# TITLE PAGE

**Protocol Title:**

A Phase 2a, Randomized, Open-Label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

**Protocol Number:** ALXN1820-SCD-201

**Amendment Number:** 1.0

**Compound:** ALXN1820

**Study Phase:** Phase 2a

**Short Title:**

Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Study of ALXN1820 in Adult Patients with Sickle Cell Disease

**Sponsor Name:** Alexion Pharmaceuticals, Inc.

**Legal Registered Address:**

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**Regulatory Agency Identifying Number(s):**

| | |
|---|---|
| NCT: | Pending |
| EudraCT: | 2022-001615-74 |

**Approval Date:** 22 August 2022

**Sponsor Signatory:**

[redacted]

23-Aug-2022 | 09:48:42 EDT

[redacted], Clinical Development Sciences

**Date**

**Medical Monitor Name and Contact Information will be provided separately.**

# INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines for Good Clinical Practice (GCP), and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Primary Site Address of Investigator

_____

Date

# PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 1.0 (22 August 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for the Amendment:**

The main purpose of this global protocol amendment is to clarify the individual and study stopping rules as well as the inclusion/exclusion criteria. These and other changes are described in the table below.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | Intervention Groups and Duration has been changed. The text indicated in **bold** font has been added:<br><br>The end of study (EOS) for each individual patient is anticipated to be Day 211 (210 days) **or the timepoint at which complement activity has returned to a normal range or 80% of baseline if later than Day 211.**<br><br>The EOS for each individual patient is anticipated to be Day 169 (168 days) **or the timepoint at which complement activity has returned to a normal range or 80% of baseline if later than Day 169.** | Included to further enhance safety measures. |
| 1.2 Schema | Footnote a has been added to the schema. See text indicated in **bold** font below.<br><br>**[a] Follow-up Period may be longer than 18 weeks for those patients whose complement activity has not returned to the normal range or 80% of baseline.** | Included to further enhance safety measures. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities, Table 6 and Table 8 | Table caption has been changed. The text indicated in ~~strikethrough~~ has been deleted and the text indicated in **bold** has been added.<br><br>Table 6: Schedule of Activities – Day 99 ~~t~~**T**hrough ~~Day 211~~**End of Follow-up Period**, Cohorts 1 and 2<br><br>Table 8: Schedule of Activities – Day 57 ~~t~~**T**hrough ~~Day 169~~**End of Follow-up Period** for Multiple ~~d~~**D**ose Follow-up (Optional Cohort 3) | Updated as a result of the changes made to the Follow-up Period to enhance patient safety. |
| 1.3 Schedule of Activities, Table 6 and Table 8 | Day 211 (Table 6) and Day 169 (Table 8) column titles have been changed. Text indicated in ~~strikethrough~~ has been deleted.<br>Day 211/~~EOS~~/ET/Unscheduled<br>Day 169/~~EOS~~/ET/Unscheduled | Updated as a result of the changes made to the Follow-up Period to enhance patient safety. |
| 1.3 Schedule of Activities, Table 6 and Table 8 | Text in **bold** has been added. Added "**Complement Activity Follow-up**" column (with a time window of ± 14 days) with the following footnote:<br>**If CAP activity has not returned to a normal range or 80% of the baseline level at the end of the Follow-up Period, patients may have additional Follow-up Visits every 12 weeks until CAP activity has been confirmed to either have returned to a normal range or 80% of the baseline level. This visit may be completed at home.** | Included to further enhance safety measures. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1 Inclusion Criteria | Inclusion Criterion 7 has been changed. The text indicated in **bold** font has been added; text indicated in ~~strikethrough~~ has been deleted:<br>Patients receiving hydroxyurea must have been on a stable dose for ≥ 3 months prior to providing informed consent, with no anticipated need for dose adjustment during the study. For patients who previously used hydroxyurea but are not currently on hydroxyurea treatment **(due to non-responsiveness, intolerance, or unwillingness to take hydroxyurea), hydroxyurea treatment** must ~~be stopped~~ **have been discontinued** at least 30 days prior to providing informed consent. | Included to define the conditions under which being "not currently on hydroxyurea treatment" is acceptable for study participation. |
| 5.2 Exclusion Criteria | Added Exclusion Criterion 7. The text in **bold** font has been added:<br>**History of complement deficiency.** | Included to further enhance the safety of the participants allowed in the study. |
| 5.2 Exclusion Criteria | Added Exclusion Criterion 8. The text in **bold** font has been added:<br>**History of *N meningitidis*, *S pneumoniae*, or *H influenzae* infection.** | Included to further enhance the safety of the participants allowed in the study. |
| 7.2 Stopping Criteria | Section 7.2 has been changed. The text in **bold** font has been added and the text in ~~strikethrough~~ has been deleted:<br>**7.2 Stopping Criteria**<br>**7.2.1. Individual Stopping Rules**<br>Participants should be considered for discontinuation from intervention if any of the following occur during the study:<br>• Serious hypersensitivity reaction;<br>• **Grade 3 or higher injection site reactions;**<br>• Severe uncontrolled infection; | Included individual and study stopping rules to further enhance safety measures. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | • **Serious *N meningitidis*, *S pneumoniae*, or *H influenzae* infections;**<br>• Use of disallowed medication as defined in Section 6.5.2;<br>• Pregnancy or planned pregnancy; or<br>• Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator or Alexion, presents a substantial clinical risk to the patient with continued study drug dosing.<br>**7.2.2 Study Stopping ~~Criteria~~ Rules**<br>~~Please see Section 7.1~~<br>**The study may be terminated at the recommendation of the DMC, if the following occur and are deemed to be related to the study drug:**<br>• **Two or more meningococcal infections;**<br>• **Two or more serious (≥ Grade 3) pneumococcal infections;**<br>• **Two or more serious (≥ Grade 3) *H influenzae* infections;**<br>• **One meningococcal, pneumococcal, or *H influenzae* infection resulting in a fatal outcome.** | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.1.9 Study and Site Start and Closure | Text indicated in ~~strikethrough~~ has been deleted and text indicated in **bold** has been added.<br>A study site is considered closed when all participants have completed ~~the EOS~~ **the last study visit** or Early Discontinuation Visit, all data have been collected and entered into the electronic data capture system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed. | Removed reference to EOS Visit because the protocol no longer has a clearly demarked EOS Visit. |
| 10.10 Protocol Amendment History | New section added. | For completeness. |
| Throughout | Minor editorial and document formatting revisions. | Minor; therefore, have not been summarized. |

Abbreviations: AE = adverse event; CAP = complement alternative pathway; EOS = end of study; DMC = Data Monitoring Committee

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A Phase 2a, Randomized, Open-label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

**Short Title:** Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Study of ALXN1820 in Adult Patients with Sickle Cell Disease

**Rationale:** ALXN1820 (anti-properdin/anti-serum albumin bispecific single variable domain on a heavy chain [VHH] antibody) is a novel properdin blocking agent being developed for the treatment of diseases involving dysregulated complement activity. The ALXN1820 molecule is bispecific, comprising a VHH antibody domain that binds and blocks properdin, connected via a linker to a VHH domain that binds serum albumin, thereby conferring an extended circulatory half-life to the molecule. ALXN1820 formulation is designed for subcutaneous (SC) administration. The purpose of this study is to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of multiple doses and dosing regimens of ALXN1820 SC in patients with Sickle Cell Disease (SCD).

The study will include up to 3 cohorts. Data from this study are anticipated to help design future studies in patients with SCD and other complement-mediated diseases.

**Objectives and Endpoints**

**Table 1: Mapping Objectives to Endpoints for Patients with Sickle Cell Disease**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the safety and tolerability of ALXN1820 SC in patients with SCD | Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory, and electrocardiogram results through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| **Secondary** | |
| To assess the multiple-dose PK of ALXN1820 SC | Serum ALXN1820 multiple-dose PK profiles through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| To assess the PD effects of ALXN1820 SC | Change in serum concentrations of total and free properdin over time through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3)<br>Change in CAP activity using the Wieslab AP assay through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| To assess the effect of ALXN1820 on complement biomarkers | Change from baseline in complement biomarkers through Week 12 (Cohorts 1 and 2) |

**Table 1: Mapping Objectives to Endpoints for Patients with Sickle Cell Disease**

| Objectives | Endpoints |
|---|---|
| To assess the effect of ALXN1820 on hemolysis | Change from baseline in hemoglobin levels at Week 12 (Cohorts 1 and 2)<br>Change from baseline in hemolysis markers (eg, lactate dehydrogenase, reticulocytes, and bilirubin) and hemopexin at Week 12 (Cohorts 1 and 2) |
| To assess the immunogenicity of ALXN1820 SC | Incidence of ADAs to ALXN1820 through Day 211 (Cohorts 1 and 2) and through Day 169 for Optional Cohort 3 |
| **Exploratory** | |
| To explore the effect of ALXN1820 on vaso-occlusion markers | Change from baseline in VOC related biomarkers through Week 12 (Cohorts 1 and 2) |
| To explore the clinical efficacy of ALXN1820 SC in SCD | VOC events (rate of VOC, time to first VOC) through Week 12 (Cohorts 1 and 2) |

Abbreviations: ADA = antidrug antibody; AP = alternative pathway; CAP = complement alternative pathway; PD = pharmacodynamics(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; SCD = sickle cell disease; TEAE = treatment-emergent adverse event; VOC = vaso-occlusive crisis.

## Overall Design

This is a Phase 2a study, with up to 3 multiple dose cohorts of open-label ALXN1820 SC in adult patients with SCD (HbSS and HbSß$^0$-thalassemia).

The study will be conducted in up to 30 adult patients with SCD enrolled in up to 3 open-label cohorts (Cohorts 1, 2 and 3 [optional]) to receive multiple SC doses of open-label ALXN1820. ALXN1820 will be administered as described in Table 2.

**Table 2: ALXN1820-SCD-201 Dosing Cohorts**

| Cohort | N | Study Drug | Route of Administration | Planned Dose | Number of Doses/Dose Interval |
|---|---|---|---|---|---|
| 1 | Up to 12<br>maximum of 6 on stable dose of hydroxyurea | ALXN1820 | SC | 300 mg | QW × 13 |
| 2 | Up to 12<br>maximum of 6 on stable dose of hydroxyurea | ALXN1820 | SC | 600 mg | Q4W × 4 |

**Table 2: ALXN1820-SCD-201 Dosing Cohorts**

| Cohort | N | Study Drug | Route of Administration | Planned Dose | Number of Doses/Dose Interval |
|---|---|---|---|---|---|
| 3 (optional) | Up to 6 maximum of 3 on stable dose of hydroxyurea | ALXN1820 | SC | 300 mg | Q2W × 4 |

Abbreviations: N = number of participants; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous; SCD = Sickle Cell Disease.

The dose and dosing interval for Cohorts 1 and 2 was determined using cumulative safety data, an interim PK/PD analysis from participants enrolled in Study ALXN1820-HV-101, and data from the 6-month Good Laboratory Practice (GLP) toxicology study in monkeys. Optional Cohort 3 will be initiated after evaluation of safety and PK/PD data from Cohorts 1 and 2, at Alexion's discretion.

Cohort 1 and Cohort 2 will run in parallel, and patients will be randomized 1:1 to either of the cohorts on determination of eligibility. The decision to initiate Optional Cohort 3 will be made at Alexion’s discretion and will be based on analysis of PK/PD and safety after at least 8 patients from Cohorts 1 and 2 (4 from each cohort) have enrolled. Furthermore, enrollment of Optional Cohort 3 will start after Cohorts 1 and 2 are fully enrolled. Each cohort will be stratified to ensure patients with SCD who are treated with a stable dose of hydroxyurea and patients with SCD who are not currently treated with hydroxyurea are included. The Treatment Period will be 12 weeks for Cohorts 1 and 2, and 6 weeks for Cohort 3. For patients who were previously treated with hydroxyurea but are not currently on hydroxyurea, treatment must have been stopped at least 30 days prior to providing informed consent.

At Alexion’s discretion, and after consultation with the Data Monitoring Committee (DMC), additional participants with SCD may be enrolled as replacement participants if a participant discontinues during the Dosing Period for reasons other than drug-related adverse events (AEs).

**Disclosure Statement** This is an open-label, parallel group intervention study with up to 3 treatment arms.

**Number of Participants:**

Up to 30 adult patients with SCD (HbSS and HbSß$^0$-thalassemia) will be enrolled in up to 3 cohorts and will receive multiple open-label SC doses of ALXN1820. The cohorts will enroll both patients with SCD who are being treated with a stable dose of hydroxyurea and patients with SCD who are not currently treated with hydroxyurea. For patients who were previously treated with but are not currently on hydroxyurea, treatment must have been stopped at least 30 days prior to providing informed consent.

