years of age at Screening. Pediatric FACIT Fatigue will be used for patients < 18 years of age at Screening.

^c On dosing days, patient-reported assessments will be performed prior to dosing.

^d Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated examination.

Table 2: Schedule of Study Visits and Assessments: Extension Period Day 183 to Day 911 (Continued)

- ^e Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (millimeters of mercury [mm Hg]), pulse oximetry, heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken predose.
- ^f Serum sample for LDH isozyme testing will only be collected at selected sites at any/all timepoints prior to ALXN1210 dosing, dependent on sample testing availability.
- ^g Assessment for safety, as well as the primary and secondary endpoints.
- ^h Serum samples for PK/PD analysis will be collected predose (within 0.5 hours prior to the start of infusion) and EOI (within 0.5 hours after the EOI) on Days 351, 575, 743, and 911; EOI (within 0.5 hours after the EOI) on Day 183. End of infusion samples will be drawn from the patient's opposite, noninfused arm. In order to minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. For patients who discontinue treatment but remain in the study, 1 PK/PD sample at any time will be collected as per protocol schedule until approximately 39 weeks after the last dose of ALXN1210. In case of retreatment, if the patient starts the retreatment on a scheduled visit which does not include PK/PD sample collection, PK/PD samples must be collected predose and at EOI. If a supplemental dose is administered, PK/PD samples will be collected predose and at EOI. All collection times will be recorded in the eCRF.
- ⁱ Collection will be predose on days of dosing and for days without dosing, at any time that visit day. All collection times will be recorded in the eCRF.
- ^j Collection will be predose on days of dosing and for days without dosing, at any time that visit day. All collection times will be recorded in the eCRF.
- ^k Collection will be predose on days of dosing and for days without dosing, at any time that visit day, and combined with urine stabilizing buffer. All collection times will be recorded in the eCRF.
- ^l A predose serum sample will be collected on Days 351, 575, 743, and Day 911. For patients who discontinue treatment but remain in the study, ADA sample will be collected at any time during the visits until approximately 39 weeks after the last dose of ALXN1210. In case of retreatment, if the patient starts the retreatment on a scheduled visit which does not include ADA sample collection, a predose ADA sample must be collected. If a supplemental dose is administered, a predose ADA sample will be collected. All collection times will be recorded in the eCRF.
- ^m Review the Clinical Trial Participant Safety Information Card with the patient and discuss the importance of carrying the safety card at all times, and the risks ALXN1210 treatment, including the risk of meningococcal infection.
- ⁿ Concomitant medications must be collected at all study visits (and at the 56 [± 5]-day follow-up phone call for patients who terminate the study early) and checked against the prohibited medication listed in [Section 9.7](#).
- ^o Extension Period begins at the start of Day 183 dosing. The dose of ALXN1210 is based on the patient's body weight recorded at the last visit or more recently. For patients who discontinue ALXN1210 treatment, remain in the study, and further receive retreatment, the dosing details are provided in [Section 8.3.2.1](#).

Table 3: Schedule of Study Visits and Assessments: Extension Period Day 967 to Day 1863

Period	Extension Period																
	967	1023	1079	1135	1191	1247	1303	1359	1415	1471	1527	1583	1639	1695	1751	1807	1863/ ET/EOS
Study Day	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Window (day)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-Fatigue questionnaire /Pediatric FACIT-Fatigue questionnaire ^{b,c}				X				X				X				X	X
EQ-5D-3L questionnaire ^c				X				X				X				X	X
Physical examination																	X
Abbreviated physical examination ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of extra-renal signs or symptoms of aHUS				X				X				X				X	X
Vital signs ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG ^f																	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LDH isozymes ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and coagulation ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD sampling ⁱ			X ⁱ			X ⁱ			X ⁱ				X ⁱ			X ⁱ	X ⁱ
Exploratory APC activity ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory serum and plasma biomarkers ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory urine biomarkers ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ADA) ^m			X ^m			X ^m			X ^m				X ^m			X ^m	X ^m
Review safety card ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ^o	←Monitor continuously→																
Adverse events	←Monitor continuously→																
ALXN1210 administration ^p	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = antidrug antibody; APC = alterative pathway of complement; aHUS = atypical hemolytic uremic syndrome; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; EOS = end of study; EQ-5D-3L = EuroQol five dimensions 3 level; ET = early termination; FACIT = functional assessment of chronic illness therapy; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; QoL = quality of life
Note: If a patient terminates from the study early, ET assessments will be conducted as soon as possible. A follow-up phone call will be performed 8 weeks (56 days) ± 5 days following the patient’s last dose of ALXN1210 to collect information on concomitant medications, nonpharmacological therapies and procedures, and adverse events. Patients who discontinue ALXN1210 treatment, but remain in the study without treatment, should continue attending their scheduled protocol visits until Day 1863 (Section 8.3.2). For patients who discontinue ALXN1210 treatment, remain in the study, and further receive retreatment should undergo assessments as described in Section 8.3.2.1.

^a Female patients of childbearing potential only. Serum pregnancy test on the ET visit day only; urine or serum pregnancy test at all other required time points. A negative pregnancy test result is required prior to administering ALXN1210 to female patients of childbearing potential at the indicated study visits.

^b FACIT Fatigue version 4 will be used for patients ≥ 18 years of age at Screening. Pediatric FACIT Fatigue will be used for patients < 18 years of age at Screening.

Table 3: Schedule of Study Visits and Assessments: Extension Period Day 967 to Day 1863 (Continued)

- ^c On dosing days, patient-reported assessments will be performed prior to dosing.
- ^d Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated examination.
- ^e Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic BP (millimeters of mercury [mm Hg]), pulse oximetry, heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]). On dosing days, vital signs will be taken predose.
- ^f Single 12-lead ECG will be collected at Day 1863 or ET. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- ^g Serum sample for LDH isozyme testing will only be collected at selected sites at any/all timepoints prior to ALXN1210 dosing, dependent on sample testing availability.
- ^h Assessment for safety, as well as the primary and secondary endpoints.
- ⁱ Serum samples for PK/PD analysis will be collected predose (within 0.5 hours prior to the start of infusion) and EOI (within 0.5 hours after the EOI) on Days 1079, 1247, 1415, 1639, and 1807; and at any time on Day 1863 or ET. End of infusion samples will be drawn from the patient's opposite, noninfused arm. In order to minimize needle sticks to the patient, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the postdose sample must be drawn from the opposite, noninfused arm. For patients who discontinue treatment, but remain in the study, 1 PK/PD sample at any time will be collected as per protocol schedule until approximately 39 weeks after the last dose of the study drug. In case of retreatment, if the patient starts the retreatment on a scheduled visit which does not include PK/PD sample collection, PK/PD samples must be collected predose and at EOI. If a supplemental dose is administered, PK/PD samples will be collected predose and at EOI. All collection times will be recorded in the eCRF.
- ^j Collection will be predose on days of dosing and for days without dosing, at any time that visit day. All collection times will be recorded in the eCRF.
- ^k Collection will be predose on days of dosing and for days without dosing, at any time that visit day. All collection times will be recorded in the eCRF.
- ^l Collection will be predose on days of dosing and for days without dosing, at any time that visit day, and combined with urine stabilizing buffer. All collection times will be recorded in the eCRF.
- ^m A predose serum sample will be collected on Days 1079, 1247, 1415, 1639, and 1807. A serum sample will also be collected at any time on Day 1863 or ET. For patients who discontinue treatment but remain in the study, ADA sample will be collected at any time during the visits until approximately 39 weeks after the last dose of ALXN1210. In case of retreatment, if the patient starts the retreatment on a scheduled visit which does not include ADA sample collection, a predose ADA sample must be collected. If a supplemental dose is administered, a predose ADA sample will be collected. All collection times will be recorded in the eCRF.
- ⁿ Review the Clinical Trial Participant Safety Information Card with the patient and discuss the importance of carrying the safety card at all times, and the risks ALXN1210 treatment, including the risk of meningococcal infection.
- ^o Concomitant medications must be collected at all study visits (and at the 56 [± 5]-day follow-up phone call for patients who terminate the study early) and checked against the prohibited medication listed in [Section 9.7](#).
- ^p The dose of ALXN1210 is based on the patient's body weight recorded at the last visit or more recently. For patients who discontinue ALXN1210 treatment, remain in the study, and further receive retreatment, the dosing details are provided in [Section 8.3.2.1](#).

8. STUDY POPULATION

A total of approximately 55 patients with documented aHUS will be enrolled and assigned to treatment with ALXN1210 at approximately 200 investigative sites globally. The study will enroll at least 6 and up to 10 adolescent (12 to < 18 years of age at Screening) patients and at least 10 and up to 25 patients with prior kidney transplants. A minimum of 30 patients who meet all laboratory criteria for TMA (platelet count of < 150,000 per microliter, LDH $\geq 1.5 \times$ upper limit of normal (ULN), hemoglobin \leq lower limit of normal (LLN), and serum creatinine level \geq ULN) as determined by the central laboratory at Day 1, will be enrolled.

