4. Lactate dehydrogenase (LDH) values at Screening as follows:
   a. For patients not currently treated with eculizumab, LDH level ≥ 1.5 × upper limit of normal (ULN).
   b. For patients who are currently taking eculizumab, LDH ≤ 1.5× ULN (sample must be obtained on a scheduled eculizumab-dosing day prior to dose administration [ie, at trough eculizumab level] and analyzed by the central laboratory).
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 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 cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
6. Patients must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to national and local vaccination schedule guidelines, as appropriate.
7. Female patients of childbearing potential (ie, have achieved menarche) 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. 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]) and comply with the study visit schedule.

Exclusion Criteria:

1. Platelet count < 30,000/mm^3 (30×10^9/L) at Screening.
2. Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.
3. History of bone marrow transplantation.
4. History of *N meningitidis* infection.
5. History of unexplained, recurrent infection.
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
7. History of malignancy within 5 years of Screening with the exception of adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix.
8. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient's participation in an investigational clinical trial.
9. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Screening, coexisting chronic anemia unrelated to PNH) that would make them unlikely to tolerate the requirements of the protocol.
10. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to Day 1.
11. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
12. Females who plan to become pregnant or are currently pregnant or breastfeeding.
13. Females of childbearing potential who have a positive pregnancy test result at Screening or on Day 1.
14. 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.
15. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.
16. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Sponsor, might interfere with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.

Abbreviation	Definition
q4w	once every 4 weeks
q8w	once every 8 weeks
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

weight, and head circumference [the latter only in patients who are ≤ 3 years of age]), electrocardiograms (ECGs), laboratory assessments, and incidence of AEs and serious adverse events (SAEs). The proportion of patients who develop antidrug antibodies (ADAs) will also be assessed.

statistically powered for hypothesis testing. This approach was discussed in the context of the agreed pediatric investigation plan of ALXN1210 in PNH (EMEA-002077-PIP01-16).

The disease pathophysiology and clinical response to ALXN1210 treatment is expected to be similar between adult and pediatric PNH populations, as demonstrated in the eculizumab clinical development program. Thus, the efficacy parameters in this study of ALXN1210 are modelled on those selected for study in adult patients with PNH.

The safety parameters being evaluated are commonly used in clinical trials per International Conference on Harmonisation (ICH) and good clinical practice (GCP) guidance documents.

7.3. Schedule of Assessments

The Schedule of Assessments is provided in Table 1 for the Screening and Primary Evaluation Period and in Table 2 and Table 3 for the Extension Period.

Refer to Appendix A and 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. All tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the electronic case report forms (eCRFs).

Additionally, if a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters must be analyzed at the central laboratory. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters. For purposes of defining breakthrough hemolysis, assessment of LDH must be based on a central laboratory value.

If a supplemental dose of study drug is administered, PK/PD samples will be collected predose and at end of infusion (EOI) and a physical examination including vital signs (blood pressure, heart rate, respiratory rate, temperature) will be performed. If the loading dose for patients ≥ 5 to < 10 kg is administered as 2 separate infusions < 24 hours apart (as described in Section 9.2), blood samples for PK/PD analysis will be collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample).

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

Period	**Screening**	**Initial Evaluation Period**							
Study Day	**–28 to –1**	**1**	**15**	**43**	**71**	**99**	**127**	**155**	**183[a]/ET**
Window (day)	**N/A**		**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±2**
Informed consent	X								
Confirmation or administration of meningococcal vaccination[b]	X	X							
Confirmation of *H influenza type B and S pneumoniae* vaccination (per local/national guidelines)	X								
Medical history and demographics	X								
PNH clone size[c]	X	X			X				X
Head circumference (patients ≤ 3 years of age only)	X	X	X	X	X	X	X	X	X
Height and weight[d]	X	X	X	X	X	X	X	X	X
Pregnancy test[e]	X	X	X		X		X		X
Record transfusions (during and between visits)	X	X	X	X	X	X	X	X	X
PNH symptomatology[f]	X	X	X	X	X	X	X	X	X
Pediatric FACIT-Fatigue questionnaire[g]		X	X		X		X		X
Physical examination	X								X
Abbreviated physical examination[h]		X	X	X	X	X	X	X	
Vital signs[i]	X	X	X	X	X	X	X	X	X
Safety 12-Lead ECG[j]	X				X				X
Chemistry including LDH[k]	X[l]	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation[k]	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[k]	X	X	X		X		X		X
PK/PD sampling[m]		X	X		X		X		X
Immunogenicity (ADA)[n]		X			X		X		X
Review safety card[o]		X	X	X	X	X	X	X	X
Breakthrough hemolysis[p]		←Monitor continuously→							
Concomitant medications	X	←Monitor continuously→							
Adverse events	X	←Monitor continuously→							
ALXN1210 administration (patients weighing < 20 kg)[q,r]		X[s]	X	X	X	X	X	X	
ALXN1210 administration (patients weighing ≥ 20 kg)[q]		X[s]	X		X		X		

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LDH = lactate dehydrogenase; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; WBC = white blood cell

Note: If a patient discontinues from the study, an ET visit will be performed, and the Sponsor and site monitor should be notified as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (± 5 days) following the patient's last ALXN1210 dose to collect concomitant medications, procedures, and adverse events.