**Intervention Groups and Duration:**

The planned study duration is approximately 38 weeks for Cohorts 1 and 2: up to 56 days (8 weeks) for Screening, 84 days (12 weeks) for the Treatment Period, and 126 days (18 weeks) for the Follow-up Period. Patients will attend outpatient visits during the Treatment and Follow-

up Period with the option to stay at the inpatient facility. The end of study (EOS) for each individual patient is anticipated to be Day 211 (210 days) or the timepoint at which complement activity has returned to a normal range or 80% of baseline if later than Day 211.

The planned study duration is approximately 32 weeks for optional Cohort 3: up to 56 days (8 weeks) for Screening, 42 days (6 weeks) for the Treatment Period, and 126 days (18 weeks) for the Follow-up Period. Patients will attend outpatient visits during the Treatment and Follow-up Period with the option to stay at the inpatient facility. The EOS for each individual patient is anticipated to be Day 169 (168 days) or the timepoint at which complement activity has returned to a normal range or 80% of baseline if later than Day 169.

A schematic view of the study is presented in Figure 1.

**Data Monitoring Committee:** This study will use an independent DMC to monitor safety and to perform the planned interim analyses of the study.

**Statistical Analyses – All Cohorts:**

Populations for Analysis

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Safety | All participants who receive at least 1 dose of study drug |
| Enrolled Set | All participants who sign the ICF and passed inclusion/exclusion criteria. |
| Full Analysis Set (FAS) | All participants in the Enrolled Set who have been randomized and received at least 1 dose of study drug. |
| Per Protocol Set (PPS) | All participants in the Enrolled Set without any major protocol deviation. |
| Pharmacokinetic | All participants who receive at least 1 dose of the study drug and have at least 1 post-dose PK sample |
| Pharmacodynamic | All participants who receive at least 1 dose of study drug and who have evaluable properdin concentration data CAP or CCP activity data |
| Immunogenicity | All participants who have a predose and at least 1 postdose ADA sample collected that can be analyzed |

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CCP = complement classical pathway; ICF = informed consent form; PK = pharmacokinetic(s).

Safety Analysis

All safety analyses will be performed on the Safety Population and will be reported by each cohort and treatment arm.

Safety analyses will include an analysis of all treatment-emergent adverse events (TEAEs), electrocardiograms (ECG's), clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. The prevalence of AEs and serious adverse events (SAEs) will be summarized, by System Organ Class (SOC) and Preferred Term for each cohort and treatment arm and overall, within each treatment arm, by relationship to study drug. AEs will also be

summarized by cohort and overall by severity. SAEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

All concomitant medications will be coded using the World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

Efficacy Analysis

Absolute and percentage change from baseline in complement biomarkers, hemoglobin and hemolysis markers will be evaluated at the end of the Treatment Period (12 weeks) for Cohort 1 and Cohort 2. Time to hemoglobin response (defined as an increase in hemoglobin levels of > 1g/dL from baseline) will be evaluated at the end of the Treatment Period (12 weeks) for Cohort 1 and Cohort 2.

Pharmacokinetic Analysis

The individual serum concentration data from participants who receive ALXN1820 SC with actual sampling dates and times, will be used to characterize the PK by population PK analysis approach.

Pharmacodynamic Analysis

The PD effects of all ALXN1820 SC doses administered will be evaluated by assessing changes in serum total and free properdin concentrations and complement alternative pathway (CAP) activity using the Wieslab alternative pathway (AP) assay. In addition, complement classical pathway activity and other measures of properdin activity over time may be considered as deemed appropriate (Section 8.6).

Immunogenicity Analysis

Immunogenicity, as measured by incidence of antidrug antibody (ADA) to ALXN1820 will be summarized.

Exploratory Analysis

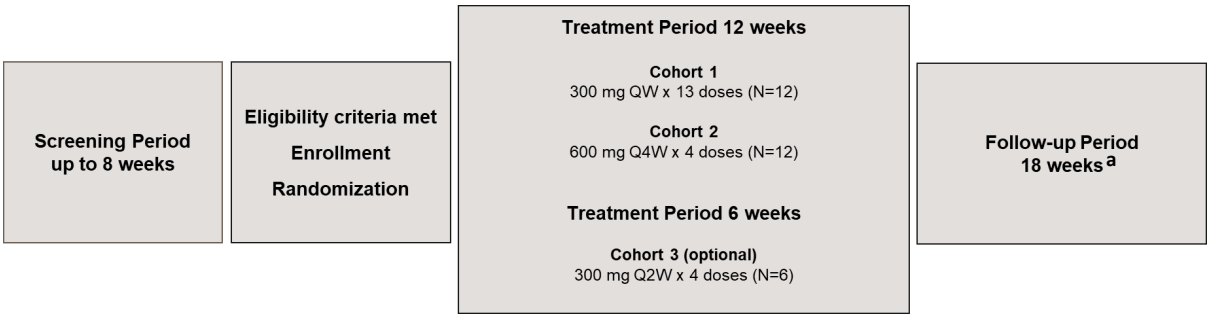
Additional exploratory analyses on biomarker assays and clinical efficacy endpoints may be conducted. Details of these analyses will be presented in the statistical analysis plan (SAP).

Interim Analysis

An interim analysis may be performed after at least12 patients from Cohorts 1 and 2 (6 from each cohort) have enrolled and completed the Treatment Period (12 weeks). Details of this analysis will be presented in the SAP.

## 1.2. Schema

**Figure 1: Study ALXN1820-SCD-201 Schematic for Cohorts 1, 2, and 3**




[a] Follow-up Period may be longer than 18 weeks for those patients whose complement activity has not returned to the normal range or 80% of baseline.
Abbreviations: N = number of participants; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SCD = sickle cell disease
Note: Optional Cohort 3 will be initiated at Alexion's discretion and will be based on analysis of PK/PD and safety after at least 8 patients from Cohorts 1 and 2 (4 from each cohort) have enrolled. Furthermore, enrollment of Optional Cohort 3 will start after Cohorts 1 and 2 are fully enrolled.

## 1.3. Schedule of Activities (SoA)

The SoA for once weekly (QW) dosing for multiple-dose Cohort 1 for Screening through Day 85 is presented in Table 3.

The SoA for once every 4 weeks (Q4W) dosing for multiple-dose Cohort 2 for Screening through Day 85 is presented in Table 4.

Table 5 presents the SoA for intensive PK/PD sampling for a subset of participants in Cohorts 1 and 2. Table 6 presents the SoA for Cohorts 1 and 2 for Day 99 through the end of the Follow-up Period.

The SoA for once every 2 weeks (Q2W) dosing for optional multiple-dose Cohort 3 for Screening through Day 43 is presented in Table 7. Table 8 presents the SoA for Cohort 3 for Day 57 through the end of the Follow-up Period.

**Table 3: Schedule of Activities – Screening Through Day 85 (Cohort 1) – QW Dosing**

| **Study Day** | **Screening Day –56 to Day –1** | **Day 1** | **Day 8** | **Day 15** | **Day 22** | **Day 29** | **Day 36** | **Day 43** | **Day 50** | **Day 57** | **Day 64** | **Day 71** | **Day 78** | **Day 85** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Window (Day)** | **NA** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** | **± 1** |
| Informed consent[a] | X | | | | | | | | | | | | | |
| Eligibility criteria[b] | X | X | | | | | | | | | | | | |
| Randomization[c] | | X | | | | | | | | | | | | |
| Confirmation of or administration of meningococcal vaccination[d] | X | | | | | | | | | | | | | |
| Confirmation of or administration of HiB and *S pneumoniae* vaccination | X | | | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | | |
| Physical examination | X | X | | | | | | | | | | | | |
| Abbreviated physical examination | | | | | | X | | | | X | | | | X |
| Height, weight, and BMI[e] | X | X | | | | X | | | | X | | | | X |
| Hematology[f] | X | X | | | | X | | | | X | | | | X |
| Clinical chemistry[f] | X | X | | | | X | | | | X | | | | X |
| Coagulation[f] | X | X | | | | X | | | | X | | | | X |
| Hepatitis B and C screen | X | | | | | | | | | | | | | |
| HIV (types 1 and 2) screen | X | | | | | | | | | | | | | |
| Serum/urine pregnancy test[g] | X | X | | | | X | | | | X | | | | X |

**Table 3: Schedule of Activities – Screening Through Day 85 (Cohort 1) – QW Dosing**

| Study Day | Screening Day –56 to Day –1 | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 | Day 50 | Day 57 | Day 64 | Day 71 | Day 78 | Day 85 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Window (Day)** | NA | NA | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 | ± 1 |
| Urinalysis (including spot urine) | X | X | | | | X | | | | X | | | | X |
| Vital sign measurements[h] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Triplicate ECG[i] | X | X | | X | | X | | | | X | | | | X |
| Study drug administration QW | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK samples[j] | | X | | X | | X | | X | | X | | X | | X |
| Blood sample for PD panel[j,k] | | X | | X | | X | | X | | X | | X | | X |
| Injection site reaction[l] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Biomarkers[m] | X | X | | X | | X | | X | | X | | X | | X |
| Immunogenicity (ALXN1820 ADA)[n] | | X | | X | | X | | | | | | | | X |
| Assessment of VOC[o] | X | ←Monitor continuously→ | | | | | | | | | | | | |
| Review patient diary[p] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Review safety card[q] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | ←Monitor continuously (after ICF is signed)→ | | | | | | | | | | | | | |
| Adverse events[r] | ←Monitor continuously (after ICF is signed)→ | | | | | | | | | | | | | |

[a] Signed and dated IEC-approved informed consent must be obtained before any study-specific screening procedures are performed.
[b] Eligibility will be assessed at Screening and Day 1.
[c] Randomization will occur following confirmation of all eligibility requirements.

## Table 3: Schedule of Activities – Screening Through Day 85 (Cohort 1) – QW Dosing

[d] To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines). Participants who initiate study intervention treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.
[e] Height and BMI only at Screening.
[f] Non-fasting blood samples will be obtained.
[g] Serum pregnancy test is required for all female participants of childbearing potential (ie, have achieved menarche) to confirm that a female participant is not pregnant prior to first dosing. A urine pregnancy test can be performed if the Screening visit is within 3 weeks of Day 1 visit. A urine (or serum if required by local site policy) pregnancy test is to be performed at all other required timepoints.
[h] At Screening, supine and standing (orthostatic) blood pressures will be performed.
[i] Predose triplicate 12-lead ECGs will be performed on Day 1 only and will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing (If this schedule is not feasible, ECGs performed with at least 20 min apart is acceptable). If the scheduled dosing is delayed, predose ECGs performed within 4 hours of dosing do not need to be repeated. Postdose ECGs will be performed within 30 min before PK/PD sample collection.
[j] PK and PD samples are collected at pre-dose and between 2 and 4 hours post dose.
[k] PD samples will be collected to assess serum total and free properdin and CAP activity.
[l] Injection site reaction evaluation will be conducted on dosing days and if a reaction occurs, the evaluation will continue until the reaction is fully resolved.
[m] Blood samples for biomarkers will be collected 2 times prior to receiving the first dose (collect once during Screening and then again at Day 1 pre-dose, the 2 collections should be at least 2 weeks apart). Collection of blood (for serum, citrated and K2-EDTA, or P100 plasma) and urine.
[n] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[o] If a VOC occurs, samples will be collected as per unscheduled visit.
[p] The patient will record symptoms of VOC in a paper diary throughout the study. The Investigator or qualified designee will review the patient diary at every visit.
[q] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[r] Collection of adverse events and serious adverse events will begin after ICF signing.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; CAP = complement alternative pathway; ECG = electrocardiogram; HiB = *Haemophilus influenzae* type B; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; MCV4 = tetravalent meningococcal conjugate vaccine; NA = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QW = once weekly; VOC = vaso-occlusive crisis.