Individuals who do not satisfy the criteria for participation in this study (screen failure) may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Patients may be rescreened a maximum of 2 times.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

8.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria and none of the exclusion criteria:

1. Male or female patients ≥ 12 years of age and weighing ≥ 40 kg at the time of consent.
2. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:
 - a. Platelet count < 150,000 per microliter (μL) during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
 - b. LDH $\geq 1.5 \times$ upper limit of normal (ULN) during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin \leq lower limit of normal (LLN) for age and gender during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
 - c. Serum creatinine level \geq ULN during the Screening Period in adults (≥ 18 years of age), or $\geq 97.5^{\text{th}}$ percentile for age ([Appendix A](#)) at Screening in adolescents (12 to < 18 years of age) (patients who require dialysis for acute kidney injury are also eligible).
3. Among patients with a kidney transplant:
 - a. Known history of aHUS prior to current kidney transplant, **or**
 - b. No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (eg, suspending or reducing the dose) of calcineurin inhibitor ([CNI]; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor ([mTORi]; eg, sirolimus, everolimus).
4. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.
5. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of,

initiating study drug. Patients who receive a meningococcal vaccine less than 2 weeks before initiating ALXN1210 treatment must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.

6. Patients < 18 years of age must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines.
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance ([Section 9.10](#)) for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.
8. Willing and able to give written informed consent and comply with the study visit schedule. For patients < 18 years of age, patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/ Institutional (or Independent) Ethics Committee [IEC]).

Evaluation of Inclusion Criteria 2a and 2b may be based on local laboratory results within 28 days prior to the start of the Screening Period or laboratory results obtained during the Screening Period from a local or central laboratory. If a local laboratory is used to define eligibility, additional samples will be collected during the Screening Period for LDH, platelet count, hemoglobin and serum creatinine and tested at the central laboratory. If patients are found to not meet the eligibility criteria for serum creatinine (Inclusion Criterion 2c) based on central laboratory results, they must not be enrolled into the study; if the subject has received the first dose of ALXN1210 the patient must be withdrawn from the study, and may be replaced. All analyses in this study will be based on results from the central laboratory. A central laboratory result for Inclusion Criterion 2c may not be available prior to first dose; results received after the first dose indicating that eligibility is not satisfied could lead to discontinuation and replacement of the patient.

8.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

1. Known familial or acquired 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13' (ADAMTS13) deficiency (activity < 5%). Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.
2. Known Shiga toxin-related hemolytic uremic syndrome (ST-HUS) as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin producing bacteria. Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.

3. Positive direct Coombs test. Eligibility may be defined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent. In these cases informed consent will be provided prior to collecting the data for the trial.
4. Known Human Immunodeficiency Virus (HIV) infection.
5. Unresolved meningococcal disease.
6. Patients with a confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics.
7. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.
8. Pregnancy or breastfeeding.
9. Heart, lung, small bowel, pancreas, or liver transplant.
10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria ([Appendix B](#)).
11. Among patients without a kidney transplant, history of kidney disease other than aHUS, such as:
 - a. Known kidney biopsy finding suggestive of underlying disease other than aHUS
 - b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg small kidneys for age)
 - c. Known family history and/or genetic diagnosis of noncomplement mediated genetic renal disease (eg, focal segmental glomerulosclerosis)
12. Identified drug exposure-related HUS.
13. Receiving PE/PI, for 28 days or longer, prior to the start of Screening for the current TMA.
14. History of malignancy within 5 years of Screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
15. Bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) within the last 6 months prior to the start of Screening.
16. HUS related to known genetic defects of cobalamin C metabolism.
17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), or antiphospholipid antibody positivity or syndrome.
18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD).
19. Patients receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening.

20. Patients receiving other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless:
 - a. part of an established post-transplant antirejection regimen, or
 - b. patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or
 - c. steroids are being used for a condition other than aHUS (eg, asthma).
21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.
22. Prior use of eculizumab or other complement inhibitors.
23. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
24. Any medical or psychological condition that, in the opinion of the Investigator or Sponsor, could increase the risk to the patient by participating in the study or confound the outcome of the study.
25. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
26. Use of tranexamic acid within 7 days prior to Screening is prohibited.

Laboratory results for Exclusion Criterion number 1 and/or Exclusion Criterion number 2 may not be available prior to first dose. Later results for Exclusion Criterion number 1 and/or Exclusion Criterion number 2 could lead to discontinuation and replacement of the patient (please refer to [Section 8.3](#) for potential discontinuation and replacement details).

8.3. Discontinuation

8.3.1. Early Termination of Patients From the Study

The criteria for early termination of patients from the study include:

- Withdrawal of consent: A patient has the right to withdraw from the study at any time.
- Patient with prior kidney transplant developing AMR (C4d positive renal biopsy) and for whom rituximab is deemed the appropriate therapy: patient must be terminated from the study and receive standard of care therapy.
- Intake of certain prohibited medications as described in [Section 9.7](#).
- Patient who is receiving ALXN1210 as a part of retreatment ([Section 8.3.2.1](#)) chooses to discontinue ALXN1210.
- The Sponsor Medical Monitor or the Investigator deems it is in the best interest of the patient.

If a patient terminates from the study early, the Sponsor and site monitor will be notified and the assessments specified for the Early Termination (ET) visit (as shown in the Schedule of

Assessments, [Section 7.3, Table 3](#)) will be performed as soon as possible. In addition, a follow-up phone call will be performed 8 weeks (56 days) \pm 5 days following the patient's last dose of ALXN1210, to collect concomitant medications, nonpharmacological therapies and procedures, and AEs.

At the time of the termination, if there is an ongoing AE or an unresolved laboratory result that in the opinion of the investigator, is significantly outside of the reference range and clinically significant ([Section 11.4](#)), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

The reason for early termination will be recorded on the eCRF.

Patients who terminate early from the study will not be replaced.

8.3.2. Discontinuation of ALXN1210 Treatment and Continuation in the Study

Patients who discontinue ALXN1210 treatment will be allowed to continue in the study for the remainder of the visits without receiving ALXN1210 dosing.

Patients should be permanently discontinued from ALXN1210 treatment if any of the following occur during the study:

- Serious infusion reaction (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to [Appendix C](#)) or serum sickness-like reactions manifesting 1 to 14 days after drug administration;
- Pregnancy or planned pregnancy; or
- The Sponsor Medical Monitor or the Investigator deems it is in the best interest of the patient.

The Investigator should notify the Medical Monitor as soon as possible prior to discontinuing a patient's study treatment and provide the rationale for discontinuing.

If a patient is discontinued from ALXN1210 treatment, but remains in the study, patient should continue attending his or her scheduled protocol visits until Day 1863. During these visits, all assessments except for ALXN1210 administration as described in the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)) should be performed. The PK/PD (1 sample at any time) and ADA samples will be collected as per protocol schedule until about 39 weeks after the last dose of the study drug.

Any patient who discontinues the ALXN1210 treatment but remains in the study and develops abnormal TMA parameter (as specified in [Section 8.3.2.1](#)) before Day 1863, will have the opportunity for retreatment ([Section 8.3.2.1](#)). If the study drug is discontinued again (after retreatment), then the patient will be terminated from the study and ET procedures and follow-up will be performed as described in [Section 8.3.1](#).

The reason for the treatment discontinuation will be recorded on the eCRF.

If a female patient is permanently discontinued from ALXN1210 treatment due to pregnancy, the Investigator will attempt to follow-up until the outcome of the pregnancy ([Section 11.8](#)).

8.3.2.1. Retreatment of Patients who Discontinue ALXN1210 Treatment

A patient who discontinues ALXN1210 treatment, but remains in the study, and develops abnormal TMA parameter (as indicated by criteria No. 1 below) before Day 1863, may be restarted on ALXN1210, if all 3 conditions below are fulfilled:

1. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, or kidney injury based on any one of the following laboratory findings:
 - Platelet count $< 150,000/\mu\text{L}$, or
 - LDH $> 1.5 \times \text{ULN}$ with hemoglobin $\leq \text{LLN}$ for age and gender, or
 - Serum creatinine $\geq \text{ULN}$ in adults (≥ 18 years of age), or $\geq 97.5^{\text{th}}$ percentile for age ([Appendix A](#)) in adolescents (12 to < 18 years of age).

Note: The TMA laboratory parameter must be confirmed on at least one repeated measure. The above laboratory results can be obtained at either the central laboratory (preferable) or the site's local laboratory.

2. The Investigator believes that the patient will potentially benefit from retreatment, initiates a discussion with the Sponsor Medical Monitor, and provides a medically justified rationale. The Investigator and Medical Monitor mutually agree on retreatment, and the decision is documented.
3. The patient agrees to the consent addendum for retreatment.

If the decision to re-treat with ALXN1210 occurs on a scheduled study visit, then dosing may begin on that day.

