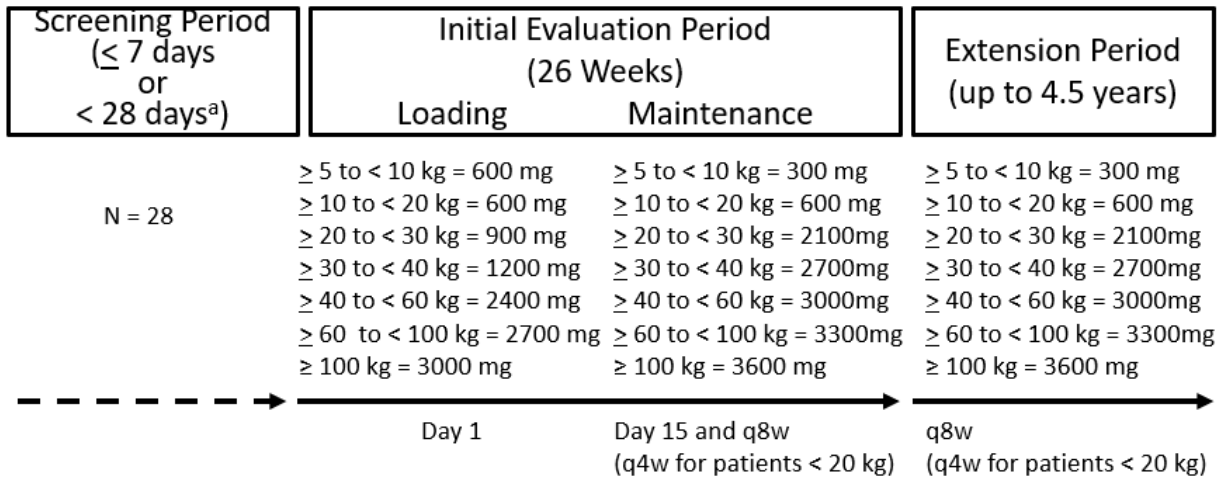
d. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
e. Change from baseline in QoL, as measured by Pediatric FACIT Fatigue questionnaire
f. TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study

3. To characterize the PK/PD of ALXN1210:
   a. Changes in serum ALXN1210 concentration over time
   b. Changes in serum free C5 concentrations over time
   c. Changes in serum free C5 and serum ALXN1210 concentration in patients who discontinue treatment in the Extension Period, but remain in the study
4. To evaluate the long-term safety and efficacy of ALXN1210

Study Design and Methodology:
This is a Phase 3, single-treatment arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ALXN1210 administered by intravenous (IV) infusion in approximately 23 to 28 pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS. The study has 2 cohorts. Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced adolescent patients (12 to < 18 years of age). The study consists of a Screening Period (of up to 7 days for Cohort 1 or up to 28 days for Cohort 2), 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.



Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks
[a] The Screening Period is up to 7 days for complement inhibitor treatment-naïve patients (ie, Cohort 1) and up to 28 days for eculizumab-experienced adolescent patients (ie, Cohort 2).

Consenting patients in Cohort 1 will be screened for study eligibility up to 7 days prior to Day 1. Consenting patients in Cohort 2 will be screened for study eligibility up to 28 days prior to Day 1; first dose of study drug will be given 14 days from the eligible patient's last dose of eculizumab. Patients who are eligible based on the Inclusion and Exclusion Criteria will be enrolled into the Initial Evaluation Period and receive a weight-based loading dose of ALXN1210 on Day 1, followed by weight-based maintenance treatment with ALXN1210 on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg, for a total of 26 weeks of treatment. Weight-based dosing is based on the patient's body weight recorded on Dose Regimen Decision Days (if the Dose Regimen Day is a dosing day, body weight will be recorded predose), as shown in the table below:

Body Weight Range (kg)[a]	**Loading Dose (mg)**	**Maintenance Doses (mg)**	**Maintenance Dosing Frequency**
≥ 5 to < 10	600	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w

Abbreviation	Definition
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
q4w	once every 4 weeks
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