**Table 4: Schedule of Activities – Screening Through Day 85 (Cohort 2) – Q4W Dosing**

| Study Day | Screening Day –56 to Day –1 | Day 1 | Day 15 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 |
|---|---|---|---|---|---|---|---|---|
| Window (Day) | NA | NA | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 |
| Informed consent[a] | X | | | | | | | |
| Eligibility criteria[b] | X | X | | | | | | |
| Randomization[c] | | X | | | | | | |
| Confirmation of or administration of meningococcal vaccination[d] | X | | | | | | | |
| Confirmation of or administration of HiB and *S pneumoniae* vaccination | X | | | | | | | |
| Medical history and demographics | X | | | | | | | |
| Physical examination | X | X | | | | | | |
| Abbreviated physical examination | | | | X | | X | | X |
| Height, weight, and BMI[e] | X | X | | X | | X | | X |
| Hematology[f] | X | X | | X | | X | | X |
| Clinical chemistry[f] | X | X | | X | | X | | X |
| Coagulation[f] | X | X | | X | | X | | X |
| Hepatitis B and C screen | X | | | | | | | |
| HIV (types 1 and 2) screen | X | | | | | | | |
| Serum/urine pregnancy test[g] | X | X | | X | | X | | X |
| Urinalysis (including spot urine) | X | X | | X | | X | | X |
| Vital sign measurements[h] | X | X | X | X | X | X | X | X |
| Triplicate ECG[i] | X | X | X | X | | X | | X |

## Table 4: Schedule of Activities – Screening Through Day 85 (Cohort 2) – Q4W Dosing

| **Study Day** | **Screening Day –56 to Day –1** | **Day 1** | **Day 15** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** |
|---|---|---|---|---|---|---|---|---|
| Window (Day) | NA | **NA** | **± 3** | **± 3** | **± 3** | **± 3** | **± 3** | **± 3** |
| Study drug administration Q4W | | X | | X | | X | | X |
| PK samples[j] | | X | X2 | X | X | X | X | X |
| Blood sample for PD panel [j,k] | | X | X | X | X | X | X | X |
| Injection site reaction[l] | | X | X | X | X | X | X | X |
| Biomarker[m] | X | X | X | X | X | X | X | X |
| Immunogenicity (ALXN1820 ADA)[n] | | X | X | X | | | | X |
| Assessment of VOC[o] | X | ←Monitor continuously→ | | | | | | |
| Review patient diary[p] | X | X | X | X | X | X | X | X |
| Review safety card[q] | X | X | X | X | X | X | X | X |
| Concomitant medications | ←Monitor continuously (after ICF is signed at Screening)→ | | | | | | | |
| Adverse events[r] | ←Monitor continuously (after ICF is signed at Screening)→ | | | | | | | |

[a] Signed and dated IEC-approved informed consent must be obtained before any study-specific screening procedures are performed.
[b] Eligibility will be assessed at Screening and Day 1.
[c] Randomization will occur following confirmation of all eligibility requirements.
[d] To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines). Participants who initiate study intervention treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.
[e] Height and BMI only at Screening.
[f] Non-fasting blood samples will be obtained.
[g] Serum pregnancy test is required for all female participants of childbearing potential (ie, have achieved menarche) to confirm that a female participant is not pregnant prior to first dosing. A urine pregnancy test can be performed if the Screening visit is within 3 weeks of Day 1 visit. A urine (or serum if required by site policy) local pregnancy test is to be performed at all other required timepoints.
[h] At Screening, supine and standing (orthostatic) blood pressures will be performed.
[i] Predose triplicate 12-lead ECGs will be performed on Day 1 only and will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing (If this schedule is not feasible, ECGs performed with at least 20 min apart is acceptable). If the scheduled dosing is delayed, predose ECGs performed within 4 hours of dosing do not need to be repeated. Postdose ECGs will be performed within 30 min before PK/PD sample collection.
[j] PK and PD samples are collected at pre-dose and between 2 and 4 hours post dose.

## Table 4: Schedule of Activities – Screening Through Day 85 (Cohort 2) – Q4W Dosing

[k] PD samples will be collected to assess serum total and free properdin and CAP activity.
[l] Injection site reaction evaluation will be conducted on dosing days and if a reaction occurs, the evaluation will continue until the reaction is fully resolved.
[m] Blood samples for biomarkers will be collected two times prior to receiving the first dose (collect once during Screening and then again at Day 1 pre-dose, the 2 collections should be at least 2 weeks apart). Collection of blood (for serum, citrated and K2-EDTA, or P100 plasma) and urine.
[n] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[o] If a VOC crisis occurs, samples will be collected as per unscheduled visit.
[p] The patient will record symptoms of VOC in a paper diary throughout the study. The Investigator or qualified designee will review the patient diary at every visit.
[q] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[r] Collection of adverse events and serious adverse events will begin after ICF signing.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; CAP = complement alternative pathway; ECG = electrocardiogram; HiB = *Haemophilus influenzae* type B; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; MCV4 = tetravalent meningococcal conjugate vaccine; NA = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q4W = once every 4 weeks; VOC = vaso-occlusive crisis.

**Table 5: Optional PK/PD Sampling for Intensive PK/PD for Subset of Patients in Cohort 1 and 2**

| **Study Day**[a] | **Day 2 (24 hours post Day 1 dose (± 4 hours)** | **Day 4 (72 hours post Day 1 dose, ± 24 hours)** | **Day 86 (24 hours post Day 85 dose (± 4 hours)** | **Day 88 (72 hours post Day 85 dose, ± 24 hours)** | **Day 92 (168 hours post Day 85 dose, ± 24 hours)** |
|---|---|---|---|---|---|
| PK samples | X | X | X | X | X |
| Blood sample for PD panel[b] | X | X | X | X | X |

[a] A subset of Cohort 1 and 2 patients may undergo a more intensive PK/PD sampling specified in this table. All other assessments are to be performed per Table 3, Table 4, and Table 6.
[b] PD samples will be collected to assess serum total and free properdin and CAP activity.
Abbreviations: CAP = complement alternative pathway; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

## Table 6: Schedule of Activities – Day 99 Through End of Follow-up Period, Cohorts 1 and 2

| **Study Day** | **Day 99** | **Day 127[a]** | **Day 155** | **Day 183[a]** | **Day 211 /ET/ Unscheduled** | **Complement Activity Follow-up[b]** |
|---|---|---|---|---|---|---|
| Window (Day) | **± 3** | **± 3** | **± 3** | **± 3** | **± 3** | **±14** |
| Physical examination | | | | | X | |
| Abbreviated physical examination | X | | X | | | |
| Vital sign measurements | X | | X | | X | |
| Triplicate ECG | X | | X | | X | |
| Hematology[c] | X | | X | | X | |
| Clinical chemistry[c] | X | | X | | X | |
| Coagulation[c] | X | | X | | X | |
| Urinalysis (including spot urine) | X | | X | | X | |
| Serum/urine pregnancy test | X | | X | | X | |
| PK samples | X | | X | | X | |
| Blood samples for PD panel (serum total and free properdin, CAP activity) | X | | X | | X | X |
| Biomarkers[d] | X | | X | | X | |
| Immunogenicity (ALXN1820 ADA)[e] | | | X | | X | |
| Assessment of VOC[f] | ←Monitor continuously→ | | | | | |
| Review patient diary[g] | X | X | X | X | X | X |
| Review safety card[h] | X | X | X | X | X | X |
| Concomitant medications | ←Monitor continuously→ | | | | | |
| Adverse events[i] | ←Monitor continuously→ | | | | | |

[a] Visit may be performed remotely (phone or video calls).

[b] If CAP activity has not returned to a normal range or 80% of the baseline level at the end of the Follow-up Period, patients may have additional Follow-up Visits every 12 weeks until CAP activity has been confirmed to either have returned to a normal range or 80% of the baseline level. This visit may be completed at home.

## Table 6: Schedule of Activities – Day 99 Through End of Follow-up Period, Cohorts 1 and 2

[c] Non-fasting blood samples will be obtained.
[d] Collection of blood (for serum, citrated and K2-EDTA, or P100 plasma) and urine.
[e] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[f] Assessment of VOC must be performed by a healthcare provider.
[g] The patient will record symptoms of VOC in a paper diary throughout the study. The Investigator or qualified designee will review the patient diary at every visit.
[h] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns on the part of the participant.
[i] Collection of adverse events and serious adverse events will begin after ICF signing

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; ECG = electrocardiogram; ET = early termination; ICF = informed consent form; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; PD = pharmacodynamic(s); PK = pharmacokinetic(s); VOC = vaso-occlusive crisis.

## Table 7: Schedule of Activities – Screening Through Day 43 (Optional Cohort 3) – Q2W Dosing

| Study Day | Screening Day –56 to Day –1 | Day 1 | Day 15 | Day 29 | Day 43 |
|---|---|---|---|---|---|
| Window (Day) | NA | NA | ± 3 | ± 3 | ± 3 |
| Informed consent[a] | X | | | | |
| Eligibility criteria[b] | X | X | | | |
| Randomization[c] | | X | | | |
| Confirmation of or administration of meningococcal vaccination[d] | X | | | | |
| Confirmation of or administration of HiB and *S pneumoniae* vaccination | X | | | | |
| Medical history and demographics | X | | | | |
| Physical examination | X | X | | | |
| Abbreviated physical examination | | | | X | |
| Height, weight, and BMI[e] | X | X | | X | |
| Hematology[f] | X | X | | X | |
| Clinical chemistry[f] | X | X | | X | |
| Coagulation[f] | X | X | | X | |
| Hepatitis B and C screen | X | | | | |
| HIV (types 1 and 2) screen | X | | | | |
| Serum/urine pregnancy test[g] | X | X | X | X | X |
| Urinalysis | X | X | | X | |
| Vital sign measurements[h] | X | X | X | X | X |
| Triplicate ECG[i] | X | X | X | X | |
| Study drug administration Q2W | | X | X | X | X |
| PK samples[j] | | X | X | X | X |
| Blood sample for PD panel [j,k] | | X | X | X | X |
| Injection site reaction[l] | | X | X | X | X |

## Table 7: Schedule of Activities – Screening Through Day 43 (Optional Cohort 3) – Q2W Dosing

| Study Day | Screening Day –56 to Day –1 | Day 1 | Day 15 | Day 29 | Day 43 |
|---|---|---|---|---|---|
| Window (Day) | NA | NA | ± 3 | ± 3 | ± 3 |
| Biomarker[m] | X | X | X | X | X |
| Immunogenicity (ALXN1820 ADA)[n] | | X | X | X | |
| Assessment of VOC[o] | X | ←Monitor continuously→ | | | |
| Review patient diary[p] | X | X | X | X | X |
| Review safety card[q] | X | X | X | X | X |
| Concomitant medications | ←Monitor continuously (after ICF is signed at Screening)→ | | | | |
| Adverse events[r] | ←Monitor continuously (after ICF is signed at Screening)→ | | | | |

[a] Signed and dated IEC-approved informed consent must be obtained before any study-specific screening procedures are performed.
[b] Eligibility will be assessed at Screening and Day 1.
[c] Randomization will occur following confirmation of all eligibility requirements.
[d] To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines). Participants who initiate study intervention treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.
[e] Height and BMI only at Screening.
[f] Non-fasting blood samples will be obtained
[g] Serum pregnancy test is required for all female participants of childbearing potential (ie, have achieved menarche) to confirm that a female participant is not pregnant prior to first dosing. A urine pregnancy test can be performed if the Screening Visit is within 3 weeks of Day 1 Visit. A urine (or serum if required by site policy) local pregnancy test is to be performed at all other required timepoints.
[h] At Screening, supine and standing (orthostatic) blood pressures will be performed.
[i] Predose triplicate 12-lead ECGs will be performed on Day 1 only and will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing (If this schedule is not feasible, ECGs performed with at least 20 min apart is acceptable). If the scheduled dosing is delayed, predose ECGs performed within 4 hours of dosing do not need to be repeated. Postdose ECGs will be performed within 30 min before PK/PD sample collection.
[j] PK and PD samples are collected at pre-dose and between 2 and 4 hours post dose.
[k] PD samples will be collected to assess serum total and free properdin and CAP activity.
[l] Injection site reaction evaluation will be conducted on dosing days and if a reaction occurs, the evaluation will continue until the reaction is fully resolved.
[m] Blood samples for biomarkers will be collected 2 times prior to receiving the first dose (collect once during Screening and then again at Day 1 pre-dose, the 2 collections should be at least 2 weeks apart). Collection of blood (for serum, citrated and K2-EDTA, or P100 plasma) and urine.
[n] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[o] If a VOC crisis occurs, samples will be collected as per unscheduled visit.
[p] The patient will record symptoms of VOC in a paper diary throughout the study. The Investigator or qualified designee will review the patient diary at every visit.
[q] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical study participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns of the participant.
[r] Collection of adverse events and serious adverse events will begin after ICF signing.

## Table 7: Schedule of Activities – Screening Through Day 43 (Optional Cohort 3) – Q2W Dosing

Abbreviations: ADA = antidrug antibody; BMI = body mass index; CAP = complement alternative pathway; ECG = electrocardiogram; HiB = *Haemophilus influenzae* type B; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; MCV4 = tetravalent meningococcal conjugate vaccine; NA = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q2W = every 2 weeks; VOC = vaso-occlusive crisis.