- Patient will receive a loading dose of ALXN1210 IV based on the weight recorded at the last visit or more recently (2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg). All assessments will be performed per the protocol schedule ([Table 2](#) and [Table 3](#)). If start of the retreatment occurs on a visit which does not include PK/PD sample collection, PK/PD samples will be collected predose and at EOI, along with a predose ADA sample.
- Two weeks after the loading dose, the patient will receive a supplemental maintenance dose of ALXN1210 IV at an unscheduled visit, based on the weight at the last visit or more recently (≥ 40 to < 60 kg = 3000 mg; ≥ 60 to < 100 kg = 3300 mg; ≥ 100 kg = 3600 mg). An abbreviated physical examination will be conducted, vital signs will be collected, and the safety card will be reviewed with the patient. Pharmacokinetic/PD samples will be collected predose and at EOI along with a predose ADA sample.
- Six weeks after the supplemental maintenance dose, the patient will return to the site at the scheduled study visit. At this visit, patient will receive maintenance dose of ALXN1210, undergo all assessments per the protocol schedule ([Table 2](#) and [Table 3](#)), and then continue to attend the visits every 8 weeks per the protocol schedule.

If the decision to re-treat with ALXN1210 occurs between scheduled study visits:

- A supplemental loading dose of ALXN1210 may be administered. An abbreviated physical examination will be conducted, vital signs will be collected, and the safety card will be reviewed with the patient. Pharmacokinetic/PD samples will be collected predose and at EOI along with a predose ADA sample.
- The Medical Monitor and the Investigator will determine administration of maintenance dose of ALXN1210 further to facilitate alignment with Schedule of Assessment ([Table 2](#) and [Table 3](#)) as appropriate. The timing of subsequent visits may be modified to accommodate realignment to Schedule of Assessment, these will not be considered deviations to visit windows.

8.3.3. Discontinuation of Study/Site Termination by Sponsor or Health Authority

The Sponsor or Health Authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the study drug
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations
- Submission of knowingly false information from the Investigator to the Sponsor and/or regulatory authorities

Should the study be terminated early, the Sponsor will notify the national competent authority and the IRB/IEC according to local requirements.

8.3.4. Replacements

If it is determined at any point that a patient's Screening data does not satisfy Inclusion Criterion number [2c](#), Exclusion Criterion number [1](#), and/or Exclusion Criterion number [2](#), after receiving at least 1 dose of investigational product (eg, patient local laboratory data used to confirm eligibility criteria are subsequently determined by a central laboratory to no longer satisfy eligibility criteria), the patient will be discontinued from the study and may be replaced. Early termination procedures will be performed on patients who are terminated early ([Section 8.3.1](#)) and all AEs will be collected until 56 days after the patient's last dose of study drug ([Section 11.7.6.1](#)).

As described in [Section 15.3](#), the Full Analysis Set (FAS) will be based on a modified intent to treat (mITT) approach, and the patients discontinued from the study for the reasons described above will be excluded from the FAS. The aim of the replacement process is to yield a FAS that includes the planned number of patients all satisfying key inclusion and exclusion criteria.

8.3.5. End of Study Definition

The end of the study is defined as the date of the last patient's last visit in the Extension Period.

9. STUDY TREATMENT

9.1. Materials and Supplies

9.1.1. Description of Study Drugs

ALXN1210, a recombinant, humanized anti-C5 monoclonal antibody composed of two 448 amino acid heavy chains and two 214 amino acid light chains, is an IgG2/4 kappa immunoglobulin consisting of human constant regions, and murine complementarity-determining regions grafted onto human framework light- and heavy-chain variable regions. ALXN1210 is produced in Chinese hamster cells and was designed through minimal targeted engineering of eculizumab by introducing 4 unique amino acid substitutions to its heavy chain to extend antibody half-life. ALXN1210 and eculizumab share over 99% primary amino acid sequence identity and have very similar pharmacology.

ALXN1210 drug product is supplied for clinical studies as a sterile, preservative-free 10-mg/mL solution in single-use vials and designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Refer to [Table 4](#) and the current IB for additional information.

Table 4: Study Drug

Product Name	ALXN1210
Dosage Form	Concentrated solution (10 mg/mL) for infusion
Route of Administration	Intravenous infusion
Physical Description	Clear to translucent, slight whitish color, practically free from particles
Manufacturer	Alexion Pharmaceuticals, Inc. or Contracted Manufacturing Organization

9.1.2. Study Drug Packaging and Labeling

ALXN1210 is packaged in United States Pharmacopeia (USP)/ European Union Pharmacopeia (EP) Type 1 borosilicate glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits. Please refer to the ALXN1210 Pharmacy Manual for details.

ALXN1210 orders will be released to each site upon receipt of all required documents based upon applicable regulations and once the site is activated in IXRS[®].

9.1.3. Study Drug Storage

Upon arrival of the study drug kits at the study site, the pharmacist (or trained designee) should promptly remove the study drug kits from the shipping cooler and store them in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. ALXN1210 should not be frozen. Study drug must be stored in a secure, limited-access storage area, and the temperature must be monitored daily.

The admixed drug product should be at room temperature prior to administration. The material must **not** be heated (eg, by using a microwave or other heat source) other than by ambient air temperature.

Please consult the Pharmacy Manual for further information regarding the storage conditions of reconstituted ALXN1210.

9.1.4. Study Drug Preparation and Infusion

ALXN1210 must NOT be administered as an IV push or bolus injection. Infusions of study drug should be prepared using aseptic technique. The patient's required dose of ALXN1210 will be further diluted into commercially available saline (0.9% sodium chloride; country-specific pharmacopeia) at the volume specified in Table 5. ALXN1210 admixture will be administered to the patient using an IV tubing administration set via an infusion pump. Use of a 0.2 micron filter is required during infusion.

Table 5: Dosing Reference Chart for ALXN1210 Dose Preparation

Dose Type	Body Weight (kg) ^a	Dose (mg)	ALXN1210 Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Minimum Infusion Duration minutes (hours)	Maximum Infusion Rate (mL/hour)
Loading	≥ 40 to < 60	2400	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700	270	270	540	102 (1.7)	318
	≥ 100	3000	300	300	600	108 (1.8)	333
Maintenance	≥ 40 to < 60	3000	300	300	600	140 (2.4)	250
	≥ 60 to < 100	3300	330	330	660	120 (2.0)	330
	≥ 100	3600	360	360	720	132 (2.2)	328

Please refer to the Pharmacy Manual for additional dose preparation instructions.

^a Body weight as recorded at the last study visit or more recently.

Doses of study drug must only be prepared and dispensed by qualified study personnel. Study drug is to be dispensed only to enrolled patients who are confirmed eligible for participation in this study. Once study drug is prepared for a patient, it can only be administered to that patient. Vials of study drug are for one-time use only and any drug product remaining in the vial should not be used for another patient. Any drug remaining in the infusion tubing or infusion bag should not be used for another patient.

Further details on preparation and dose administration of ALXN1210, as well as disposal of study drug, can be found in the Pharmacy Manual.

9.1.5. Study Drug Handling and Disposal

All clinical study material provided to the Investigator will be stored in a secure place, and allocated and dispensed by appropriately trained persons. Detailed records of the amounts of the investigational product received, dispensed, and destroyed will be maintained.

Unless otherwise notified, 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 pharmacy standard operating procedures (SOPs) for clinical study drugs. To satisfy regulatory requirements regarding drug accountability, at the end of the study all remaining ALXN1210 inventory will be reconciled and destroyed or returned to Alexion according to applicable regulations.

Please refer to the ALXN1210 Pharmacy Manual for further information.

9.2. Treatments Administered

Patients will receive ALXN1210 for 26 weeks during the Initial Evaluation Period. ALXN1210 will be administered as an IV infusion over approximately 2 hours. **ALXN1210 must NOT be administered as an IV push or bolus injection.**

The dose regimen for ALXN1210 during the Initial Evaluation Period is based on the patient's last recorded study visit body weight (Table 6). Patients will receive a loading dose of ALXN1210 IV on Day 1, followed by maintenance dosing of ALXN1210 IV on Day 15 and q8w thereafter.

Table 6: Loading and Maintenance Treatment Regimens

Body Weight ^a	Loading Dose (Day 1)	Maintenance Dose (Days 15, 71, and 127)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

^a Body weight as recorded at the last study visit.

After the Initial Evaluation Period, all patients will roll over into an Extension Period (which will continue until the product is registered or approved [in accordance with country-specific regulations] or for up to 4.5 years, whichever occurs first) during which all patients will receive ALXN1210 q8w.

The actual time of all dose administrations (including any retreatment/supplemental dose for retreatment [Section 8.3.2.1]) will be recorded in the patient's eCRF.

9.3. Method of Assignment to Treatment

This is an open-label study. Patients who satisfy all criteria for enrollment will be assigned to study treatment with ALXN1210 at the Baseline Visit (Day 1). The interactive voice- or web-response system (IxRS) will be used to assign vials containing ALXN1210 to each patient.

9.4. Rationale for Selection of Doses in the Study

The weight-based dosages of ALXN1210 in this study (Table 6) are premised on PK/PD data from early development studies in healthy adult volunteers as well as the available data from patients with PNH in an ongoing Phase 1b dose-finding study (ALXN1210-PNH-103) and an ongoing Phase 2 proof-of-concept study (ALXN1210-PNH-201). The selection of ALXN1210 dose regimen for patients with aHUS is based on targeting immediate, complete and sustained inhibition of terminal complement in patients with PNH, which is expected to correspond to immediate, complete and sustained inhibition of terminal complement in patients with aHUS.