2. To evaluate the efficacy of ALXN1210 by the following measures:
    a. Dialysis requirement status
    b. Observed value and change from baseline in eGFR
    c. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
    d. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
    e. Change from baseline in QoL, as measured by Pediatric FACIT Fatigue questionnaire
    f. TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study
3. To characterize the PK/PD of ALXN1210:
    a. Changes in serum ALXN1210 concentration over time
    b. Changes in serum free C5 concentrations over time
    c. Changes in serum free C5 and serum ALXN1210 concentration in patients who discontinue treatment in the Extension Period, 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 for Cohort 1 is Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 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 for Cohort 1 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 Pediatric FACIT Fatigue questionnaire (patients ≥ 5 years of age)
9. TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study

The secondary efficacy endpoints for Cohort 2 are the following and will be measured through 26 weeks and over the entire study period:

1. Dialysis requirement status
2. Observed value and change from baseline in eGFR
3. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
4. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
5. Change from baseline in QoL, as measured by Pediatric FACIT Fatigue questionnaire (patients ≥ 5 years of age)
6. TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study

6.2.3. Pharmacokinetic and Pharmacodynamic Endpoints

The following PK/PD endpoints are applicable for Cohort 1 and Cohort 2:

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

6.2.4. Safety Endpoints

For Cohort 1 and Cohort 2, the safety and tolerability of ALXN1210 will be evaluated by physical examinations, vital signs, physical growth (height, weight, and head circumference [the latter only in patients ≤ 2 years of age]) electrocardiograms (ECGs), laboratory assessments, and incidence of AEs and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADA) will also be assessed.

6.2.5. Exploratory Endpoints

The following exploratory endpoints are applicable for Cohort 1 and Cohort 2:

6.2.5.1. Biomarkers

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).

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 guardian) may decline from providing a sample for exploratory genetics and still participate in the study.

6.2.5.3. Extra-renal Signs or Symptoms of aHUS

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

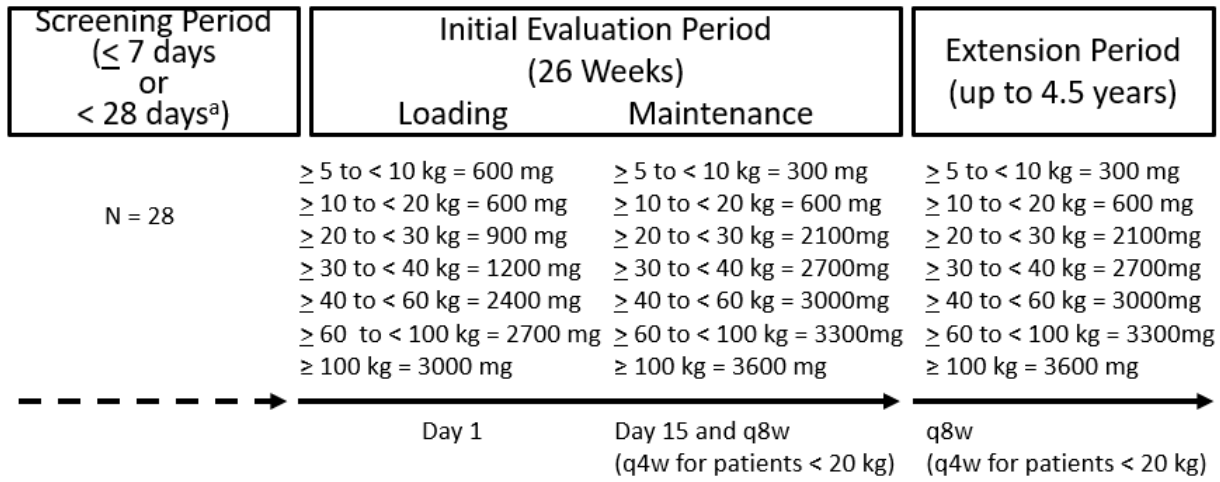
7. INVESTIGATIONAL PLAN

7.1. Summary of Study Design

Study ALXN1210-aHUS-312 is a Phase 3, open-label, single-treatment arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ALXN1210 administered by intravenous (IV) infusion to approximately 23 to 28 pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS. The study has 2 cohorts. Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced adolescent patients (12 to < 18 years of age). The study consists of 3 periods: a Screening Period (of up to 7 days for Cohort 1 patients or up to 28 days for Cohort 2 patients), 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.

Figure 1 illustrates the study design.

Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-aHUS-312



Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks
[a] The Screening Period is up to 7 days for complement inhibitor treatment-naïve patients (ie, Cohort 1) and up to 28 days for eculizumab-experienced adolescent patients (ie, Cohort 2).