**Table 8: Schedule of Activities – Day 57 Through End of Follow-up Period for Multiple Dose Follow-up (Optional Cohort 3)**

| **Study Day** | **Day 57** | **Day 85** [a] | **Day 113** | **Day 141**[a] | **Day 169 /ET/ Unscheduled** | **Complement Activity Follow-up**[b] |
|---|---|---|---|---|---|---|
| Window (Day) | **± 3** | **± 3** | **± 3** | **± 3** | **± 3** | **±14** |
| Physical examination | | | | | X | |
| Abbreviated physical examination | X | | X | | | |
| Vital sign measurements | X | | X | | X | |
| Triplicate ECG | X | | X | | X | |
| Clinical chemistry[c] | X | | X | | X | |
| Hematology[c] | X | | X | | X | |
| Coagulation[c] | X | | X | | X | |
| Urinalysis | X | | X | | X | |
| Serum/urine pregnancy test | X | | X | | X | |
| PK samples | X | | X | | X | |
| Blood samples for PD panel (serum total and free properdin, CAP activity) | X | | X | | X | X |
| Biomarkers[d] | X | | X | | X | |
| Immunogenicity (ALXN1820 ADA)[e] | | | X | | X | |
| Assessment of VOC[f,g] | ←Monitor continuously→ | | | | | |
| Review patient diary[g] | X | X | X | X | X | X |
| Review safety card[h] | X | X | X | X | X | X |
| Concomitant medications | ←Monitor continuously→ | | | | | |
| Adverse events[i] | ←Monitor continuously→ | | | | | |

[a] Visit may be performed remotely (phone or video calls).

[b] If CAP activity has not returned to a normal range or 80% of the baseline level at the end of the Follow-up Period, patients may have additional Follow-up Visits every 12 weeks until CAP activity has been confirmed to either have returned to a normal range or 80% of the baseline level. This visit may be completed at home.

**Table 8: Schedule of Activities – Day 57 Through End of Follow-up Period for Multiple Dose Follow-up (Optional Cohort 3)**

[c] Non-fasting blood samples will be obtained.
[d] Collection of blood (for serum, citrated and K2-EDTA, or Plasma P100 plasma) and urine.
[e] In case of any suspected case of hypersensitivity or anaphylaxis additional samples for the assessment of ADA may be collected at or near the time of the event.
[f] Assessment of VOC must be performed by a healthcare provider.
[g] The patient will record symptoms of VOC in a paper diary throughout the study. The Investigator or qualified designee will review the patient diary at every visit.
[h] The Investigator or qualified designee will meet with the participant at each visit to ensure they carry the clinical trial participant safety card at all times and to review the potential meningococcal infection risks of ALXN1820, and to address any safety concerns on the part of the participant.
[i] Collection of adverse events and serious adverse events will begin after ICF signing.

Abbreviations: ADA = antidrug antibody; CAP: complement alternative pathway; ECG = electrocardiogram; ET = early termination; ICF = informed consent form; K2-EDTA = dipotassium ethylenediaminetetraacetic acid; PD = pharmacodynamic(s); PK = pharmacokinetic(s); VOC = vaso-occlusive crisis.

# 2. INTRODUCTION

## 2.1. Study Rationale

ALXN1820 (anti-properdin/anti-serum albumin bispecific VHH antibody) is a novel properdin blocking agent being developed for the treatment of diseases involving dysregulated CAP activity. The ALXN1820 molecule is bispecific, comprising a VHH antibody domain that binds and blocks properdin connected via a linker to a VHH domain that binds serum albumin, thereby conferring an extended circulatory half-life to the molecule.

ALXN1820 binds to properdin with a high affinity to prevent stabilization of the CAP complement component C3 (C3) and complement component C5 (C5) convertases that cleave C3 and C5 into their activation products. Quantitative blockade of properdin has been shown to be safe in human based on experience with the properdin binding antibody ALXN1510 (see Section 4.3). ALXN1820 is currently being evaluated in an ongoing Phase 1 study in healthy adult participants (Study ALXN1820-HV-101), and doses and dosing regimens for participants in this study were determined using cumulative safety data and an interim PK/PD analysis from participants enrolled in the ongoing Phase 1 study as well as data from the 6-month GLP toxicology in monkeys.

The purpose of this study in patients with SCD is to evaluate the safety, tolerability, efficacy, PK, PD, and immunogenicity of multiple doses and dosing regimens of ALXN1820 administered subcutaneously (ALXN1820 SC).

The study will include up to 3 cohorts with multiple SC doses and dosing regimens of open-label ALXN1820 in adult patients with SCD. Data from this study are anticipated to help design future studies in patients with SCD and other complement-mediated diseases.

## 2.2. Background

A detailed description of the chemistry, pharmacology, and toxicology data available for ALXN1820 is provided in the Investigator's Brochure (IB).

### 2.2.1. Chemistry

ALXN1820 is a recombinant, humanized VHH bispecific antibody that binds to human properdin and serum albumin. The antibody consists of a single polypeptide chain of 256 amino acids, which is comprised of an anti-albumin domain at the N-terminus that is fused to a C-terminal anti-properdin domain via a 15 amino acid linker. The variable region domains that form the serum albumin and properdin binding sites consist of llama complementarity determining regions grafted into human germline frameworks. Within the framework regions, llama residues at 11 positions were left unchanged to maintain antigen binding, aqueous solubility, and overall stability. There are 2 intrachain disulfide bonds, 1 disulfide bond localized in each VHH domain. The theoretical average molecular mass of the antibody is 27,350.2 Da. At pH 7.4, ALXN1820 exhibited a binding dissociation constant ($K_D$) of 323 pM for human properdin and $K_D$ of 439 pM for human serum albumin. The $IC_{50}$ for blockade of human CAP hemolysis by ALXN1820 (20% v/v final serum) was 29 nM. ALXN1820 blocked C3 fragment, properdin and complement component C9 (C9) deposition onto a myeloperoxidase substrate by

human serum (20%v/v) with $IC_{50}$ values of approximately 20 nM (C3), 15 nM (properdin) and 19 nM (C9).

### 2.2.2. Nonclinical Pharmacology

In a study of the potency of blockade of in vitro CAP hemolysis by ALXN1820 using sera across a range of species, significant species cross reactivity was observed only when using sera from cynomolgus and rhesus macaque. CAP hemolytic activities in the sera of mouse, rat, guinea pig, minipig, beagle and rabbit were not inhibited by the highest concentration of ALXN1820 examined (> 100 µg/mL). The $IC_{50}$ for blockade of cynomolgus CAP hemolysis by ALXN1820 (20% v/v final serum) was 47 nM. ALXN1820 exhibited a binding $K_D$ of 2.9 nM for cynomolgus properdin and $K_D$ of 2.1 nM for cynomolgus serum albumin. ALXN1820 blocked C3 fragment, properdin and C9 deposition onto a myeloperoxidase substrate by cynomolgus monkey serum (20%v/v) with $IC_{50}$ values of approximately 11 nM (C3), 9 nM (properdin) and 17 nM (C9). The lack of species cross reactivity beyond primates described above prevented testing the biologic activity of ALXN1820 in traditional rodent models of diseases involving dysregulated complement activity. Collectively therefore, the nonclinical in vitro and in vivo studies to assess the pharmacologic, PK, PD and toxicologic properties of ALXN1820 are being performed in cynomolgus monkeys.

### 2.2.3. Toxicology

Nonclinical safety profile of ALXN1820 has been evaluated in an in vitro GLP tissue cross reactivity (TCR) study and in both a non-GLP and GLP in vivo studies in cynomolgus monkeys. In GLP toxicology studies ALXN1820 was administered by intravenous (IV) administration (up to single dose of 100 mg/kg) and SC administration (up to 26 weekly doses of 300 mg/kg/week). ALXN1820 did not demonstrate any non-specific binding to human tissues in the TCR study. Based on the absence of any adverse systemic or local toxicity in cynomolgus monkeys, 300 mg/kg/week was considered the no observed adverse effect level (NOAEL) for SC administration and 100 mg/kg was considered as the NOAEL for IV administration of ALXN1820. Systemic exposures (maximum observed serum concentration [$C_{max}$] and area under the concentration-time curve from time 0 to 168 hours [$AUC_{0\text{-}168}$] of 8,570 µg/mL and 1,160,000 µg·hr/mL, respectively), after the last dose at the NOAEL in the SC group, yielded exposure multiples of ~30-fold to the projected exposures at the anticipated human dose of 300 mg QW. Antidrug antibodies, when observed in a very small number of monkeys, did not have any impact on systemic exposure or toxicity profile.

## 2.3. Benefit/Risk Assessment

There may be potential benefits to patients with SCD (See Section 2.3.2).

Identified and potential risks are described below. More detailed information about the known and expected benefits and risks and reasonably expected AEs of ALXN1820 may be found in the IB. Potential risk mitigation strategies are described in Table 9.

### 2.3.1. Risk Assessment

Besides the first-in-human (FIH) Phase 1 Study ALXN1820-HV-101 in healthy participants, this study is the second human exposure to ALXN1820 and the first exposure to patients with SCD.

As there is limited clinical experience to date, the potential risks are based on the class of the molecule and its mechanism of action. No potential risks were identified from the repeat dose toxicity study in cynomolgus monkeys with ALXN1820 after 26 weekly SC doses up to 300 mg/kg/week or after a single IV dose up to 100 mg/kg and no safety concerns in healthy participants have been identified as of 11 Mar 2022 after 5 weekly SC doses up to 150 mg or after a single SC dose of 1200 mg.

#### 2.3.1.1. *Neisseria meningitidis* Infections

Increased susceptibility to infection with *Neisseria meningitidis* is a known risk associated with properdin deficiency and has been well described with properdin-deficient patients (Figueroa, 1991). Similar to properdin deficiency, the main risk associated with the use of ALXN1820 (properdin inhibitor) is expected to be the risk of meningococcal infections. Specific risk mitigation measures are in place to address this risk.

Clinically, the risk of *N. meningitidis* is mitigated in patients with properdin deficiency by vaccinating all patients against *N. meningitidis* with tetravalent meningococcal conjugate vaccine (MCV4) and serogroup B vaccines before dosing.

Patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines). Participants who initiate study intervention treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination. Every effort should be made to start the meningococcal vaccination series at least 14 days prior to randomization.

Additionally, participants may be treated with prophylactic antibiotics at the Investigator's discretion.

#### 2.3.1.2. Immunogenicity and Hypersensitivity

ALXN1820 has the potential to be immunogenic and may be associated with hypersensitivity reactions. Some healthy participants are also known to have pre-existing antibody to VHH antibodies. Antibodies to ALXN1820 have been observed in 14 of 100 healthy participant serum samples tested in an in vitro screening assay.

Monitoring of immunogenicity for ALXN1820 is in place for this study as specified in the SoA (Section 1.3).

**Table 9: Potential Risks and Mitigation Strategies**

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Treatment with ALXN1820** | | |
| Meningococcal infection | ALXN 1820 blocks properdin which can result in increased susceptibility to *Neisseria meningitidis*, likely with fulminant clinical manifestations. | Participants must be vaccinated against all available serotypes of *N. meningitidis* (A, C, Y, W 135, and B). However, vaccination may not be sufficient to prevent meningococcal infection.<br>Prophylactic antibiotics will be used at the investigator's discretion. Timing for meningococcal vaccinations can be mandated per local/national guidelines.<br>(See Sections 1.3, 2.3.1.1 and 8.2.9)<br>Participants will be provided a safety card to carry at all times and for 5 months after the final dose of ALXN1820. |
| Immunogenicity | Treatment with any therapeutic protein may induce an immune response. Occasionally, this immune response is clinically meaningful. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies, without any clinical consequence, to severe, life-threatening conditions. Potential clinical consequences also may include severe hypersensitivity-type reactions, decrease in efficacy and induction of autoimmunity. | Algorithm for hypersensitivity reaction management; Stopping rules and staggered dosing |

### 2.3.1.3. Coronavirus Disease 2019

The SARS-COV-2 disease (coronavirus disease 2019 [COVID-19]) global pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they may be related to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.7.

### 2.3.2. Benefit Assessment

The potential benefit of ALXN1820 treatment for SCD is being measured by assessments of anemia and hemolysis. An increase in hemoglobin by ≥ 1g/dL from baseline is considered clinically meaningful. In addition, a positive treatment effect would also be shown by a decrease in hemolysis, including improvements in the serum levels of markers of hemolysis (ie, lactate dehydrogenase [LDH], indirect bilirubin, and haptoglobin). Other exploratory endpoints (vaso-occlusive crisis [VOC], etc.) may be assessed.

### 2.3.3. Overall Benefit: Risk Conclusion

ALXN1820 has been and is being evaluated in an ongoing Phase 1 Study ALXN1820-HV-101. Study ALXN1820-SCD-201 is the second human exposure to ALXN1820.

Study ALXN1820-SCD-201 will be conducted in patients with SCD, and dosing will be initiated based on review of safety, tolerability, and PK/PD data from Study ALXN1820-HV-101. The doses administered in the current study are expected to produce exposure lower than the highest exposure tested in Study ALXN1820-HV-101, and the expected exposure in patients will be lower than the NOAEL exposure established in 6-week and 6-month GLP monkey toxicology studies. Strict inclusion/exclusion criteria, with a robust safety monitoring and risk mitigation plan are in place. A DMC will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose modification or termination of the study. The selected doses are intended to deliver complete inhibition of properdin, providing potential benefit of ALXN1820 to patients with SCD, with a positive benefit/risk ratio.