9.5. Special Treatment Considerations

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. Please refer to Appendix C for guidance on identifying and managing potential drug infusion reactions.

9.6. Prior and Concomitant Medications and Nonpharmacologic Procedures

Prior medications (including vitamins and herbal preparations)—including those discussed in the exclusion criteria ([Section 8.2](#)) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the patient takes or undergoes within 28 days prior to the start of Screening until the first dose of ALXN1210—will be recorded on the patient’s eCRF. In addition, history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug, and for patients < 18 years of age at the time of enrollment, vaccination history for Hib and *Streptococcus pneumoniae* must be collected from birth.

All medication use and procedures undertaken during the study will be recorded in the patient’s source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications.

Concomitant medications will be recorded from the first infusion of study drug through 56 days after the patient’s last dose of study drug. Any changes in concomitant medications also will be recorded in the patient’s source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient’s standard of care during the study, or for the treatment of any AE, along with the allowed medications described below may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient’s source document/medical chart and eCRF.

9.7. Prohibited Medications and Procedures

Patients are prohibited from receiving any of the following medications and procedures at any time after the first dose of study drug for all patients in the study (even those who discontinue ALXN1210 treatment but remain in study) until completion of the study or early termination of the patient from the study:

- Eculizumab or other complement inhibitors
- Use of any other investigational drug or device as part of a clinical trial.
- IVIg (unless for an unrelated medical need e.g. hypogammaglobinemia)
- Rituximab
- PE/PI
- New dialysis within the first 48-hour period following the first dose of ALXN1210 unless there is a compelling medical need as assessed by (1) hypervolemia unresponsive to diuretics, (2) refractory electrolyte imbalance, or (3) new-onset uremic encephalopathy. Exceptions must be approved prior to administration of dialysis on a case-by-case basis by the Sponsor.

The following concomitant medications and procedures are allowed under certain circumstances and with the following restrictions:

- Use of other immunosuppressive therapies (such as steroids, mTORi [eg, sirolimus, everolimus], CNI [eg, cyclosporine or tacrolimus]) during the study are not allowed unless: a) part of an established post-transplant antirejection regime, or b) patient has

confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or c) steroids are being used for a condition other than aHUS (eg, asthma), or d) steroids initiated empirically prior to enrollment and are being tapered as standard of care.

Any patients receiving other complement inhibitors (including eculizumab) or undergoing PE/PI after the first dose of study drug will be withdrawn from the study.

9.8. Vaccination

Due to its mechanism of action, the use of ALXN1210 increases the patient's susceptibility to infection. To reduce the risk of infection, all patients must be vaccinated against *N. meningitidis*.

Patients must be vaccinated against *N. meningitidis* within 3 years prior to, or at the time of, receiving the first dose of ALXN1210. Patients who will be treated with drug less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).

It is recognized that some patients who have not been vaccinated against *N. meningitidis* within 3 years prior to receiving the first dose of ALXN1210 may not be able to receive a vaccination at the time of the first dose. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients will be provided a safety card to carry with them at all times and for 8 months after last dose of ALXN1210.

Additional discussion and explanation of the potential risks, signs, and symptoms will occur at specific time points as part of the review of the patient safety card and throughout the study as described in the Schedule of Assessments (Table 1, Table 2, and Table 3).

Patients < 18 years of age must also be vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines, prior to, or at the time of, receiving the first dose of ALXN1210.

Vaccination status for *N. meningitidis*, Hib, and *S. pneumoniae* will be recorded on the patient's eCRF.

9.9. Treatment Compliance

Patients will be administered study drug in a controlled setting under the supervision of the Investigator or designee, thereby ensuring compliance with study drug administration. The Investigator or designee will ensure that all patients are adequately informed on the specific

dosing regimen required for compliance with the study protocol, ensure that the patient receives the appropriate dose at the designated time points during the study and that adequate safety monitoring occurs during the infusion ([Section 9.5](#)).

9.10. Contraception Guidance

Before receiving study drug, female patients who consider themselves to be postmenopausal must provide evidence of menopause based on a combination of amenorrhea for at least 1 year and increased serum follicle-stimulating hormone (FSH) level (> 30 IU/L) (eg, in the absence of hormone replacement therapy, dietary phytoestrogens).

Female patients of childbearing potential must use a highly effective or acceptable method of contraception (as defined below), starting at Screening and continuing for at least 8 months after the last dose of study drug.

Highly effective contraceptive methods include:

1. Hormonal contraception associated with inhibition of ovulation
2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Vasectomized partner, provided that the partner is the patient's sole sexual partner
6. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Acceptable contraceptive methods include:

1. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study drug. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male patients must not donate sperm while on treatment and for at least 8 months after the last dose of study drug.

10. EFFICACY ASSESSMENTS

10.1. Primary Efficacy Assessment

The primary efficacy assessment is Complete TMA Response during the 26-week Initial Evaluation Period. The criteria for Complete TMA Response are the following:

1. Normalization of platelet count
2. Normalization of LDH
3. $\geq 25\%$ improvement in serum creatinine from baseline

Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, to be classified as having met the primary efficacy endpoint.

10.2. Secondary Efficacy Assessments

The following secondary efficacy assessments will be measured during the study:

1. Dialysis requirement status
2. Time to Complete TMA Response
3. Complete TMA Response status over time
4. Observed value and change from baseline in eGFR
5. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
6. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
7. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
8. Change from baseline in QoL, as measured by EQ-5D-3L (all patients), FACIT Fatigue Version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires
9. TMA parameters in patients who discontinue treatment but remain in the study

11. SAFETY ASSESSMENTS

The Investigator or his/her designee will meet with patients to discuss the potential safety risks of ALXN1210 and to give the Investigator the opportunity to address any of the patient's safety concerns regarding the study.

The collection of AEs will be monitored from the time informed consent is obtained until study completion. Investigators are instructed to follow any AEs through to their conclusion (resolution or stabilization) as described in [Section 11.7.6](#). In the event of patient withdrawal from the study, AE monitoring should continue through the last patient's last study visit if possible.

The timing of the clinical and laboratory assessments to be performed is specified in the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)). Any clinically significant abnormal results should be followed until resolution or stabilization.

11.1. Demographic/Medical History

11.1.1. Demographics and Baseline Characteristics

A review of demographic parameters, including age, gender, race, and ethnicity will be performed. A complete medical history will be taken and documented. Weight and height will be recorded. Height will be measured at Screening only.

11.1.2. Disease Characteristics

The patient's aHUS medical history, including onset of first aHUS symptom and date of diagnosis, will be documented at the Screening Visit.

11.1.3. Medical History

The patient's medical history, including prior and concomitant conditions/disorders, will be recorded at the Screening Visit. Medication (prescription or over-the-counter, including vitamins and/or herbal supplements) use within 28 days prior to the start of Screening will also be recorded. Meningococcal vaccination within 3 years prior to the first dose of study drug, and for patients < 18 years of age at the time of enrollment, vaccination history for *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* from birth, will also be recorded, as described in [Section 9.6](#).

11.2. Physical Examinations

A physical examination will include the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal system. An abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms.

11.3. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes, and will include systolic and diastolic BP (millimeters of mercury [mm Hg]), pulse oximetry, heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).

11.4. Laboratory Assessments

Samples for serum pregnancy, hematology, chemistry, coagulation, and urinalysis will be performed at the times specified in the Schedule of Assessments (Table 1, Table 2, and Table 3). Specific laboratory assessments are provided in Appendix D. Samples for laboratory assessments will be collected before each study drug administration.

Evaluation of Inclusion Criteria 2a and 2b may be based on local laboratory results within 28 days prior to the start of the Screening Period or laboratory results obtained during the Screening Period from a local or central laboratory. If a local laboratory is used to define eligibility, additional samples will be collected during the Screening Period for LDH, platelet count, hemoglobin and serum creatinine and tested at the central laboratory. If patients are found to not meet the eligibility criteria for serum creatinine (Inclusion Criterion 2c) based on central laboratory results, they must not be enrolled into the study; if the subject has received the first dose of ALXN1210 the patient must be withdrawn from the study, and may be replaced. All analyses in this study will be based on results from the central laboratory. Laboratory results for Exclusion Criterion 1, Exclusion Criterion 2, and/or a central laboratory result for Inclusion Criterion 2c may not be available prior to first dose; results received after the first dose indicating that eligibility is not satisfied could lead to discontinuation and replacement of the patient. Please refer to the Laboratory Manual for time windows for collection and detailed instructions for collecting, processing, storing, and shipping blood samples for safety assessments. Laboratory reports will be made available to the Investigators in a timely manner for clinical management of patients.

It is anticipated that some laboratory values may be outside the normal value range due to the underlying disease. The Investigators should use their medical judgment when assessing the clinical significance of these values. Clinical significance is defined as any variation in laboratory measurements that has medical relevance and which results in a change in medical care. If clinically significant laboratory changes from baseline value are noted, the changes will be documented as AEs on the AE eCRF. The Investigator will also assess the relationship to study treatment for all clinically significant out-of-range values (Section 15.9.3). The Investigator will continue to monitor the patient through additional laboratory assessments until (1) values have returned to the normal range or baseline level, or (2) in the judgment of the Investigator, values that are outside the normal range are not related to the administration of study drug or other protocol-specific procedures.