[a] The primary 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.

Patients may have an opportunity to receive ALXN1210 administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Home infusions may be considered only for patients who have tolerated previous drug infusions well, without clinically significant infusion reactions, at the study site.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Information about AEs, concomitant medications, and signs and symptoms of breakthrough hemolysis must be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE or breakthrough hemolysis, the patient will need to be evaluated at the study site.

Monitoring, treatment, and management of infusion reactions for patients receiving drug infusions at home are described in detail in the home health care manual and Appendix B.

9.11. Contraception Guidance

Female patients of childbearing potential (ie, who have achieved menarche) 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

The description of the MAVE including the method of diagnosis (eg, magnetic resonance imaging, ultrasound, angiogram), date of diagnosis, and date resolved (or ongoing) will be collected on the eCRF as part of the patient's medical history (prior to baseline).

A MAVE is defined as follows:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (nontraumatic; nondiabetic)
- Amputation (nontraumatic; nondiabetic)
- Dermal thrombosis
- Other, specify

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 D. 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 laboratory manual. If a suspected event of breakthrough hemolysis occurs, an unscheduled visit must take place at which a sample is collected for analysis of LDH and PK/PD by the central laboratory.

Laboratory assessments will be tested at a central laboratory facility. 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 14.9.3). 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 Testing

For females of childbearing potential (ie, have achieved menarche), a serum or urine pregnancy test (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 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.

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

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.

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, PK/PD, safety, and activity of ALXN1210.

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 for 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.

Transfusions are treated as efficacy endpoints (see Section 6.2). Transfusions administered in the inpatient or outpatient setting should not be captured as AEs or SAEs unless identified as such by the Investigator.

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

As noted in Section 9.8, C5 inhibition is known to increase susceptibility to infections caused by *N meningitidis*. The following event is an important identified risk 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 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 an 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.

Abbreviation: AE = adverse event

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

Alexion procedures for the reporting of suspected unexpected serious adverse reactions (SUSARs) are in accordance with United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries, as well as 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 56 days after the last dose of study drug for patients with ET or until 56 days after the last dose of study drug for patients who complete the study. 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 Drug Safety (GDS) 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.

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 GDS 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 the paper SAE contingency form. Facsimile transmission or email may be used in the event of electronic submission failure.

Email: PI

Facsimile: PI (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 GDS via Safety Gateway.

If applicable, additional information such as relevant medical records should be submitted to Alexion GDS 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 GDS 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 Investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site, as required per IRB/IEC standard operating procedures (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 Lactation

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 a spouse or partner, will use a highly effective or acceptable method of contraception.

In the event of a pregnancy event, pregnancy data will be collected during this study for all patients and a 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 post approval, 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 GDS 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 GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

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 and PT. 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.

14.9.2. Physical Examination, Vital Signs, and Growth

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 treatment group.

Height, weight, and head circumference (the latter only for patients ≤ 3 years of age) will be summarized descriptively at baseline and postbaseline time points and for changes from baseline by treatment group.

By-patient data listings will be provided.

14.9.3. Clinical Laboratory Tests

Changes in clinical chemistry, hematology, and urinalysis results from baseline to postbaseline study time points will be summarized descriptively. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. Listings of patients with abnormal results will be provided.

14.9.4. Electrocardiograms

By-patient data listings of ECG parameters will be provided. Changes from baseline in ECG intervals (PR, RR, QT, and QTcF) will be provided. QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

14.9.5. Immunogenicity

Incidence and titers for ADAs to ALXN1210 will be summarized in tabular format.

14.10. Pharmacokinetic/Pharmacodynamic Analyses

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

Investigational Product, Dosage, and Mode of Administration:
ALXN1210 loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg will be administered by IV infusion. Dosages are based on the patient's body weight recorded on dosing day or the most recently recorded weight, as shown in the table below:

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency
≥ 5 to < 10	600[b]	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 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] Dose regimen will be based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.
[b] With the agreement of the Alexion Medical Monitor, the 600 mg loading may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart

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

Planned Duration of Treatment: 26-week Primary 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 years, whichever occurs first, except in Norway where the Extension Period will be 4 years.