The data obtained from this study is expected to inform future clinical studies in patients with SCD.

# 3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 10.

**Table 10: Mapping Objectives to Endpoints for Patients with Sickle Cell Disease**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the safety and tolerability of ALXN1820 SC in patients with SCD | Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory, and electrocardiogram results through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| **Secondary** | |
| To assess the multiple-dose PK of ALXN1820 SC | Serum ALXN1820 multiple-dose PK profiles through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| To assess the PD effects of ALXN1820 SC | Change in serum concentrations of total and free properdin over time through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3)<br>Change in CAP activity using the Wieslab AP assay through Day 211 (Cohorts 1 and 2) and through Day 169 (Optional Cohort 3) |
| To assess the effect of ALXN1820 on complement biomarkers | Change from baseline in complement biomarkers through Week 12 (Cohorts 1 and 2) |
| To assess the effect of ALXN1820 on hemolysis | Change from baseline in hemoglobin levels at Week 12 (Cohorts 1 and 2)<br>Change from baseline in hemolysis markers (eg, lactate dehydrogenase, reticulocytes, and bilirubin) and hemopexin at Week 12 (Cohorts 1 and 2) |
| To assess the immunogenicity of ALXN1820 SC | Incidence of ADAs to ALXN1820 through Day 211 (Cohorts 1 and 2) and through Day 169 for Optional Cohort 3 |
| **Exploratory** | |
| To explore the effect of ALXN1820 on vaso-occlusion markers | Change from baseline in VOC related biomarkers through Week 12 (Cohorts 1 and 2) |
| To explore the clinical efficacy of ALXN1820 SC in SCD | VOC events (rate of VOC, time to first VOC) through Week 12 (Cohorts 1 and 2) |

Abbreviations: ADA = antidrug antibody; AP = alternative pathway; CAP = complement alternative pathway; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; SCD = sickle cell disease; TEAE = treatment-emergent adverse event; VOC = vaso-occlusive crisis.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a Phase 2a study, with up to 3 multiple dose cohorts of open-label ALXN1820 SC in adult patients with SCD (HbSS and HbSß$^0$-thalassemia).

The study will be conducted in up to 30 adult patients with SCD enrolled in up to 3 open-label cohorts (Cohorts 1, 2 and 3 [optional]) to receive multiple SC doses of open-label ALXN1820. ALXN1820 will be administered as described in Table 11.

**Table 11: ALXN1820-SCD-201 Dosing Cohorts**

| Cohort | N | Study Drug | Route of Administration | Planned Dose | Number of Doses/Dose Interval |
|---|---|---|---|---|---|
| 1 | Up to 12<br>maximum of 6 on stable dose of hydroxyurea | ALXN1820 | SC | 300 mg | QW × 13 |
| 2 | Up to 12<br>maximum of 6 on stable dose of hydroxyurea | ALXN1820 | SC | 600 mg | Q4W × 4 |
| 3 (optional) | Up to 6<br>maximum of 3 on stable dose of hydroxyurea | ALXN1820 | SC | 300 mg | Q2W × 4 |

Abbreviations: N = number of participants; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous.

The dose and dosing intervals for Cohorts 1 and 2 were determined using cumulative safety data, an interim PK/PD analysis from participants enrolled in Study ALXN1820-HV-101, and data from the 6-month GLP toxicology study in monkeys. Optional Cohort 3 will be initiated after evaluation of safety and PK/PD data from Cohorts 1 and 2.

Cohort 1 and Cohort 2 will run in parallel, and patients will be randomized 1:1 to either of the cohorts on determination of eligibility. The decision to initiate Optional Cohort 3 will be made at Alexion's discretion and will be based on analysis of PK/PD and safety after at least 8 patients from Cohorts 1 and 2 (4 from each cohort) have enrolled. Furthermore, enrollment of Optional Cohort 3 will start after Cohorts 1 and 2 are fully enrolled. Each cohort will be stratified to ensure patients with SCD who are treated with a stable dose of hydroxyurea and patients with SCD who are not currently treated with hydroxyurea are included. For patients who were previously treated with hydroxyurea but are not currently on hydroxyurea, treatment must be stopped at least 30 days prior to providing informed consent.

This study will use an independent DMC to monitor safety and to perform the planned interim analyses of the study. At Alexion's discretion, and after consultation with the DMC, additional

participants with SCD may be enrolled as replacement participants if a participant discontinues during the Dosing Period for reasons other than drug related AEs.

## 4.2. Scientific Rationale for Study Design

The initial indication for ALXN1820 will be SCD. SCD affects about 20 to 25 million people worldwide (Aliyu, 2008) and in the US, approximately 100,000 people are affected (Hassell, 2010). The prevalence of SCD newborns and SCD carriers in the EU is approximately 1 to 5 in 10,000 and 1 in 150, respectively (Engert, 2016). The few available life expectancy estimates for SCD patients in the US or EU vary widely from 45 to 65 years which is approximately 20 years lower than the general population (Gardner, 2016; Lubeck, 2019; Payne, 2020; Platt, 1994).

SCD is a group of inherited disorders. A mutation in the β-hemoglobin gene is responsible for the synthesis of sickle hemoglobin (HbS). The most common genotypes in SCD are HbSS, HbSC, and HbS$\beta^+$ thalassemia. The most common clinical manifestations of SCD are chronic hemolysis and VOC (Kato, 2018; Pecker, 2021).

HbS has abnormal physicochemical properties and is prone to polymerization under low oxygen concentration causing deformation of red blood cells (RBCs) with the characteristic sickle shape. Sickling has numerous adverse outcomes on RBCs and on multiple organs. Sickled RBCs have limited life span due to hemolysis. Hemolysis is thought to occur principally through extravascular phagocytosis (approximately 2/3) and intravascular (approximately 1/3) hemolysis, which leads to anemia. Intravascular hemolysis of sickle RBCs leads to release of free hemoglobin, which in turn activates CAP (via free heme) and depletes nitric oxide, contributing to endothelial damage. Hemolysis and sickling of the RBCs leads to endothelial cell activation with increased adhesion molecule expression and activation of neutrophils, monocytes, and platelets (Kato, 2018). VOC, as a result of these processes, leads to obstruction of blood flow to vital organs such as the kidneys, liver, lungs, and heart, promoting ischemia, acute episodes of pain, and necrosis. The ensuing ischemic/reperfusion injury leads to the generation of reactive oxygen species. This in turn leads to a chronic inflammatory state (Kato, 2018; Piel, 2017). Patients also have increased vulnerability to infections, particularly from encapsulated bacteria, as a result of functional or actual asplenia. Together, these mechanisms contribute to the development of chronic organ damage including sickle nephropathy, pulmonary hypertension, avascular necrosis of the bone, chronic lung disease, and shortened life expectancy (Kato, 2018).

Universal newborn screening is established in the US to enable early diagnosis and treatment of infants with SCD to reduce morbidity and mortality. It is recommended that all infants with HbSS and HbS$\beta^0$-thalassemia receive penicillin prophylaxis and 23-valent-pneumococcal polysaccharide vaccine to prevent invasive pneumococcal disease (Kato, 2018; Pecker, 2021).

Hydroxyurea, RBC transfusion, and opioids are the treatments commonly used to manage the symptoms of SCD. There are several approved novel drugs for the treatment of sickle cell complications in recent years: L-glutamine (Endari®), voxelotor (Oxbryta®), and crizanlizumab (Adakveo®). However, none of these treatments addresses both anemia (hemolysis) and VOC. The only curative treatment option for SCD is hematopoietic stem cell transplantation. However, this is reserved for severe patients due to the risk of life-threatening complications (Pecker, 2021).

Recently, much attention has been given to the role of the innate immune system in SCD, and in particular the role of complement activation in the pathophysiology of SCD (Tampaki, 2021; Varelas, 2021). In Investigator-initiated studies, eculizumab has demonstrated clinical effect in SCD patients with delayed hemolytic transfusion reaction, VOC, and drug-induced immune hemolytic anemia (Chonat, 2020). Compared to C5 inhibitors, CAP inhibitors have potential advantages in treatment of SCD. An increasing number of publications supports the hypothesis that sickle RBCs are the focal point of CAP activation, which triggers C3 opsonization on the cell surface as well as complement-mediated RBC hemolysis. Intravascular hemolysis is one of the main causes of anemia and also contributes to further amplification of CAP activation by releasing free heme from RBCs. C3 opsonization of sickle RBCs also promotes anemia through extravascular hemolysis via the reticuloendothelial system. Furthermore, C3 opsonization has been shown to be a key contributor to VOC. It has also been demonstrated that C3 opsonization can be precipitated by exposure of phosphatidyl serine on sickle RBCs and contributes to VOC by enhancing its interaction with adhesion molecules such as P-selectin and complement receptor 3 on activated endothelial cells (Lombardi, 2019). Thus, SCD nonclinical literature collectively underscores the role of CAP activation in SCD pathophysiology.

ALXN1820 binds with high affinity to human properdin, which is a component of the CAP, preventing it from stabilizing the CAP C3 and C5 convertases that cleave C3 and C5 into their activation products. By binding properdin, ALXN1820 prevents activation of the alternative complement system and thereby has the potential to treat SCD. In support of this, studies carried out at Alexion in a mouse model of SCD demonstrated that pretreatment of animals with an mouse anti-properdin antibody significantly ameliorated signs of hemolysis and vaso-occlusion, which are 2 main clinical features of SCD.

The current nonclinical data and data from the first in human study ALXN1820-HV-101 support further investigation of ALXN1820 as a potential for treatment of patients with SCD. This study is designed to allow preliminary evaluation of changes in SCD disease-related biomarkers and will guide the design of further clinical studies in patients with SCD.

## 4.3. Justification for Dose

The dose and the frequency of dosing will be based on all available data including the overall safety, tolerability, PK/PD modeling from the ongoing cohorts in Study ALXN1820-HV-101; available nonclinical data including PK, PD, and efficacy in SCD mouse models, and toxicology data from the GLP 6-week and 6-month studies in cynomolgus monkeys.

A preliminary PK/PD model has been established based on data from Study ALXN1820-HV-101 in healthy participants. This semi-mechanistic model assumed monovalent ALXN1820 binding to trimeric properdin with 3 binding sites. The relationship between free properdin and CAP activity was characterized by a sigmoidal $E_{max}$ model. The model provided good fits to the observed data (ALXN1820, total and free properdin, and CAP activity) judged by the model diagnostics. To estimate the therapeutic dose in SCD patients, the following assumptions have been made:

- Complete suppression of CAP activity (<1% of baseline activity) is needed for clinical efficacy based on data from mouse SCD model (described in detail in the ALXN1820 IB)

- The baseline properdin concentration is about 20% higher in sickle cell patients than in healthy subjects (Strauss, 1977)

In addition, ALXN1820 clearance in sickle cell patients was set as similar to or 40% higher (seen in other antibody treatments for SCD (Crizanlizumab, 2019)) than that of the healthy participants to evaluate the impact of increased clearance on exposure and CAP inhibition. Based on these assumptions and analysis, it is predicted that a dose of 300 mg QW could inhibit the CAP activity to < 1% of the baseline values (upper limit of the 90% prediction interval) and maintain this effect during the Treatment Period. A dose of 600 mg Q4W or 300 mg Q2W was also shown to inhibit the CAP activity < 1% during majority of the dosing interval. The CAP activity will slowly recover and return to baseline after terminating dosing of ALXN1820. The safety margin at 300 mg QW is approximately 30-fold based on the NOAEL exposure established in the 6-month (or 26-week) monkey toxicology study. The safety margin at 600 mg Q4W or 300 mg Q2W is approximately 60-fold, based on the NOAEL exposure.

## 4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study (EOS) is defined as the date the last participant completes the last visit as shown in the SoA (Section 1.3).

# 5. STUDY POPULATION

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

## 5.1. Inclusion Criteria

**Age**

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

**Type of Participant and Disease Characteristics**

2. Confirmed diagnosis of SCD (HbSS, or HbS$\beta^0$-thalassemia).

**Weight**

3. Body weight ≥ 40 kg (inclusive) at Screening.

**Sex**

4. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Female participants of childbearing potential and male participants with female partners of childbearing potential must be willing to follow protocol-specified contraception guidance while on treatment and for at least 6 months after last dose of study drug (described in Section 10.4).

**Other Inclusion Criteria**

5. Hemoglobin between 5.5 and 10 g/dL at Screening.
6. Have had 1 to 10 VOCs in the past 12 months.
7. Patients receiving hydroxyurea must have been on a stable dose for ≥ 3months prior to providing informed consent, with no anticipated need for dose adjustment during the study. For patients who previously used hydroxyurea but are not currently on hydroxyurea treatment (due to non-responsiveness, intolerance, or unwillingness to take hydroxyurea), hydroxyurea treatment must have been discontinued at least 30 days prior to providing informed consent.
8. Patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines). Participants who initiate study intervention treatment less than 14 days after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until at least 2 weeks after vaccination.
9. *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccination are up to date according to current national/local vaccination guidelines for patients with SCD.
10. Must be willing to abide by all study requirements and restrictions.