11.4.1. Pregnancy Screen

For females of childbearing potential, a serum or urine pregnancy test (ie, beta-human chorionic gonadotropin [β -hCG]) will be performed according to the Schedule of Assessments (Table 1, Table 2, and Table 3).

11.4.2. Hematology

Blood samples will be analyzed for the hematology parameters listed in [Appendix D](#).

11.4.3. Serum Chemistry

Blood samples will be analyzed for the serum chemistry parameters listed in [Appendix D](#). Indirect bilirubin is calculated from total and direct bilirubin values; therefore, indirect bilirubin results will not be available if direct bilirubin is below the limit of quantification.

Serum FSH level will be measured during Screening for postmenopausal female patients to confirm their postmenopausal status.

Chemistry assessments will be performed at the time points specified in the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)). The eGFR will be calculated for all visits at which serum chemistries are collected using the Modification of Diet in Renal Disease formula in patients ≥ 18 years of age and Schwartz formula in patients < 18 years of age.

11.4.4. Coagulation

Blood samples will be analyzed for the coagulation parameters listed in [Appendix D](#).

11.4.5. Urinalysis and Urine Chemistry

Urine samples will be analyzed for the parameters listed in [Appendix D](#). A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal.

Urine samples will also be analyzed to measure proteins and creatinine in order to calculate the urine total protein:creatinine ratio.

11.5. Electrocardiograms

For each patient, single 12-lead digital ECGs will be collected according to the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

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 CRF. For any clinically significant abnormal ECG results, the Investigator must contact the Medical Monitor to discuss the patient's continued eligibility to participate in this protocol.

11.6. Immunogenicity

Blood samples will be collected to test for presence and titer of ADAs to ALXN1210 in serum prior to study drug administration as indicated in the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)). Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ALXN1210.

Please refer to the Laboratory Manual for time windows for collection and detailed instructions for collecting, processing, storing, and shipping blood samples for immunogenicity analysis.

11.7. Adverse Event Management

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the start of the study, admissions for social reasons or convenience), and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error.

Cases of pregnancy that occur during maternal or paternal exposure to investigational product are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Adverse events should be recorded from the time of signed consent. An AE reported after informed consent but before study drug administration will be considered a pretreatment AE.

Alexion has reporting standards for AEs that are to be followed as described in [Section 11.7.6](#) regardless of applicable regulatory requirements that may be less stringent.

11.7.1. Targeted Adverse Events

The following events are important identified risks in this study:

- Meningococcal infections

11.7.2. Severity Assessment

The severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher. A grading (severity) scale is provided for each AE term. Each CTCAE term is a Lowest Level Term (LLT) per the Medical Dictionary for Regulatory Activities (MedDRA[®]). Each LLT will be coded to a MedDRA preferred term (PT).

Grade refers to the severity of the AE. The CTCAE assigns a grade of 1 through 5, with unique clinical descriptions of severity for each AE ([Table 7](#)).

Table 7: Adverse Event Severity Grading Scale

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) ^a
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^b
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event

^a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Any change in the severity of an AE should be documented based on specific guidelines in the eCRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for a SAE as described in [Section 11.7.4](#).

11.7.3. Causality Assessment

An Investigator must provide a causality assessment (Unrelated, Unlikely, Possible, Probable, or Definite) for all AEs (both serious and nonserious) based upon the Investigator's medical judgment and the observed symptoms associated with the event ([Table 8](#)). This assessment must be recorded on the eCRF and any additional forms as appropriate.

Table 8: Causality Assessment Descriptions

Assessment	Description
Not Related/Unrelated	Suggests that there is no causal association between the investigational product and the reported event.
Unlikely Related	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	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	Suggests that a reasonable temporal sequence of the event with the investigational product administration exists and the likely causal 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 Investigator'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, reappearance on rechallenge.

11.7.4. Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening (ie, patient was at risk of death at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

The expectedness of an SAE will be determined by Alexion, based on the current version of the IB.

Information pertaining to the collection and reporting of SAEs is provided in [Section 11.7.6](#).

11.7.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

11.7.6. Collection and Reporting of Adverse Events

11.7.6.1. All Adverse Events

All AEs (serious and nonserious) will be collected from the signing of the informed consent form (ICF) until 8 weeks (56 days) after the last dose of study drug. For patients who discontinue study drug, but remain in the study, AE data collection will continue at subsequent visits per the Schedule of Assessments, until the patient's last visit. For patients who terminate early from the study, an ET visit will be conducted as soon as possible, and a follow-up phone call will be performed 8 weeks (\pm 5 days) following the patient's last dose of the study drug. All AEs must be recorded on the eCRF upon the Investigator or his/her staff becoming aware of their occurrence.

Investigators will be instructed to report the SAE including their assessment (eg, severity, seriousness, and potential relatedness to study drug) to Alexion Global Pharmacovigilance (GPV) within 24 hours of first awareness of the event via the Safety Gateway.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly capture the circumstances and data leading to any such dose interruption or discontinuation of treatment in the AE and Exposure pages of the eCRF.

11.7.6.2. Serious Adverse Events

All SAEs will be recorded regardless of the Investigator's assessment of causality. No time limit exists on reporting SAEs that are thought to be causally related to the study drug. Investigators are at liberty to report SAEs irrespective of causality at any time.

For all SAEs, the Investigator must provide the following:

- Appropriate and requested follow-up information in the time frame detailed below
- Causality of the SAE(s)
- Treatment of/intervention for the SAE(s)
- Outcome of the SAE(s)
- Supporting medical records and laboratory/diagnostic information

All SAEs must be reported to Alexion GPV within 24 hours of the Investigator or site staff awareness. These timelines for reporting SAE information to the sponsor need to be followed for the initial SAE report and for all follow-up SAE information.

The Investigator or designee must record the SAE data in the eCRF and verify the accuracy of the information with corresponding source documents. The SAE report should be submitted electronically via the Safety Gateway.

In the event that either the electronic data capture (EDC) or the Safety Gateway is unavailable at the site(s), the SAE must be reported on paper. Facsimile transmission or email may be used in the event of electronic submission failure.

Email: PPD [REDACTED]

Facsimile: PPD [REDACTED] (NOTE: A local facsimile number will be provided for non-US sites)

When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GPV via Safety Gateway.

If applicable, additional information such as relevant medical records should be submitted to Alexion GPV via the email address or fax number noted above.

All paper forms and follow-up information submitted to the sponsor outside of the Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

11.7.7. Sponsor Reporting Requirements

Alexion GPV or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the sponsor from the Reference Safety Document.

11.7.8. Investigator Reporting Requirements

The Investigator must fulfill all local regulatory obligations required for the study Investigators. It is the PI's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site, as required per IRB/IEC SOPs. Investigators will also be notified of all SUSAR events that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs as per IRB/IEC SOPs.

11.8. Exposure During Pregnancy and Breastfeeding

Pregnancy data will be collected during this study for all patients and female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the patient discontinues study drug or withdraws from the study.

If a female patient or a patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GPV via fax or email ([Section 11.7.6.2](#)). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GPV. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion Global Pharmacovigilance or designee via email or facsimile ([Section 11.7.6](#)).

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 may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

11.9. Safety Monitoring

The Alexion medical monitor, GPV physician, or both will monitor safety data throughout the course of the study.

Alexion will review all information pertaining to the SAEs within the time frames mandated by company procedures. The Alexion medical monitor will, as appropriate, consult with the GPV safety physician, to review trends in safety data.

12. PHARMACOKINETICS AND PHARMACODYNAMICS ASSESSMENTS

Blood samples for determination of serum drug concentrations and PD assessments will be collected before and after administration of study drug at the time points indicated in the Schedule of Assessments ([Table 1](#), [Table 2](#), and [Table 3](#)). The actual date and time (24-hour clock time) of each sampling will be recorded. The number of PK samples obtained for any given patient will not exceed the currently planned number of time points.

End of infusion (EOI) blood samples for PK and PD assessment should be collected from the arm opposite to the arm used for infusing drug. Please refer to the Laboratory Study Manual for details on sample collection, including blood volume requirements.

Assessments for PK/PD are as follows:

1. Changes in serum ALXN1210 concentration over time
2. Changes in free C5 concentrations
3. Changes in free C5 and ALXN1210 concentration in patients who discontinue treatment but remain in the study

13. EXPLORATORY ASSESSMENTS

13.1. Biomarker and APC Activity Assessments

Exploratory biomarker analyses will evaluate changes from baseline in biomarkers which may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, sTNFR1), endothelial activation/damage (eg, sVCAM-1, thrombomodulin), coagulation (eg, D-dimer), and renal injury (eg, cystatin C). Additional analysis may include evaluation of ALXN1210 excretion in urine, cRBC hemolysis, total C5, autoantibodies to complement proteins (eg, anti-factor H) and APC activity (eg, Modified Ham's test, complement deposition assays).