Endpoints:
Primary endpoint:
- PK/PD parameters (trough and peak) at Baseline and Weeks 2, 10, 18, and 26
  - PK: maximum serum concentration (C_{max}), trough serum concentration (measured at end of dosing interval at steady state; C_{trough}), accumulation ratio
  - PD: change in free C5 concentrations and in chicken red blood cell (cRBC) hemolytic activity over time

Secondary endpoint:
- Percentage change in LDH from baseline to Day 183 (Week 26)
- Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion through Day 183 (Week 26)
- Change in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients ≥ 5 years of age), from baseline to Day 183 (Week 26)
- Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
- Percentage change in free hemoglobin from baseline to Day 183 (Week 26)
- Proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia, major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:
  - For patients who enter the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × ULN after prior LDH reduction to < 1.5 × ULN on therapy
  - For patients who enter the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN

Safety
The safety and tolerability of ALXN1210 will be evaluated from baseline to Week 26 and throughout the extension period by physical examinations, vital signs, physical growth, electrocardiograms (ECGs), laboratory

5. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a progressive, debilitating, and life-threatening disease characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure. PNH has an estimated worldwide incidence of 1.3 per million population (Hill, 2006). The onset of PNH is typically in adulthood, with pediatric cases accounting for < 5% of reported cases (Ware, 1991). Given the extremely small target population, studies of children with PNH have been limited to case reports, case series, and a small clinical trial (Reiss, 2014).

In adults, the clinical manifestations of PNH include hemoglobinuria, chronic renal insufficiency, erectile dysfunction, thrombosis, abdominal pain, dyspnea, and dysphagia (Parker, 2005). In contrast, children with PNH usually present with nonspecific symptoms related to the underlying bone marrow disorder, such as pallor, fatigue, or jaundice, with hemoglobinuria appearing less commonly (Ware, 1991). Clinical evaluation in pediatric patients also reveals bone marrow failure syndromes, such as aplastic anemia and refractory cytopenia (van den Heuvel-Eibrink, 2007). Once the bone marrow disorder is resolved in the child or the PNH clone expands (the cause of which is still unknown), the disease eventually evolves into one more typically seen in adults at presentation. Thus, pediatric patients can be expected to suffer substantial morbidity related to hemolysis, as seen in adult PNH patients (Parker, 2005).

The ALXN1210 clinical program in patients with PNH includes a Phase 3 study in adults with PNH who are naïve to eculizumab therapy, a Phase 3 study in adults with PNH who are stable on eculizumab therapy, a Phase 1b dose-ranging study, and a Phase 2 dose regimen optimization study. Each of these studies also includes a 2-year extension phase. In addition, a Phase 1 study to assess the pharmacokinetic (PK) profile of ALXN1210 in healthy Japanese subjects has been completed.

In this Phase 3, open-label study, the PK, pharmacodynamics (PD), efficacy, and safety of ALXN1210 will be assessed in pediatric patients with PNH. The study design rationale is further discussed in Section 7.2.

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

As described above, PNH is an ultra-rare, progressive, debilitating, and life-threatening disease, driven by chronic uncontrolled complement activation. The resulting inflammation and cellular damage lead to systemic complications, principally through intravascular hemolysis and thrombophilia (Brodsky, 2014; Socie, 1996). Chronic intravascular hemolysis due to continuous activation of the complement pathway leads to the release of free hemoglobin, nitric oxide consumption and persistent smooth muscle cell contraction, chronic anemia, and an increased risk of severe thromboembolism. Patients with PNH are at risk of substantial morbidity and mortality and altered quality of life (QoL). The current standard of care for the treatment of PNH is eculizumab (Soliris®), a recombinant humanized monoclonal antibody (mAb) that binds to human complement component 5 (C5) and inhibits the activation of terminal complement.

7. INVESTIGATIONAL PLAN

7.1. Summary of Study Design

This is a Phase 3, open-label, single-arm multicenter study to evaluate the PK/PD, safety, and efficacy of ALXN1210 administered by intravenous (IV) infusion to pediatric patients (< 18 years of age) with PNH. The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period.

Consenting patients will be screened for study eligibility up to 4 weeks prior to Day 1. Patients who satisfy all of the inclusion criteria and all of the exclusion criteria will be enrolled into the Primary 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 once every 8 weeks (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. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab.

An interim analysis of data, including ALXN1210 PK and free C5 levels, will be conducted after 4 patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. Enrollment of patients will proceed without interruption while the analysis is ongoing. The accrued safety and PK/PD data will be assessed to ensure that ALXN1210 treatment is well tolerated and is providing adequate complement inhibition. Based on this review, the dose regimen may be adjusted. In addition, an independent Data Monitoring Committee (DMC) will review safety data from the study on a regular basis.

After completion of all pre-dose assessments on Day 183, all patients will enter an Extension Period and continue to receive ALXN1210 according to the appropriate weight-based regimen. The Extension Period will continue until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years. The end of study is defined as the last patient's last visit or follow-up (whether on site or via phone call) in the Extension Period.