**Informed Consent**

11. Capable of giving signed informed consent (or assent, as applicable) as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

## 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Planned initiation, termination, or dose alteration of hydroxyurea during the study.
2. Receiving Voxelotor (OXBRYTA) or crizanlizumab (ADAKVEO) within 60 days of providing informed consent.
3. Receiving treatment with recombinant human erythropoetins (eg, epoetin alfa).
4. Treated with complement inhibitors within 6 months prior to the first dose.
5. Patients who are on chronic transfusion or receive a transfusion within 60 days of first dose.
6. Any significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk.
7. History of complement deficiency.
8. History of *N meningitidis*, *S pneumoniae*, or *H influenzae* infection.
9. History of malignancy with the exception of a nonmelanoma skin cancer or carcinoma *in situ* of the cervix that has been treated with no evidence of recurrence within 5 years.
10. Evidence of hepatitis B (positive hepatitis surface antigen [HBsAg] or positive core antibody (anti-HBc) with negative surface antibody [anti-HBs]) or hepatitis C viral infection (hepatitis C virus [HCV] antibody positive, except for patients with documented successful treatment and documented sustained virologic response) at Screening.
11. Active systemic bacterial, viral, or fungal infection within 14 days prior to dosing.

**Prior/Concurrent Clinical Study Experience**

12. Participation (ie, last protocol-required study visit) in a clinical study within 90 days or 5 half-lives of the investigational agent, whichever is longer, before initiation of dosing on Day 1.
13. Participation in more than 1 clinical study of a monoclonal antibody (mAb), or participation (ie, last protocol required study visit) in a clinical study of a mAb within the 6 months or 5 half-lives of the mAb, whichever is longer, prior to Screening, during which the participant was exposed to the active study drug.

**Diagnostic assessments**

14. Severe renal impairment (estimated glomerular filtration rate [eGFR] $< 30$ mL/min/1.73 $m^2$) or on chronic dialysis.

**Other Exclusions**

15. Female participants who are pregnant or breastfeeding.
16. History of allergy or hypersensitivity to excipients of ALXN1820 (eg, polysorbate 80).

## 5.3. Lifestyle Considerations

Not applicable, Study ALXN1820-SCD-201 does not include any specific lifestyle considerations.

## 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study drug due to failure to meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any SAEs and any related concomitant medication, occurring during the Screening Period.

Participants who do not meet the criteria for participation in this study (ie, screen failures) due to a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Any abnormal laboratory parameter(s) results outside of the reference range at Screening may be repeated per the Investigator's discretion for the purpose of further determining eligibility.

# 6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. For Study ALXN1820-SCD-201 the study intervention is ALXN1820 and also referred to as study drug throughout this study protocol.

## 6.1. Study Intervention Administered

The ALXN1820 study drug composition and doses to be administered (open-label, SC) in this study are presented in Table 12.

**Table 12: Dose Reference Chart for Study ALXN1820-SCD-201**

| Characteristics | ALXN1820 SC |
|---|---|
| **Dosage formulation** | ALXN1820 is formulated at pH 5.4 and each vial contains 300 mg of ALXN1820 in 20 mM sodium acetate, 250 mM sucrose, and 0.05% polysorbate-80.<br>The concentration is 150 mg/mL. |
| **Unit dose strength(s)/dosage level(s)** | 300 mg, 600 mg |
| **Route of administration** | SC |
| **Dosing instructions** | ALXN1820 SC will be administered as a single manual push for the 300 mg dose and as 2 manual pushes for the 600 mg dose. |
| **Packaging and labeling** | Each vial will be packaged into a kit. There will be 1 vial per kit. Both vials and kits will be labeled according to the protocol and local regulatory requirements. |
| **Manufacturer** | Alexion |

Abbreviation: SC = subcutaneous.

In the event of missed doses, unscheduled dosing may be required to ensure therapeutic coverage. The unscheduled dose will be determined by the study Clinical Pharmacologist on an individual basis.

## 6.2. Preparation/Handling/Storage/Accountability

Details regarding preparation, handling, storage, accountability, and administration of the study drug are discussed below. Additional guidance is provided in the pharmacy manual.

1. ALXN1820 is to be stored at 2 - 8°C. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3. The pharmacy staff at the Investigator's site will be responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The site's pharmacy will assemble the supplies into individual, labelled participant dose syringes and perform Qualified Person certification of the assembled product. Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

All eligible participants who meet all inclusion and no exclusion criteria in Cohorts 1, 2, and optional Cohort 3 will receive open-label ALXN1820.

## 6.4. Study Intervention Compliance

The administration of study intervention to participants will be under the supervision of the Investigator or their designee to ensure that participants receive the appropriate dose at the appropriate time points during the study.

The date and time of each dose administered in the clinic will be recorded in the source documents and case report form (CRF).

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

## 6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.5.1. Allowed Medicine and Therapy

Multivitamins, contraceptives, and paracetamol (ie, acetaminophen, at doses of ≤ 2 g/day) are permitted for use during the study at the Investigator's discretion. Topical skin products should not be administered at the site of study drug injection from 24 hours prior until 24 hours following study drug administration.

See Section 8.2.9 for details on administration and duration of treatment with prophylactic antibiotics as concomitant medication to mitigate the risk of *N. meningitidis* infection associated with complement inhibition.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required. Concomitant procedures are not allowed unless medically indicated.

Medication and therapy for SCD are allowed except for those presented in Section 6.5.2.

### 6.5.2. Disallowed Medicine and Therapy

During the Screening and Treatment Period, if patients are not currently treated with hydroxyurea, hydroxyurea should not be initiated. If patients are on stable dose of hydroxyurea, the dose of hydroxyurea should not be altered or terminated. The use of voxelotor, crizanlizumab, erythropoetins, other complement inhibitors, and transfusion are not allowed. If any of the above medication/therapy is used, the patient will be discontinued as per Section 7.1. The above medications/therapy are allowed during the safety Follow-Up period.

## 6.6. Dose Modification

Decisions to continue or modify dosing will be made by the Investigator and/or DMC after review of the safety data. The DMC may also make recommendations regarding safety issues, study conduct, or study suspension.

## 6.7. Intervention After the End of the Study

No follow-up intervention is planned.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2. Stopping Criteria

### 7.2.1. Individual Stopping Rules

Participants should be considered for discontinuation from intervention if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Grade 3 or higher injection site reactions;
- Severe uncontrolled infection;
- Serious *N meningitidis*, *S pneumoniae*, or *H influenzae* infections;
- Use of disallowed medication as defined in Section 6.5.2;
- Pregnancy or planned pregnancy; or
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator or Alexion, presents a substantial clinical risk to the patient with continued study drug dosing.

### 7.2.2. Study Stopping Rules

The study may be terminated at the recommendation of the DMC, if the following occur and are deemed to be related to the study drug:

- Two or more meningococcal infections;
- Two or more serious (≥ Grade 3) pneumococcal infections;
- Two or more serious (≥ Grade 3) *H influenzae* infections;
- One meningococcal, pneumococcal, or *H influenzae* infection resulting in a fatal outcome.

## 7.3. Participant Discontinuation/Withdrawal From the Study

All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and electronic case report form (eCRF).

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants who discontinue during the Screening or Dosing Period for reasons other than drug-related AEs may be replaced.

## 7.4. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, email, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to lost to follow up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

# 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue ALXN1820.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA, if consistent with site standard operating procedures.

## 8.1. Efficacy Assessments

Timing for collection of assessments for Cohort 1 is detailed in Section 1.3, Table 3, and Table 6. Timing for intensive collection of PK and PD samples for Cohorts 1 and 2 is detailed in Section 1.3, Table 5. Timing for collection of assessments for Cohort 2 are detailed in Section 1.3, Table 4 and Table 6. If conducted, timing for collection of assessments for optional Cohort 3 are detailed in Table 7 and Table 8.

### 8.1.1. Change in Complement Biomarkers

The following complement markers (absolute and percentage change from baseline) will be measured during the study:

- complement component Ba (Ba)
- complement component C3a (C3a)
- soluble complement component C5B-9 (sC5B9)

Other complement markers may be evaluated, if feasible.

### 8.1.2. Change in Biomarkers Related to VOC

The following markers of VOC (absolute and percentage change from baseline) may be measured during the study:

- Hemopexin
- Nitric oxide
- Inflammatory markers (eg, interleukin-1)
- Cell adhesion markers (eg, soluble P-selectin)

Other markers may be evaluated, if feasible.

### 8.1.3. Change in Hemoglobin

Blood samples will be collected for assessment of hemoglobin changes from baseline.

### 8.1.4. Markers of Hemolysis

The following markers of hemolysis will be measured during the study:

- Serum LDH levels
- Absolute reticulocyte count
- Serum indirect bilirubin
- Serum haptoglobin and hemopexin

### 8.1.5. Assessment of VOC

Sickle cell disease–related pain crises (VOC) will be collected throughout the study per detailed in the SoA (Section 1.3).

Patients will be issued a paper diary to record symptoms of VOC after signing the informed consent. The diary will be collected by the Investigator or designee at every visit to the site and a new diary will be provided.

## 8.2. Safety Assessments

Planned time points for all safety assessments for all cohorts are provided in the SoA (Section 1.3).

### 8.2.1. Physical Examination

A complete physical examination will include, at a minimum, assessments of the general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system.

An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Height, weight and BMI will be recorded per Section 1.3, SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.2. Vital Signs

Vital sign measurements will be taken after the participant has been resting in the supine or semi-recumbent position for at least 5 minutes and will include temperature (tympanic or oral), respiratory rate, supine blood pressure, and pulse. Ideally, the same arm for each participant should be used for BP and pulse measurements. Orthostatic (standing) blood pressure will only be measured at Screening.

The timing of vital sign measurements is described in the SoA (Section 1.3).

Out of range blood pressure or pulse measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as AEs.

### 8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be recorded at the time points described in the SoA (Section 1.3) to obtain heart rate, PR, QRS, and QT intervals. 12-lead ECG recordings will be made after the participants have been resting in a supine position for at least 10 minutes.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession but no more than 2 minutes apart.

#### 8.2.3.1. Safety Review of 12-lead Electrocardiograms

All recorded ECGs will be reviewed by the Investigator or qualified designee. If a participant shows an abnormal ECG, additional safety recordings may be made, and the abnormality will be followed to resolution.

### 8.2.4. Clinical Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. Clinical laboratory assessments will be performed by a central laboratory unless otherwise specified.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

### 8.2.5. Clinical Safety Laboratory Assessments

#### 8.2.5.1. Virus Serology

Blood samples collected at Screening will be analyzed for HIV-1, HIV-2, HbsAg, HBc antibody (anti-HBc IgG + IgM, if IgG positive), and HCV antibody titers.

### 8.2.6. Pregnancy

Pregnancy testing must be performed on all women of childbearing potential (WOCBP) at the time points specified in the SoA (Section 1.3). Pregnancy tests (local urine testing will be standard unless serum testing is required by local regulation or ethic committees) may also be performed at any time during the study at the Investigator's discretion.

WOCBP must have a negative pregnancy test (serum if required per country regulations) before study intervention administration.

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until termination of the pregnancy.
- If a pregnancy is reported, the Investigator should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedure outlined in Section 10.4.3.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy alone is not considered an AE.
- If a participant becomes pregnant, the study intervention must be immediately discontinued, and Alexion must be notified as per Section 10.4.3. Each pregnancy will be followed to term and Alexion should be notified regarding the outcome (Section 10.4.3).

### 8.2.7. Injection Site Evaluation

Subcutaneous injection site evaluations will be performed at the time points specified in the SoA (Section 1.3). Injection site reactions will not be recorded as AEs unless deemed clinically significant.

### 8.2.8. Injection-associated Reactions

Injection-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) occurring during or within 24 hours of the start of SC injection that are assessed by the Investigator to be related to the study drug.

### 8.2.9. Vaccine and Antibiotic Prophylaxis

To mitigate the risk of *N. meningitidis* infection associated with complement inhibition, participants will be administered the following:

1. Patients will be vaccinated with MCV4 and serogroup B meningococcal vaccinations, if available at least 14 days before dosing, if not already vaccinated within 3 years before the first dose (or per national/local guidelines).
2. Patients will be treated with prophylactic antibiotics at the Investigator's discretion.

Patients must be vaccinated against other pathogens (e.g. *Haemophiles influenzae, Streptococcus pneumoniae*) according to current national/local guidelines.