Consenting patients in Cohort 1 will be screened for study eligibility up to 7 days prior to Day 1. Consenting patients in Cohort 2 will be screened for study eligibility up to 28 days prior to Day 1; first dose of study drug will be given 14 days from the eligible patient's last dose of eculizumab. Patients who are eligible based on the Inclusion and Exclusion Criteria will be enrolled into the Initial Evaluation Period and receive a loading dose of ALXN1210 on Day 1, followed by maintenance treatment with ALXN1210 on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. The loading dose and maintenance dose will be based on the patient's body weight recorded on Dose Regimen Decision Days (Table 7). If the Dose Regimen Day is also dosing day, body weight will be recorded predose with dosing that day based on the previous Dose Regimen Day body weight.

An initial analysis, including review of ALXN1210 PK and serum free C5 levels, will be conducted after 4 complement inhibitor treatment-naïve (ie, Cohort 1) patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. In addition, safety data will be reviewed by an independent Data Monitoring Committee (DMC). Enrollment of patients will proceed without interruption while the analysis is ongoing. The primary purpose of this review is to assure patients are achieving adequate complement inhibition during this study with goal of achieving complete terminal complement blockade. Based on this review, if dose adjustment is considered needed and tolerable, subsequent treatment for all patients will continue at the adjusted dose regimen. After the Initial Evaluation Period, patients will roll over into an Extension Period in which all patients continue their weight-based maintenance dose of ALXN1210 on Day 183 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, until the product is registered or approved (in accordance with country-specific regulation) or for up to 4.5 years, whichever occurs first. Note, q4w visits during the Extension Period are not applicable for patients weighing ≥ 20 kg and receiving ALXN1210 q8w. The end of trial is defined as the last patient's last visit or follow-up (whether on site or via phone call) of the 4.5-year Extension Period, whichever is later.

7.2. Discussion of Design

This Phase 3, open-label, study will evaluate the PK/PD, efficacy, safety and tolerability of ALXN1210 in the treatment of pediatric patients with aHUS. This amendment is designed to gain experience in adolescent patients switching from eculizumab to ALXN1210. The study has 2 cohorts. Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced adolescent patients (12 to < 18 years of age). As the prevalence of newly diagnosed aHUS is lower in adolescents than in adults and younger ages, evaluation of ALXN1210 in an adolescent switch patient cohort (Cohort 2) will provide sufficient safety and PK data in this group to understand the safety and PK profile of ALXN1210 across the range of age groups.

Four pediatric age groups were selected to test potential dose regimens across a series of body weight categories for the predicted C_{max} and trough serum concentrations of ALXN1210. The doses and regimen are expected to result in a complete terminal complement blockade after the first dose for all aHUS patients within each body weight group and to maintain ALXN1210 concentrations below the maximum ALXN1210 concentrations achieved in Phase 2. At least 4 patients are planned for the birth to < 2 year, 2 to < 6 year, and 6 to < 12 year age groups. At least 8 patients are planned for the 12 to < 18 year age group.

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, Table 3, and Table 4.

Refer to the Laboratory Manual for details on the number of samples and volumes for all sampling and tests during the study. An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used as detailed in the Study Operations Manual.

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.

In the event that a supplemental dose is administered or the loading dose for patients ≥ 5 to < 10 kg is administered as 2 separate infusions no more than approximately 24 hours apart (as described in Section 9.2), an abbreviated physical examination will be conducted, vital signs will be collected, and the safety card will be reviewed with the patient. If a supplemental dose is administered, PK/PD samples will be collected predose and at end of infusion (EOI); a negative pregnancy test result is required prior to administering study drug to female patients of childbearing potential. If a loading dose is administered as 2 separate infusions < 24 hours apart, PK/PD samples will be collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample).

1. Dialysis requirement status
2. Observed value and change from baseline in eGFR
3. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
4. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
5. Change from baseline in QoL, as measured by Pediatric FACIT Fatigue questionnaire (patients ≥ 5 years of age)
6. TMA parameters in patients who discontinue treatment in the Extension Period, but remain in the study

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 [mmHg]), 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 (Section 7.3). Specific laboratory assessments are provided in Appendix E. Samples for laboratory assessments will be collected before each study drug administration. An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used as detailed in the Study Operations Manual.