Please refer to the Laboratory Study Manual for details on sample collection, including blood volume requirements. Biomarker samples may be analyzed after study completion.

13.2. Genetics

For patients who sign an additional optional consent, a whole blood sample for exploratory genetics can be drawn anytime during the study. Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ALXN1210. A patient (or legal guardian) may decline from providing a sample for exploratory genetics and still participate in the study.

Please refer to the Laboratory Study Manual for details on sample collection, including blood volume requirements.

13.3. Additional Signs or Symptoms of aHUS and Resource Utilization

Resource utilization will be assessed using the Resource Utilization Patient Questionnaire ([Appendix H](#)) and additional signs or symptoms of aHUS will be assessed using the Patient-reported aHUS Symptoms Questionnaire ([Appendix I](#)).

The Investigator will evaluate extra-renal signs or symptoms of aHUS using a composite of clinical laboratory measurements (eg, troponin I, amylase, and lipase), vital signs (eg, heart rate, respiratory rate, pulse oximetry), and an organ system review.

14. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Perform start-up training to instruct the Investigators and study personnel. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by email, telephone, or facsimile.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

Authorized representatives of the sponsor, a regulatory authority, or an IRB/IEC 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 International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

14.1. Data Collection and Storage

All clinical data will be recorded promptly and accurately in the EDC system. When recorded electronically, CRFs will be electronically generated. All raw data will be preserved in order to maintain data integrity. The Investigator or designee will assume the responsibility of ensuring the completeness, accuracy, and timeliness of the clinical data.

The EDC system is fully validated and compliant with CFR Title 21 Part 11. The EDC system will maintain a complete audit trail of all data changes. At each scheduled monitoring visit, the Investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the EDC system.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient receiving study drug.

The Investigator will allow the sponsor's representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

14.2. Records Retention

The Investigator 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 or longer if required per local regulations. If it becomes necessary for the sponsor or the sponsor's designee or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15. STATISTICAL METHODS AND PLANNED ANALYSES

15.1. General Considerations

All data collected will be presented in summary tables and tabulations. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. All analyses will be performed using SAS[®] release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients. Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each patient will be determined by appropriate medical and statistical personnel. Any and all exclusions will be documented in patient listings.

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP) before database lock and analysis. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary or key secondary objectives or the study conduct. Any other change to the data analysis methods described in the protocol or SAP, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data may be conducted as deemed appropriate.

An interim CSR will be prepared at the end of the 26-week Initial Evaluation Period, which will include efficacy, safety, and PK/PD analyses. A final CSR to summarize long-term efficacy, safety, and PK/PD will be produced at study completion. Available exploratory data will be summarized after study completion but may not be included in the CSR.

For patients who discontinue ALXN1210 treatment, but remain in study, their data will be summarized along with data from patients remaining on treatment for 8 weeks (56 days) after their last dose of study drug. Data beyond this point will be presented in separate supplemental listings strictly limited to these patients. If such patients start retreatment with ALXN1210, their data from the time of study treatment restart will also be presented in separate supplemental listings limited to patients who will have restarted study treatment. However, data on AE, concomitant medications, and nonpharmacologic therapies and procedures from the time of treatment restart will be considered treatment emergent or concomitant, and will be summarized as such, combined with data from patients who remained on treatment throughout the study.

Pharmacokinetic/PD and ADA data from patients who discontinue ALXN1210 treatment, but remain in study, will be summarized along with data from patients remaining on treatment, until 8 weeks after their last dose of study drug. Data beyond this point will be presented in separate supplemental listings limited to these patients. If such patients start retreatment with ALXN1210, their PK/PD and ADA data from the time of study treatment restart will also be presented in separate supplemental listings limited to patients who will have restarted study treatment.

15.2. Determination of Sample Size

Approximately 55 patients will be enrolled in this study in order to yield at least 50 evaluable patients by Day 183. This sample size is deemed appropriate to provide complete safety information and the necessary precision level for the planned estimation. Assuming a proportion of Complete TMA response of 65%, 50 patients would yield a 95% confidence interval (CI) for the proportion of response with a half-width of approximately 15%.

The sample size was increased to 55 patients to account for a potential 10% drop-out rate, thus yielding a total planned sample size of 55 patients.

15.3. Analysis Sets

Efficacy analyses will be performed on the FAS. The analysis of the FAS will be the primary analysis.

The FAS will be based on a mITT approach where patients that were enrolled and treated based on verification of inclusion and exclusion criteria through local laboratory results and the assumption that all inclusion and exclusion criteria were satisfied will be excluded from the FAS if it is later shown that certain of the inclusion and exclusion criteria were in fact not satisfied once all Screening laboratory results are available. Based on the above, the FAS will include all patients who receive at least 1 dose of ALXN1210, have at least 1 postbaseline efficacy assessment, and meet all of the following criteria:

- Patients who satisfy Inclusion Criterion number 2c
- Patients who satisfy Exclusion Criterion number 1
- Patients who satisfy Exclusion Criterion number 2

The FAS will be determined prior to database lock and prior to the database snapshot for the analysis performed at the end of the 26-week Initial Evaluation Period.

Safety analyses will be performed on the Safety Set, defined for all patients who receive at least 1 dose of study drug.

Pharmacokinetic and PD analyses will be performed on all patients who receive at least 1 dose of study drug and who have evaluable PK and PD data.

15.4. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history and transplant history, will be summarized for the FAS and Safety Set.

15.5. Patient Disposition

All patients will be included in the summaries of patient disposition, which will describe the frequency and percentage of patients enrolled and treated and who completed or withdrew from the study, along with reason for withdrawal from the study.

The numbers of patients who are treated, discontinue treatment (along with reason for treatment discontinuation), complete or withdraw from the Initial Evaluation Period (along with reason for

withdrawal), enter the Extension Period, and complete or withdraw from the Extension Period (along with reason for withdrawal) will be tabulated.

15.6. Prior and Concomitant Medications and Nonpharmacologic Therapies and Procedures

Each patient's prior and concomitant medication use will be coded using the World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized. Medications will be summarized by Anatomic-Therapeutic-Chemical (ATC) class and preferred drug name using frequency counts and percentages of patients in the Safety Set.

15.7. Treatment Compliance

The number of infusions received per patient will be tabulated for the FAS and Safety Set.

15.8. Efficacy Analyses

All efficacy analyses will be conducted for the FAS. The FAS is the primary analysis set for all efficacy analyses.

15.8.1. Primary Efficacy Analysis

The primary efficacy endpoint is Complete TMA Response during the 26-week Initial Evaluation Period. The primary analysis will consist in estimating the proportion of complete TMA responders among ALXN1210 treated patients. This will be performed by calculating the point estimate and a 95% CI for the proportion of complete TMA responders in ALXN1210 treated patients. The CI will be based on the asymptotic Gaussian approximation method with a continuity correction.

15.8.2. Key Secondary Efficacy Analyses

15.8.2.1. Dialysis Requirement Status

For patients requiring dialysis within 5 days prior to ALXN1210 treatment initiation, the proportion of patients no longer requiring dialysis will be summarized over time. A 2-sided 95% CI for the proportion receiving dialysis will be provided.

15.8.2.2. Time to Complete TMA Response

For the secondary efficacy endpoint of time to Complete TMA Response, Kaplan-Meier cumulative distribution curves will be generated along with 2-sided 95% CIs. The corresponding summary table will present the cumulative distribution function (CDF) estimate, the number of patients at risk, the number of patients responding, and the number of patients censored at each postbaseline time point. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to complete response.

15.8.2.3. Complete TMA Response Status Over Time

Complete TMA Response will also be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point.

15.8.2.4. eGFR Value and Change from Baseline

Kidney function evaluated by eGFR will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A value for eGFR will be imputed for patients requiring dialysis for acute kidney injury. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates may be fit to test whether changes differ from zero at each time point.

15.8.2.5. CKD Stage

CKD stage ([Appendix J](#)) will be summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 will be considered the worst category, while stage 1 will be considered the best category. A 2-sided 95% CI for the proportion will be provided for each category.

15.8.2.6. Hematologic Parameters

Hematologic parameters (platelets, LDH, hemoglobin) will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may be fit to test whether changes differ from zero at each time point.

15.8.2.7. Hemoglobin Response

The number and proportion of patients with an increase from baseline in hemoglobin ≥ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, will be summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each postbaseline time point.

15.8.2.8. Quality of Life

Quality of life will be evaluated using EQ-5D-3L (all patients; [Appendix E](#)), FACIT Fatigue version 4 Questionnaire (patients ≥ 18 years of age; [Appendix F](#)), and Pediatric FACIT Fatigue Questionnaire (patients < 18 years of age; [Appendix G](#)). The EQ-5D-3L and FACIT Fatigue data will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may be fit to test whether changes differ from zero at each time point.

15.9. Safety Analyses

All safety analyses will be performed for the Safety Set, defined for all patients who receive at least 1 dose of ALXN1210.

15.9.1. Adverse Events

The following definitions will be used for AEs:

- Pretreatment adverse events: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent adverse event: Any AE that starts during or after the first infusion of study drug. Adverse events that start 56 days or later after the last dose of study drug will not be considered as treatment emergent.
- Treatment-emergent SAE: A treatment-emergent AE (TEAE) that is serious ([Section 11.7.4](#) for definitions).