### 8.2.10. Participant Safety Card

Participants will be provided a safety card to carry with them. Risk of meningococcal infection will be explained and discussed with participants during the informed consent process, occurring at the Screening Visit. In order to increase the risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the participants during the course of the study, additional discussion and explanation of the potential risks, signs, and symptoms, as described in the ICF, will take place at specific time points throughout the study as noted in the SoA (Section 1.3).

## 8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

### 8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last follow-up visit.

All SAEs will be recorded and reported to Alexion or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

### 8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### 8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution,

stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4. Further information on follow-up procedures is provided in Section 10.3.

### 8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/IECs, and Investigators.

Suspected unexpected serious adverse reactions must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## 8.4. Treatment of Overdose

For this study, any dose of study intervention greater than that specified in the protocol will be considered an overdose. There is no specific treatment or antidote for overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose or suspected overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a sample for PK/PD analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

## 8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of ALXN1820 as specified in the SoA (Section 1.3). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The total blood volume will not exceed the volume limit for participants per national/local guidelines. The timing of sampling may be altered during the course of the study, based on newly available data (eg, to obtain data closer to the time of peak serum concentrations) to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN1820. Samples collected for analyses of ALXN1820 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to dysregulated complement activity.

## 8.6. Pharmacodynamics

Whole blood samples will be collected for measurement of serum total and free properdin concentrations, CAP activity, and potentially other measures of complement activation as specified in the SoA (Section 1.3). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion, and upon receipt of consent from the study participant. The total blood volume will not exceed the blood volume limit for participants per national/local guidelines. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PD of ALXN1820. Samples collected for analyses of ALXN1820 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Unused samples may be retained for a period of up to 25 years to perform additional assessments as necessary.

## 8.7. Genetics

Genetics are not evaluated in this study.

## 8.8. Biomarkers

Collection of samples for biomarker research (eg, exploratory) is also part of this study. See Section 10.5 for details.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):

- Blood
- Urine

Samples will be collected for testing that may include, but are not limited to, markers of complement dysregulation, inflammation, and endothelial activation/damage.

## 8.9. Immunogenicity Assessments

Antibodies to ALXN1820 (ADAs) will be evaluated in whole blood samples collected from all participants according to the SoA (Section 1.3).

Serum samples will be screened for ADAs that bind to ALXN1820. If the screen is positive, the sample will be analyzed using a confirmatory ADA assay and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies to ALXN1820 will be performed using a validated assay method by or under the supervision of Alexion. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies (as an exploratory analysis) if deemed necessary.

The actual date and time (24-hour clock time) of each sample will be recorded. Samples may be banked for a period of up to 25 years in order to perform additional safety assessments, as necessary.

Detailed instructions on the procedure for collecting, processing, storing, and shipping serum samples for immunogenicity analysis will be provided in the laboratory manual.

## 8.10. Health Economics Data and/or Medical Resource Utilization

Medical resource utilization and health economics data will not be evaluated in this study.

## 8.11. Other Assessments and Procedures

Not applicable.

# 9. STATISTICAL CONSIDERATIONS

## 9.1. Statistical Hypotheses

Not applicable.

## 9.2. Sample Size Determination

Twelve participants will be enrolled in each of Cohorts 1 and 2. In patients with stable SCD, hemoglobin level is unlikely to change. The sample size is determined based on a targeted hemoglobin change from baseline to exclude 0 g/dL with a lower 2-sided 95% confidence bound. Assuming a standard deviation of 1 g/dL, a sample size of 12 participants will provide 88% power to detect a change from baseline of 1 g/dL with a 2-sided significance level of 0.05. In the optional Cohort 3, 6 participants will be enrolled to define the exposure/response relationship of ALXN1820 by combining Cohort 1, Cohort 2 and Cohort 3 data using a PK/PD modeling approach. The Cohort 3 sample size is not determined for power purposes.

## 9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Safety | All participants who receive at least 1 dose of study drug. |
| Enrolled Set | All subjects who sign the ICF and passed inclusion/exclusion criteria. |
| Full Analysis Set (FAS) | All subjects in the Enrolled Set who have been randomized and received at least 1 dose of study drug. |
| Per Protocol Set (PPS) | All subjects in the Enrolled Set without any major protocol deviation. |
| Pharmacokinetic | All participants who receive at least 1 dose of the study drug and have at least 1 post-dose PK sample. |
| Pharmacodynamic | All participants who receive at least 1 dose of study drug and who have evaluable properdin concentration, CAP or CCP activity data. |
| Immunogenicity | All participants who have a predose and at least 1 postdose ADA sample collected. |

Abbreviations: ADA = antidrug antibody; CAP = complement alternative pathway; CCP = complement classical pathway; ICF = informed consent form; PK = pharmacokinetic(s).

## 9.4. Statistical Analyses

In general, descriptive statistics for continuous variables will include number of non-missing values, arithmetic mean, standard deviation, median, minimum, and maximum. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, maximum, geometric mean, and geometric %CV. Categorical variables will be summarized using percentages and frequency counts, by cohort and time point.

A SAP will be developed and finalized before first data cutoff/database lock and will further describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data as appropriate. This section is a high-level summary of the planned statistical analyses of the primary and secondary endpoints.

### 9.4.1. Efficacy Analyses

#### 9.4.1.1. Change in Complement Biomarkers

Absolute and percentage of change from baseline in complement biomarkers (eg, Ba, C3a and sC5B9) will be evaluated at the end of treatment (12 weeks) for Cohorts 1 and 2. Additional details will be described in the SAP.

#### 9.4.1.2. Change in Hemoglobin

Absolute and percentage change from baseline in hemoglobin will be evaluated at the end of treatment (12 weeks) for Cohorts 1 and 2. Additional details will be described in the SAP.

#### 9.4.1.3. Time to Hemoglobin Response

Hemoglobin response is defined as an increase in hemoglobin levels of > 1g/dL from baseline. Hemoglobin response will be evaluated at the end of treatment (12 weeks) for Cohorts 1 and 2. Additional details will be described in the SAP.

#### 9.4.1.4. Markers of Hemolysis

Absolute and percentage change from baseline of the markers of hemolysis (serum LDH levels, absolute reticulocyte count, serum indirect bilirubin, serum haptoglobin and hemopexin) will be evaluated at the end of treatment (12 weeks) for Cohorts 1 and 2. Additional details will be described in the SAP.

#### 9.4.1.5. Exploratory Analysis of Change in Biomarkers Related to VOC

Biomarkers related to VOC may be evaluated after end of treatment (12 week for Cohorts 1 and 2). Additional details will be described in the SAP.

### 9.4.2. Exploratory Assessment of VOC

Sickle cell disease–related pain crises (VOC) are defined as acute episodes of pain, with no medically determined cause other than a VOC event that result in a medical facility visit and treatment with either oral or parenteral narcotic agents, or with a parenteral nonsteroidal anti-inflammatory drug. Uncomplicated VOCs are defined as no occurrence of any other SCD complication during the VOC episode. Complicated VOCs are defined as the presence of a diagnosis of other SCD complications during the VOC episode. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism are considered as VOC events in this study. Complicated VOCs are also to be reported as AEs.

The following may also be assessed if available:

- Number of VOCs leading to a healthcare visit

- Number of uncomplicated VOCs, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism
- Time to first VOC after first dose of study drug

### 9.4.3. Safety Analyses

The primary endpoint for the study is safety and tolerability.

All safety analyses will be performed on the Safety Population and will be reported by each cohort.

Safety analyses will include an analysis of all TEAEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. The prevalence of AEs and SAEs will be summarized, by SOC and Preferred Term for each cohort and treatment arm and overall, within each treatment arm, and by relationship to study drug. AEs will also be summarized by cohort and treatment arm, and overall, within each treatment arm, and by severity. SAEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

Changes from baseline in vital sign measurements and laboratory assessments (eg, clinical chemistry, cell blood count with differential, and urinalysis) will be summarized by each cohort and overall. Laboratory parameter values will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE, v5.0, published 27 Nov 2017). Shift tables by cohort and treatment arm will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed postdose during the study.

All concomitant medications will be coded using the World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

#### 9.4.3.1. ECG Analysis

Cardiac assessments will be performed in the Safety Population.

The ECG parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and QTcF intervals. The average of the triplicate ECG readings at the time points collected will be calculated, and changes from pretreatment baseline values will be assessed by each cohort and treatment arm.

An outlier analysis will be performed that will summarize the absolute count, frequency and percentage of participants who meet any of the following outlier criteria at each visit by cohort and treatment arm:

- QT, QTcF interval > 450 msec
- QT, QTcF interval > 480 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec

- QT, QTcF interval increases from baseline > 60 msec

Analysis of drug-related QT/QTc interval changes relative to plasma PK concentrations may be conducted on all dose regimens. The principles of this analysis follow the statistical methods described by Garnett et al. (Garnett, 2018).

Detailed analysis will be specified in the SAP or a separate ECG analysis plan.

### 9.4.4. Other Analyses

#### 9.4.4.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Population and will be reported by cohort.

The individual serum concentration data from patients who receive ALXN1820 SC with actual sampling dates and times will be used to characterize PK using a population PK analysis approach. The details will be provided in the SAP.

#### 9.4.4.2. Pharmacodynamic Analyses

All PD analyses will be performed on the PD Population and will be reported by cohort.

The PD effects of all ALXN1820 SC doses administered will be evaluated by assessing changes in serum total and free properdin concentrations and CAP activity using the Weislab AP assay. In addition, an exploratory assessment of other measures of properdin activity over time may be considered as deemed appropriate.

#### 9.4.4.3. Immunogenicity Analysis

For assessment of immunogenicity, the incidence of confirmed positive ADAs will be summarized. Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies (if possible).

#### 9.4.4.4. Exploratory Analysis

Additional exploratory analysis on biomarker assays and clinical efficacy endpoint may be conducted. Details of these analyses will be presented in the SAP.

## 9.5. Interim Analyses

An interim analysis may be performed after at least 12 patients from Cohorts 1 and 2 (6 from each cohort) have enrolled and completed the Treatment Period to inform later phase trials. The interim analysis will include safety, efficacy, PK/PD and immunogenicity data. Details of this analysis will be presented in the SAP.

## 9.6. Data Monitoring Committee

An independent DMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The specific responsibilities of the DMC and a schedule of meetings will be described in the DMC Charter.

## 9.7. Safety Review Committee

Not applicable.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### 10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study participants or the participant's legally authorized representative prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form(s).
- Participants must be reconsented to the most current version of the informed consent form(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent [or assent] forms must remain in each participant's study file and must be available for verification at any time.
- Participants who are rescreened are required to sign a new ICF (see Section 5.4).

### 10.1.4. Data Protection

Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed, and will be required to agree to the information contained in the informed

consent and provide consent to the processing of their personal data, if required by applicable data protection law.

Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.

Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.

In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

### 10.1.5. Committees Structure

See Section 9.6.

### 10.1.6. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

### 10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

### 10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the Investigator's site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

### 10.1.9. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the last study visit or Early Discontinuation Visit, all data have been collected and entered into the electronic data capture system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or ICH GCP guidelines

Inadequate recruitment of participants by the Investigator

Discontinuation of further study intervention development

Alexion or health authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

Discovery of an unexpected, serious, or unacceptable risk of the study intervention to participants enrolled or continuing in the study

Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, IRBs/IECs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

### 10.1.10. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication to peer-reviewed, indexed (eg, PubMed, Scopus, Embase) journals within 12 to 18 months of the primary evaluation date or EOS, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.

  Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.

  Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors recommendations and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not

as individual site data. In this case, a Co-ordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

Alexion will publish Plain Language Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

- No compensation shall be provided to external Authors for authorship of publication, including drafting or revising a publication. Alexion may reimburse the presenting Author of an Alexion-supported publication for travel, lodging, and registration to present a poster or oral presentation at scientific meeting, consistent with the Alexion Global Procurement and Sourcing Procedure, the Alexion Antibribery Anticorruption Policy and the Alexion Global Travel and Expense Policy.
- Authors must disclose financial or personal affiliations that could be considered a conflict of interest in the publication.

### 10.1.11. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study drug for shipment to the site.

## 10.2. Clinical Laboratory Tests

- The protocol-required clinical laboratory tests detailed in Table 13 will be performed by a central laboratory unless otherwise specified.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at Screening. Additional local urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).