For Cohort 1, samples collected at Screening may be tested at either 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. All analyses in this study will be based on results from the central laboratory (unless the result is missing [see Section 15.12.1]). If Cohort 1 patients are found not to satisfy 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. For Cohort 1 patients, 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).

For Cohort 2, samples collected at Screening must be tested at a central laboratory; however, historical test results via chart review should be utilized for Inclusion Criterion 3 and Exclusion Criteria 1, 2, 3, and 24. 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 (Section 7.3).

11.4.2. Hematology

Blood samples will be analyzed for the hematology parameters listed in Appendix E.

11.4.3. Serum Chemistry

Blood samples will be analyzed for the serum chemistry parameters listed in Appendix E. 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.

Chemistry assessments will be performed at the time points specified in the Schedule of Assessments (Section 7.3). The eGFR will be calculated for all visits at which serum chemistries are collected using the Schwartz formula.

11.4.4. Coagulation

Blood samples will be analyzed for the coagulation parameters listed in Appendix E.

11.4.5. Urinalysis and Urine Chemistry

Urine samples will be analyzed for the parameters listed in Appendix E. 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 (Section 7.3). 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 (Section 7.3). Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, to PK/PD, safety, and activity of ALXN1210.

Table 8: 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 9). This assessment must be recorded on the eCRF and any additional forms as appropriate.

Table 9: 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.

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

Facsimile: PPD (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.

13. EXPLORATORY ASSESSMENTS

13.1. Biomarker Assessments

Exploratory biomarker analyses may be performed to 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, and autoantibodies to complement proteins (eg, anti-factor H).

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. Extra-renal Signs or Symptoms of aHUS

The Investigator will evaluate extra-renal signs or symptoms of aHUS using 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.

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

By-patient listings will be provided.

This analysis will be performed for both Cohort 1 and Cohort 2.

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. This analysis will be performed for both Cohort 1 and Cohort 2.

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). This analysis will be performed for both Cohort 1 and Cohort 2.

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. This analysis will be performed for both Cohort 1 and Cohort 2.

15.10. Pharmacokinetic/ Pharmacodynamic Analyses

Individual serum concentration data for all patients from the FAS 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.

Pharmacodynamic analyses will be performed for all patients from the FAS and who have evaluable PD data. The PD effects of ALXN1210 will be evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 concentrations over time, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate. Assessments of PK/PD relationships may be explored using data from this study or in combination with data from other studies.

≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks
[a] Body weight as recorded on Dose Regimen Decision Days. If the Dose Regimen Day is also dosing day, body weight will be recorded predose with dosing that day based on the previous Dose Regimen Day body weight.

An initial analysis, including review of ALXN1210 PK and serum free C5 levels, will be conducted after 4 complement inhibitor treatment-naïve (ie, Cohort 1) patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. In addition, safety data will be reviewed by an independent Data Monitoring Committee (DMC). Enrollment of patients will proceed without interruption while the analysis is ongoing. The primary purpose of this review is to assure patients are achieving adequate complement inhibition during this study with the goal of achieving complete terminal complement blockade. Based on this review, if dose adjustment is considered needed and tolerable, subsequent treatment for all patients will continue at the adjusted dose regimen. After the Initial Evaluation Period, patients will roll over into an Extension Period in which all patients continue their weight-based maintenance dose of ALXN1210 on Day 183 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, until the product is registered or approved (in accordance with country-specific regulation) or for up to 4.5 years, whichever occurs first. Note, q4w visits during the Extension Period are not applicable for patients weighing ≥ 20 kg and receiving ALXN1210 q8w. The end of trial is defined as the last patient's last visit or follow-up (whether on site or via phone call) of the 4.5-year Extension Period, whichever is later.

Number of Patients (planned): Approximately 23 to 28 pediatric patients with documented aHUS are planned. The minimum number of patients for each age category is as follows:

- Birth to < 2 years: 4 patients
- 2 to < 6 years: 4 patients
- 6 to < 12 years: 4 patients
- 12 to < 18 years: 8 patients

Cohort 2 patients must be 12 to < 18 years of age.

Diagnosis and Main Criteria for Inclusion and Exclusion:
Patients must satisfy all inclusion and exclusion criteria, in order to have a confirmed diagnosis of aHUS and be eligible for the study. 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. For Cohort 1, samples collected at Screening may be tested at either 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. All analyses in this study will be based on results from the central laboratory (unless the result is missing). If Cohort 1 patients are found not to satisfy 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. For Cohort 1 patients, 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.