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study treatment discontinuation, drug-related TEAEs, TEAEs during study drug administration, severe TEAEs, and SAEs will be summarized. All AEs will be coded using MedDRA version 18 or higher, and will be summarized by system organ class (SOC) and PT overall, by severity, and by relationship to treatment. Detailed by-patient listings of TEAEs, SAEs, related TEAEs, TEAEs during study drug administration, TEAEs leading to withdrawal from the study, and TEAEs leading to study treatment discontinuation will be provided.

15.9.2. Physical Examination and Vital Signs

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

Vital signs will be summarized descriptively at baseline and postbaseline time points and for changes from baseline.

By-patient listings will be provided.

15.9.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry, hematology, and urinalysis will be summarized descriptively at baseline, and at each postbaseline time point. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

15.9.4. Electrocardiograms

By-patient data listings of ECG parameters will be provided. Electrocardiograms will be evaluated and summarized as normal, abnormal not clinically significant, or abnormal clinically significant. A shift from baseline to worst on-study ECG table will be presented for ECG results. Observed values and change from baseline in ECG intervals (PR, RR, QT, and QTc) will be summarized descriptively at baseline and each postbaseline time point. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

15.9.5. Immunogenicity

Abnormal immunogenicity findings, including the incidence and titers for ADAs to ALXN1210 will be presented at each postbaseline time point in tabular format. The proportion of patients ever positive and the proportion of patients always negative may be explored.

15.10. Pharmacokinetic/Pharmacodynamic Analyses

Individual serum concentration data for all patients who receive at least 1 infusion of ALXN1210 and who have evaluable PK data will be used to derive PK parameters for ALXN1210.

Graphs of mean serum ALXN1210 concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

The PD effects of ALXN1210 administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of PK/PD relationships may be explored using data from this study or in combination with data from other studies.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 infusion of study drug and who have evaluable PD data. For PD parameters, summary tabulations of mean, SD, median, minimum, and maximum values will be presented for actual, change and percentage change from baseline. The relationship between changes in PD parameters, exploratory biomarkers, and the effects of treatment outcome may be evaluated.

15.11. Exploratory Analyses

15.11.1. Biomarker and APC Activity Analyses

For exploratory biomarker analyses, summary statistics will be presented for actual, change and percentage change from baseline.

The relationship between ALXN1210 concentration and exploratory biomarkers or the correlation between clinical benefit and key exploratory biomarkers may be assessed by graphical display. Exploratory analysis and potential relationships between clinical outcomes, PK/PD, genetic profile, and biomarker levels may also be performed. APC activity and autoantibody results will be summarized if evaluated.

15.11.2. Genetics

Exploratory genetics may be performed to investigate genetic variants in genes known to be associated with aHUS, as well as to identify novel genetic variants associated with aHUS, complement dysregulation, or metabolism or efficacy of ALXN1210.

15.11.3. Additional Signs or Symptoms of aHUS and Resource Utilization

Resource utilization will be assessed using the Resource Utilization Patient Questionnaire ([Appendix H](#)) and additional signs or symptoms of aHUS will be assessed using the Patient-reported aHUS Symptoms Questionnaire ([Appendix I](#)).

Resource Utilization Questionnaire data and Patient-reported aHUS Symptoms Questionnaire data will be summarized at baseline and each postbaseline assessment using discrete data summary statistics.

15.12. Other Statistical Issues

15.12.1. Missing or Invalid Data

If a Day 1 assessment is missing, the Screening assessment will be used as the baseline assessment.

For evaluation of Complete TMA Response during the 26-week Initial Evaluation Period (primary endpoint), patients missing an efficacy assessment that is part of the definition of Complete TMA Response while still on-study, will have their last observation carried forward (LOCF). For patients who will have terminated early from the study prior to Week 26, their data up to the time of discontinuation will be used to assess Complete TMA Response.

Missing data for QoL instruments will be handled as specified in the instructions for each instrument.

15.13. Interim Analyses

An interim analysis is planned for this study at the end of the 26-week Initial Evaluation Period after all patients have completed or withdrawn from the 26-week Initial Evaluation Period. Additionally, a second analysis to summarize long-term efficacy, safety, and PK parameters will be performed at the end of the 2-year Extension Period.

16. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

16.1. Informed Consent and Assent

The Investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each patient or the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product. The Investigator must retain the original version of the signed ICF. If the ICF is amended, the original signed, amended version must also be retained. A copy of the signed ICF(s) must be given to the patient.

As used in this protocol, the term "informed consent" includes all informed consent given by patients or, as applicable, informed consent by their legally authorized representatives if the patient is unable to provide informed consent.

16.2. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) comprising experts in relevant biomedical fields who have no direct relationship with the study will be appointed by the sponsor. The DMC will review and evaluate the accumulated study data for patient safety and make recommendations on continuing study drug administration or termination of the study. The DMC will review study information on a regular basis as outlined in the DMC charter, which is maintained separately from the study protocol.

Final decisions regarding the conduct of the study will be made by the sponsor after consultation with the DMC. All appropriate regulatory authorities and Ethics Committees will be notified of any significant action.

Each member of the DMC will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the committee.

The specific responsibilities of the DMC are described in the DMC Charter, which is maintained as a separate document.

16.3. Ethical Review

All ICFs must be compliant with the ICH guideline on GCPs.

Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the sponsor before the study may begin at the investigational sites. The IRB/IEC(s) will review the protocol as required.

16.4. Regulatory Considerations

This study will be conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The ICH GCP Guideline [E6]
3. The ICH Clinical Trials of Medicinal Products in the Pediatric Population [E11]
4. Applicable national and local laws and regulations

The Investigator or designee will promptly submit the protocol to applicable IRB/IEC(s).

Some of the obligations of the sponsor will be assigned to a third-party organization.

An identification code assigned to each patient by the EDC system will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and other study-related data.

16.4.1. Changes/Deviations to Protocol

The Investigator may need to deviate from the protocol to eliminate an immediate hazard to a trial subject without prior notification of the IRB/IEC. Any deviations from the protocol must be fully documented. The deviation and the reasons for it should be submitted to the IRB/IEC, Sponsor, and appropriate regulatory authority if required (ICH GCP E6 [R1] 4.5.4).

After the commencement of the clinical trial, the Sponsor may make changes to the protocol. If those changes are significant, the regulatory authority and applicable IRB/IEC will be notified.

16.5. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

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18. APPENDICES

APPENDIX A. COMMON CREATININE REFERENCE INTERVALS

Age (Gender) Group	97.5 th Percentile Value (mg/dL)	97.5 th Percentile Value (μmol/L)
11 to < 13 years of age	0.71	63
13 to < 15 years of age	0.81	72
15 to Adult (males)	1.18	104
15 to Adult (females)	1.02	90

Source: Adapted from [Panteghini, 2008](#); [Ceriotti, 2008](#).

APPENDIX B. ANTIBODY MEDIATED REJECTION CRITERIA

The revised (Banff 2013) classification of acute/active antibody-mediated rejection in renal allografts will be used to assess antibody mediated rejection. All 3 features must be present for diagnosis.

Criteria^{a,b,c}
Histologic evidence of acute tissue injury, including one or more of the following:
Microvascular inflammation (g score > 0 ^d and/or ptc score > 0)
Intimal or transmural arteritis (v score > 0) ^e
Acute thrombotic microangiopathy, in the absence of any other cause
Acute tubular injury, in the absence of any other apparent cause
Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
Linear C4d staining in peritubular capillaries (involving at least 10% of ptc by immunofluorescence on frozen sections, or any ptc by IHC on paraffin sections)
At least moderate microvascular inflammation (sum of g and ptc scores ≥ 2) ^f
Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated ^g
Serologic evidence of donor-specific antibodies (HLA or other antigens)

Source: [Haas, 2014a](#)

^a For all antibody-mediated rejection (ABMR) diagnoses, it should be specified in the report whether the lesion is C4d-positive [involving $\geq 10\%$ of ptc by immunofluorescence on frozen sections or any ptc by immunohistochemistry (IHC) on paraffin sections] or without evident C4d deposition (< 10% of ptc by immunofluorescence on frozen sections; completely negative by IHC on paraffin sections).

^b These lesions may be clinically acute, smoldering, or subclinical. Biopsies showing 2 of the 3 features, except those with donor specific antibody (DSA) and C4d without histologic abnormalities potentially related to AMR or cell-mediated rejection (the latter seen mainly in ABO-incompatible renal allografts) may be designated as ‘suspicious’ for acute/active ABMR.

^c Modified from [Haas, 2014b](#).

^d Recurrent/de-novo glomerulonephritis should be excluded.

^e It should be noted that these arterial lesions may be indicative of ABMR, T-cell-mediated rejection (TCMR), or mixed ABMR/TCMR. Arterial lesions are only scored in arteries having a continuous media with 2 or more smooth muscle layers.

^f In the presence of acute TCMR, borderline infiltrates, or evidence of infection, ptc score at least 2 alone is not sufficient to define moderate microvascular inflammation, and glomerulitis must be present (g score ≥ 1).