7.2. Discussion of Design and Control

This is an uncontrolled, open-label study of ALXN1210 treatment in pediatric patients. Given the ongoing ALXN1210 clinical program in adults with PNH and the data already generated in an eculizumab clinical study in pediatric patients with PNH (M07-005), a single-arm design was deemed appropriate to investigate the PK/PD, efficacy, and safety of ALXN1210 in the pediatric population. The rarity of PNH in the pediatric population precludes feasibility of a trial with a larger sample size. Ten patients should be sufficient to adequately describe PK/PD in this population while enabling study conduct within a reasonable time frame for making this important treatment available to patients, given the challenges of finding these rare pediatric patients and enrolling them into a prospective, interventional study. The proposed sample size is consistent with the principles of extrapolating the PK/PD and safety/efficacy from adults to pediatric patients given that the disease pathogenesis and mechanism of action of the drug are similar between these two population subsets. This study is descriptive in nature and not

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

[b] 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. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.

[c] WBC (granulocyte and monocyte) and RBC clone size measured by high-sensitivity flow cytometry at Screening and Day 1; RBC clone size only on Day 71 and Day 183.

[d] Height at baseline and Day 183 only; weight is collected predose on dosing days.

[e] Pregnancy testing is required only for female patients of childbearing potential (ie, have achieved menarche). Serum pregnancy test is performed at Screening and Day 183, urine (or serum if required by site policy) 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.

[f] Investigator or designee assessment of the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction. On dosing days, assessments will be performed prior to dosing.

[g] On dosing days, assessments will be performed prior to dosing. Pediatric FACIT-Fatigue only in patients ≥ 5 years of age (self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were ≥ 5 to < 8 years of age at the time of enrollment).

[h] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.

[i] Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (BP) (millimeters of mercury [mmHg]), 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.

[j] Single 12-lead ECG will be collected at Screening and predose on Day 71 and Day 183. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[k] Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line.

[l] For patients entering the study on eculizumab therapy, screening LDH should be obtained within 24 hours prior to a scheduled eculizumab dose.

[m] Serum samples for PK/PD analyses will be collected at the indicated visits. Samples will be collected predose (within 0.5 hours prior to the start of infusion) and at 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. If a supplemental dose is administered, PK/PD samples will be collected predose and at EOI. If a loading dose is administered as 2 separate infusions < 24 hours apart (as described in Section 9.2), PK/PD samples will be collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample). All collection times will be recorded in the eCRF.

[n] ADA serum samples will be collected predose on Days 1, 71, and 127 or at any time during an ET visit. Day 183 collection will occur prior to first dose in the Extension Period.

[o] Review the Clinical Trial Participant Safety Information Card with the patient/caregiver and discuss the importance of carrying the safety card at all times, and the risks associated with ALXN1210 treatment, including the risk of meningococcal infection.

[p] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD parameters will be analyzed at the central laboratory. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required LDH, PK, and PD parameters.

[q] Dose regimen is based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.

[r] Should a patient's weight change from < 20 kg to ≥ 20 kg on a "q4w only" visit, the patient will receive the q4w dose that day; at the patient's next q8w visit, the new q8w dose will be given.

[s] For patients entering the study on eculizumab therapy, Day 1 should occur 2 weeks from the patient's last dose of eculizumab.

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.

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.

Investigators are instructed to follow any AEs through to their conclusion (resolution or stabilization), as described in Section 11.7.6.

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. Head circumference will be recorded for patients who are ≤ 3 years of age.

11.1.2. Disease Characteristics

The patient's PNH medical history, including PNH symptoms, date of diagnosis, PNH clone size, pRBC transfusions, and history of any MAVEs, will be documented at the Screening Visit.

11.1.3. Medical History

The patient's medical history, including prior and concomitant conditions/disorders and transfusion history, 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. Details of prior treatment with eculizumab, including dose level and frequency, will be collected.

Meningococcal vaccination within 3 years prior to the first dose of study drug, and vaccination history for Hib and *S pneumoniae* from birth, will also be recorded, as described in Section 9.7.

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 ≤ 3 years of age]) will be assessed.

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 blood pressure (BP; millimeters of mercury [mmHg]),

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 GDS or designee via email or facsimile (Section 11.7.6.2).

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, GDS 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 GDS physician, to review trends in safety data.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ALXN1210 and who have evaluable PD data.

Descriptive statistics will be presented for all ALXN1210 PD endpoints at each sampling time (Section 7.3). The PD effects of ALXN1210 administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and change from baseline in cRBC hemolysis over time, as appropriate. Assessments of ALXN1210 PK/PD relationships may be explored using data from this study or in combination with data from other studies. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

14.11. Other Statistical Issues

14.11.1. Missing or Invalid Data

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

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