For Cohort 2, samples collected at Screening must be tested at a central laboratory; however, historical test results via chart review should be utilized for Inclusion Criterion 3 and Exclusion Criteria 1, 2, 3, and 24.

The following entry criteria are applicable for patients in both cohorts unless otherwise noted as specific for Cohort 1 or Cohort 2:

Inclusion Criteria:

1. Patients from birth up to < 18 years of age and weighing ≥ 5 kg at the time of consent who:
   a. For Cohort 1 patients, have not been previously treated with complement inhibitors
   b. For Cohort 2 patients, are between 12 and <18 years of age **and** have been treated with eculizumab according to the labelled dosing recommendation for aHUS for at least 90 days prior to Screening
2. For Cohort 1 patients, evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney

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

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

Period	**Screening**	**Initial Evaluation Period**															
Study Day	**–7 or -28[a] to –1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183[b]/ET**
Window (day)	**N/A**		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±2**
Informed consent	X																
Confirmation or administration of meningococcal vaccination[c]	X																
Medical history and demographics	X																
ADAMTS13[d]	X																
ST-HUS screen[d, e]	X																
Direct Coombs test[d]	X																
Head circumference (patients up to 2 years of age)	X	X		X			X		X		X		X		X		X
Height and weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[g]	X	X		X					X				X				X
Pediatric FACIT-Fatigue questionnaire[h]		X	X			X			X				X				X
Physical examination	X																X
Abbreviated physical examination[i]		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
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG[k]	X							X									X
Chemistry[l,f]	X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation[n,f]	X[m]	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[o]		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Exploratory serum and plasma biomarkers[p]	X					X			X				X				X
Exploratory urine biomarkers[q]		X		X					X				X				X
Exploratory urine ALXN1210[r]		X		X		X			X								
Exploratory autoantibody[s]	X																
Exploratory genetic sample[t]	X																
Immunogenicity (ADA)[u]		X							X				X				X
Review safety card[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[w]		←Monitor continuously→															
Adverse events		←Monitor continuously→															
ALXN1210 administration (patients weighing < 20 kg)[x]		X		X			X		X		X		X		X		
ALXN1210 administration (patients weighing ≥ 20 kg)[x]		X		X					X				X				
Dose Regimen Decision Day (patients on q4w or q8w schedules)[y]	X		X					X				X				X	

11. SAFETY ASSESSMENTS

The Investigator or his/her designee will meet with patients/caregivers 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 (Section 7.3). 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.

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 vaccination history for Hib and *Streptococcus pneumoniae* from birth, will also be recorded, as described in Section 9.6. For Cohort 2 patients, medical history should be used to document ADAMTS13, Shiga toxin status, and direct Coombs at the previous TMA event, if available.

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 (or qualified designee) judgment and patient symptoms. Physical growth (height, weight, and head circumference [the latter only in patients ≤ 2 years of age]) will be assessed.

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 8).

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 (56 days) ± 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.

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 (Section 7.3). 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 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 serum free C5 concentrations
3. Changes in serum free C5 and serum ALXN1210 concentration in patients who discontinue treatment in the Extension Period, but remain in the study

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.

This analysis will be performed for both Cohort 1 and Cohort 2.

15.11. Exploratory Analyses

15.11.1. Biomarker Analyses

For exploratory biomarker analyses, summary statistics may be presented for absolute, 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. Autoantibody results will be summarized if evaluated.

This analysis may be performed for both Cohort 1 and Cohort 2.

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. This analysis may be performed for both Cohort 1 and Cohort 2.

15.11.3. Extra-renal Signs or Symptoms of aHUS

Extra-renal signs or symptoms of aHUS will be summarized at baseline and each postbaseline assessment by presenting the number and proportion of patients with a specific symptom present. This analysis will be performed for both Cohort 1 and Cohort 2.

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. If the Day 1 and Screening assessments are missing, local laboratory data 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 early termination 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 when 12 to 14 complement inhibitor treatment-naïve (ie, Cohort 1) patients have completed or withdrawn from the 26-week Initial Evaluation Period. A second interim analysis is planned after all study patients have completed or withdrawn from the