^g At present, the only validated molecular marker meeting this criterion is ENDAT expression, and this has only been validated in a single center (University of Alberta). The use of ENDAT expression at other centers or other test(s) of gene expression within the biopsy as evidence of ABMR must first undergo independent validation as was done for ENDAT expression by [Sis, 2009](#).

APPENDIX C. 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, patients will be carefully observed during each infusion.

Patients who develop AEs of rash, hives, itching, or dysphagia of mild to moderate intensity during their infusion of ALXN1210 may continue to receive the infusion 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 interrupting or stopping the infusion.

Any acute reaction should be treated according to standard medical practice depending upon clinical signs and symptoms. If a patient requires medical intervention, the patient should remain at the investigational site until his or her condition stabilizes. The AE and any associated concomitant medications must be captured on the patient's source document and eCRF.

Some patients treated with IV infusions of monoclonal antibodies have experienced concurrent reactions with signs or symptoms that can be classified as acute allergic reactions/hypersensitivity reactions or cytokine release syndrome. 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; therefore, patients will be monitored closely during 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 that may indicate an infusion-related response will be graded according to CTCAE Version 4.03 or higher.

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

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines. For a Grade 1 or Grade 2 infusion reaction, the infusion should be temporarily stopped and treatment with an antihistamine (eg, diphenhydramine 25 to 50 mg orally [PO] or equivalent) and acetaminophen (650 mg orally or equivalent) may be considered. If the patient's signs and symptoms have resolved (with or without administration of the above medication), the infusion may be restarted. However, the patients should be infused at a slower rate and be monitored closely for any signs and symptoms of infusion reactions during the remainder of the infusion. Patients experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until the Investigator determines the patient is no longer at risk. Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol.

If anaphylaxis occurs according to the criteria listed below, then administration of subcutaneous epinephrine (1/1000, 0.3 to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

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 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) b. Reduced blood pressure (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 patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: [Sampson, 2006](#)

Abbreviations: BP= blood pressure; PEF = peak expiratory flow

APPENDIX D. PROTOCOL LABORATORY TESTS

<p>Hematology: Free hemoglobin Haptoglobin Hematocrit Hemoglobin Mean corpuscular hemoglobin Platelet count RBC distribution width RBC mean corpuscular volume RBC count Reticulocyte count White blood cell count White blood cell differential</p> <p>Coagulation Panel: International normalized ratio Prothrombin time Partial thromboplastin time</p> <p>Urine Chemistry: Microalbumin Creatinine Total protein</p> <p>Urinalysis: Albumin Appearance Bilirubin Blood Color Creatinine Glucose Ketone Nitrite pH Protein Specific gravity Urobilinogen</p>	<p>Clinical Chemistry: Alanine aminotransferase Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bicarbonate Blood urea nitrogen C-reactive protein Calcium Chloride Creatinine Gamma-glutamyltransferase Glucose Lactate dehydrogenase Lipase Magnesium Phosphorus Potassium Sodium Total bilirubin (direct and indirect) Total protein Troponin I Uric acid</p> <p>Pregnancy and Menopausal Status Tests: <i>(females only)</i> Beta human chorionic gonadotropin Serum follicle-stimulating hormone (postmenopausal only)</p> <p>Other: ADAMTS13 activity ADA Coombs, direct Free C5 PK Shiga toxin-related HUS screen (eg, Shiga toxin enzyme immunoassay/PCR in stool/stool culture)</p>
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Note: This table excludes exploratory tests

Abbreviations: ADA = antidrug antibodies; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APC = alternative pathway of complement; C5 = complement component 5; HUS = hemolytic uremic syndrome; PCR = polymerase chain reaction; PK = pharmacokinetic; RBC = red blood cell

APPENDIX E. EQ-5D-3L



Health Questionnaire

English version for the USA

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By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain / Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

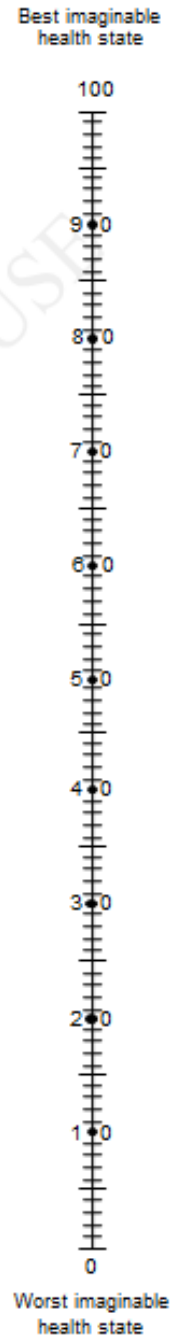
Anxiety / Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX F. FACIT-FATIGUE

FACIT Fatigue Scale (Version 4)

Header to be completed by study site	
Study Number: <u>ALXN1210-aHUS-311</u>	Subject ID: _____
Date Completed: _____	Time Completed: _____

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired.....	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day.....	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do.....	0	1	2	3	4
An16	I have to limit my social activity because I am tired.....	0	1	2	3	4

APPENDIX G. PEDIATRIC FACIT-FATIGUE

Pediatric (Paediatric) Functional Assessment of Chronic Illness Therapy – Fatigue

Header to be completed by study site	
Study Number: <u>ALXN1210-aHUS-311</u>	Subject ID: _____
Date Completed: _____	Time Completed: _____
Completed by: <input type="checkbox"/> Patient <input type="checkbox"/> Caregiver (Initials): _____	

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		None of the time	A little bit of the time	Some of the time	Most of the time	All of the time
pF1	I feel tired.....	0	1	2	3	4
pF2	I have energy (or strength).....	0	1	2	3	4
pF3	I could do my usual things at home	0	1	2	3	4
pF4	I had trouble <u>starting</u> things because I was too tired.....	0	1	2	3	4
pF5	I had trouble <u>finishing</u> things because I was too tired	0	1	2	3	4
pF6	I needed to sleep during the day	0	1	2	3	4
pF7	I got upset by being too tired to do things I wanted to do .	0	1	2	3	4
pF8	Being tired made it hard for me to play or go out with my friends as much as I'd like.....	0	1	2	3	4
pF9	I needed help doing my usual things at home.....	0	1	2	3	4
pF10	I feel weak.....	0	1	2	3	4
pF11	I was too tired to eat.....	0	1	2	3	4
pF12	Being tired made me sad.....	0	1	2	3	4
pF13	Being tired made me mad (angry)	0	1	2	3	4

APPENDIX H. RESOURCE UTILIZATION PATIENT QUESTIONNAIRE

Patient Questionnaire

RESOURCE UTILIZATION

1. Have you visited your health care provider for management of complications related to your aHUS within the past month?
 No
 Yes, specify number of health care provider visits in the past month: _____
2. Have you gone to an Emergency Room primarily for treatment of complications related to your aHUS in the past month?
 No
 Yes, specify number of emergency room visits in the past month: _____
3. Have you been admitted to the Hospital primarily for treatment of complications related to your aHUS in the past month?
 No
 Yes, specify number of hospital admissions in the past month: _____
4. Have you missed work or school as a result of complications or symptoms related to your aHUS within the past month?
 No
 Yes, specify number of work days missed in the past month: _____

GENERAL HEALTH

5. In general would you say your health is:
- Excellent Very good Good Fair Poor

WORK STATUS

6. What is your current work status?
- Work full time at a paid job
 Work part time at a paid job (less than 30 hours per week)
 Not in paid work force due to aHUS
 Not working full time due to aHUS
 Not working for pay for reasons unrelated to aHUS
 Student
 Retired
 Other, specify: _____

APPENDIX I. PATIENT-REPORTED aHUS SYMPTOMS QUESTIONNAIRE

PATIENT-REPORTED aHUS SYMPTOMS													
Date Completed: ___ / ___ / ___ <div style="text-align: center; font-size: small;"> dd mm yyyy </div>													
During the past week did you have any of the following symptoms?	Symptoms present?	If YES, how often did you have it?				If YES, how severe was it usually?				If YES, how much did it distress or bother you?			
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very Severe	Not at all	A little bit	Somewhat	Quite a bit
Yellow discoloration of eyes and/or skin (jaundice)	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chest pain	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Confusion	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Irritability	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anxiety	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Weakness	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fatigue	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Easy bruising/abdominal bleeding	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal pain	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/vomiting	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diarrhea	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swelling	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, specify:	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

APPENDIX J. GLOMERULAR FILTRATION RATE CATEGORY/STAGE IN CHRONIC KIDNEY DISEASE

GFR Category/Stage	GFR (mL/min/1.73 m ²)	Terms
G1	≥ 90	Normal or High
G2	60 - 89	Mildly Decreased ^a
G3a	45 - 59	Mildly to Moderately Decreased
G3b	30 - 44	Moderately to Severely Decreased
G4	15 - 29	Severely Decreased
G5	< 15	Kidney Failure

^a Relative to young adult level

Note: In the absence of evidence of kidney damage, neither GFR category/stage G1 nor G2 fulfill the criteria for CKD

Source: [KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2013. 3: 19-62.](#)