**Table 13: Protocol-required Laboratory Assessments**

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | Platelet count<br>Red blood cell (RBC) count<br>Hemoglobin<br>Free Hemoglobin<br>Hemoglobinopathy test (eg, hemoglobin electrophoresis, screening only)<br>Hematocrit<br>Haptoglobin<br>Hemopexin<br>RBC indices (MCV, MCH, % reticulocytes)<br>White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) |
| Clinical chemistry | Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)<br>Alkaline phosphatase<br>Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)<br>Blood urea nitrogen (optional)<br>Calcium<br>Creatinine<br>Creatine kinase<br>Hemoglobin A1C<br>Fructosamine<br>LDH<br>Potassium<br>Sodium<br>Serum albumin |

**Table 13: Protocol-required Laboratory Assessments**

| Laboratory Assessments | Parameters |
|---|---|
| | Total and direct bilirubin<br>Indirect bilirubin<br>Total protein<br>Urea |
| Coagulation | Prothrombin time, partial thromboplastin time, international normalized ratio |
| Routine urinalysis | Specific gravity<br>pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>Microscopic examination (If blood or protein is abnormal |
| Spot urine studies | Protein, albumin, creatinine, and protein-to-creatinine and albumin/creatinine ratio |
| Complement activity | Change in CAP activity using the Wieslab AP assay |
| Biomarkers | Complement biomarkers<br>Biomarkers related to VOC<br>Other biomarkers may be considered if feasible |
| Other screening tests | Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) [a]<br>Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)<br>Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), anti-HBc IgG + IgM (if IgG positive) and hepatitis C virus antibodies (anti-HCV) |

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Abbreviations: AP = alternative pathway; CAP = complement alternative pathway; CCP = complement classical pathway; HBc = hepatitis B core; IEC = Independent Ethics Committee; IgG = immunoglobulin G; IgM = immunoglobulin M; IRB = Institutional Review Board; LDH = lactate dehydrogenase; LP = lectin pathway; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; SAE = serious adverse event; VOC = vaso-occlusive crisis.

# 10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 10.3.1. Definition of AE

**AE Definition**

- An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).
- **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study intervention, whether or not considered related to the study intervention.

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

**Events Not Meeting the AE Definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience).
- 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.
- 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 study intervention 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.

| **Events Not Meeting the AE Definition** |
|---|
| • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). |

### 10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **An SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **1. Results in death** |
| **2. Is life-threatening**<br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe. |
| **3. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **4. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **5. Is a congenital anomaly/birth defect** |
| **6. Other situations:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>• Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

| **A suspected unexpected serious adverse reaction (SUSAR) is defined as:** |
|---|
| An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.<br>Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.<br>Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable. |

### 10.3.3. Recording and Follow-up of AE and/or SAE

**Recording of AE and/or SAE**

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the Alexion AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

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

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

| **Follow-up of AEs and SAEs** |
|---|
| • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information. |

### 10.3.4. Reporting of SAEs

| **SAE Reporting to Alexion via an Electronic Data Collection Tool** |
|---|
| • All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.<br>• The primary mechanism for reporting an SAE to Alexion will be the electronic data capture (EDC) system.<br>• If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure.<br>– Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347<br>• The site will enter the SAE data into the EDC system as soon as it becomes available.<br>• When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness.<br>• After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.<br>– If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email. |

| **SAE Reporting to Alexion via Paper Safety Reporting Form <to be used if EDC is not available>** |
|---|
| • All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.<br>• SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:<br>– Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347<br>• Additional follow-up information, if required or available, should be entered into the eCRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.<br>• For all SAEs, the Investigator must provide the following:<br>– Appropriate and requested follow-up information in the time frame detailed above<br>– Causality of the SAE(s)<br>– Treatment of/intervention for the SAE(s)<br>– Outcome of the SAE(s) |

**SAE Reporting to Alexion via Paper Safety Reporting Form <to be used if EDC is not available>**

  - Medical records and laboratory/diagnostic information

- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

## 10.4. Contraceptive Guidance and Collection of Pregnancy Information

### 10.4.1. Definitions

**Woman of Childbearing Potential**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

**Women in the Following Categories Are Not Considered WOCBP**

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
- **Note**: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        – A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with a single FSH measurement is insufficient. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

### 10.4.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.4.3.1 ). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

#### 10.4.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative pregnancy test ([urine or serum]) as required by local regulations before the first dose of ALXN1820. Additional requirements for pregnancy testing during and after dosing with ALXN1820 are indicated in the SoA (Section 1.3).

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

The Investigator should evaluate the potential for contraceptive method in relationship to the first dose of ALXN1820.

Female participants must not donate ova from the Day 1 Visit at least until 6 months after their final dose of ALXN1820.

A highly effective method of contraception, including at least 1 of the following must be used until 6 months after the final dose of ALXN1820.

1. Intrauterine device in place for at least 6 weeks prior to first dose of ALXN1820.
2. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of ALXN1820.
3. Bilateral tubal occlusion for at least 6 weeks prior to first dose of ALXN1820.
4. Progestogen-only hormonal contraception associated with inhibition of ovulation (implantable only) for at least 6 weeks prior to first dose of ALXN1820.
5. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of ALXN1820). Male partner is still required to use condom during heterosexual intercourse.

Female participants must not donate ova from the Day 1 Visit at least until 6 months after their final dose of ALXN1820.

Female participants of childbearing potential must use a highly effective method of contraception, including at least 1 of the following until 6 months after the final dose of ALXN1820.

1. Intrauterine device in place for at least 6 weeks prior to first dose of ALXN1820.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of ALXN1820.

3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of ALXN1820.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of ALXN1820.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of ALXN1820.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of ALXN1820). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 6 months after the final dose of ALXN1820.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together

#### 10.4.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participants in the study, regardless of his female partner's method of contraception.

Male participants who have had a vasectomy > 6 months prior to the first dose of ALXN1820 must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose ALXN1820 and those who have not had a vasectomy must use a condom with or without spermicide during heterosexual intercourse for at least 6 months after their final dose of ALXN1820.

Male participants must not donate sperm from the Day 1 Visit until 6 months after their final dose of ALXN1820.

##### 10.4.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

Male participants must not donate sperm from the Day 1 Visit until 6 months after their final dose of ALXN1820.

### 10.4.3. Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all female participants and any female spouse/partner of a male participant, who become pregnant. 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.
- If a female participant or a male participant's female sexual partner of childbearing potential becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion or designee via the same method as SAE reporting (Section 10.3). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion or designee. If additional follow-up is required, the Investigator will be requested to provide the information.
- Exposure of an infant to a Sponsor product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding" form) and any AEs experienced by the infant must be reported to Alexion or designee and submitted to Alexion within 24 hours of learning of a participant's pregnancy via facsimile or email.
- A pregnancy in and of itself is not regarded as an AE unless there is a suspicion that the study drug 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 (Section 8.2.6).
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

#### 10.4.3.1. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive ALXN1820.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

#### 10.4.3.2. Female Participants Who Become Pregnant

- 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 participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

## 10.5. Biomarkers

- Whole blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1820. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1820 and/or others of this study intervention class.
- The samples may be analyzed as part of a multi-study assessment of biomarkers in the response to ALXN1820 to understand study disease or related conditions. Analyses may be done to establish normal range of values for biomarkers which may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptors), and endothelial activation/damage (eg, soluble vascular cell adhesion molecule-1, thrombomodulin).
- The results of biomarker analyses may be reported in the clinical study report or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1820 continues but no longer than 25 years or other period as per local requirements.

## 10.6. Management of Potential Adverse Events During Study Drug Administration

Injection-associated reactions are a potential risk with the use of therapeutic protein products; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All injection-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue ALXN1820.

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Before study drug administration, the treating physician and other appropriate personnel must make certain that medication (ie, adrenaline, inhaled beta agonists, antihistamines, corticosteroids) and other equipment to treat anaphylaxis are readily available. Alexion must be notified within 24 hours of any injection site reaction requiring interruption or discontinuation of study drug. Participants who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

Participants who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol, if possible.

## 10.7. COVID-19 Risk Assessment

Sickle cell disease can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that SCD does involve some level of immune deficiency as part of its clinical presentation and evolution, there is a theoretical concern that the risk for infection may be higher than the general population. However, there is no specific data to inform this risk further. The Principal Investigator will balance the risk/benefit considerations in their participants, taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 14.

**Table 14: Potential Risks and Mitigation Measures due to COVID-19**

| Risks category | Summary of Data/ Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Potential risks** | | |
| Healthcare institution availability for non-COVID-19 related activities | COVID-19 may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities. | During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless they have the resourcing and capabilities to implement the study as per protocol. |
| Data quality and integrity | Lack of availability of site personnel to perform study assessments and capture study-specific data in a timely manner and to maintain adequate quality standards.<br><br>Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples.<br><br>Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites.<br><br>Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]). | During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities.<br><br>During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification.<br><br>During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data are missing (eg, missed study visits or participant study discontinuations due to COVID-19). |

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form.

## 10.8. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ALXN1820 administration, based on ALXN1820's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN1820.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination. Alexion suggests that participants complete vaccination series before study participation, if feasible.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 15.

**Table 15: Potential Risks and Mitigation Measures due to COVID-19 Vaccine**

| Risks Category | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Potential risks** | | |
| Data quality and integrity | Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules, and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures). | Capture specific information in the eCRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine). |

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form.

## 10.9. Abbreviations

**Table 16: Abbreviations and Specialist Terms**

| Abbreviation or Term | Explanation |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| AP | alternative pathway |
| $AUC_{0-168}$ | area under the concentration-time curve from time 0 to 168 hours |
| Ba | complement component Ba |
| BMI | body mass index |
| C3 | complement component C3 |
| C3a | complement component C3a |
| C5 | complement component 5 |
| C9 | complement component 9 |
| CAP | complement alternative pathway |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | maximum observed serum concentration |
| COVID-19 | coronavirus disease 2019 |
| CTCAE | Common Terminology Criteria for Adverse Events |
| % CV | coefficient of variation |
| DMC | Data Monitoring Committee |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EOS | end of study |
| FIH | first-in-human |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GDS | Global Drug Safety |
| GDPR | General Data Protection Regulation |
| GLP | Good Laboratory Practice |

**Table 16: Abbreviations and Specialist Terms**

| Abbreviation or Term | Explanation |
|---|---|
| HBc | hepatitis B core |
| HbS | sickle hemoglobin |
| HbsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HiB | *Haemophilus influenzae* type b |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HRT | hormonal replacement therapy |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| $K_D$ | dissociation constant |
| LDH | lactate dehydrogenase |
| mAb | monoclonal antibody |
| MCV4 | tetravalent meningococcal conjugate vaccine |
| NOAEL | no observed adverse effect level |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| QTcF | QT interval corrected using the Fridericia's formula |
| Q2W | once every 2 weeks |
| Q4W | once every four weeks |
| QW | once weekly |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous(ly) |
| sC5b9 | soluble complement component C5b-9 |

**Table 16: Abbreviations and Specialist Terms**

| Abbreviation or Term | Explanation |
|---|---|
| SCD | sickle cell disease |
| SoA | schedule of activities |
| SOC | System Organ Class |
| TCR | tissue cross reactivity |
| TEAE | treatment-emergent adverse event |
| VHH | single variable domain on a heavy chain antibody |
| VOC | vaso-occlusive crisis |
| WOCBP | woman of childbearing potential |

## 10.10. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

| **DOCUMENT HISTORY** | |
|---|---|
| **Document/Type of Amendment (Global or Country-specific)/Date** | **Summary of Key Changes in the Amendment** |
| Amendment 1.0 Global [22 August 2022] | The main rationale for this amendment is to clarify stopping rules and inclusion/exclusion criteria |
| Original protocol [13 May 2022] | Not applicable |

# 11. REFERENCES

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**Alexion Pharmaceuticals, Inc.** **12 April 2023**

**Protocol:** ALXN1820-SCD-201 Protocol Amendment 1 (22 August 2022)

**Protocol Title:** A Phase 2a, Randomized, Open-Label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

**Protocol Administrative Change Letter #2**

**Reason for Letter:** Clarify guidelines on determining whether a hospitalization or prolongation of a hospitalization are considered an AE/SAE. Clarify the timeframe between the (2) Screening Blood Biomarker sample collections. Clarify that randomization can be performed as early as one (1) business day prior to Day 1 dosing and clarify the position a patient must be in for blood pressure assessments.

To those sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative changes to the above referenced protocol version.

Protocol Sections below should include additional text noted in **bold** & underlined and remove the text noted; highlighted in gray and in ~~strikethrough~~:

1. Protocol Section 9.4.2: Exploratory Assessment of VOC:

   ~~Complicated~~ VOCs **(uncomplicated & complicated) that are considered exacerbated (increased in frequency or severity) from baseline (Day 1)** are also to be reported as AEs.

2. Protocol Section 10.3.2: Definition of SAE:

   3. Requires inpatient hospitalization or prolongation of existing hospitalization

   ~~In general, hospitalization signifies that~~ **Inpatient hospitalization is defined as** the participant has been ~~detained~~ **admitted** for ~~(usually involving at least an overnight stay)~~ **at least 24 hours.** ~~at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.~~ Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

3. Schedule of Activities: Tables 3, 4, and 7 footnotes:

   • Blood samples for biomarkers will be collected two times prior to receiving the first dose (collect once during Screening and then again on Day 1 pre-dose, the 2

collections ~~should~~ **must** be at least ~~2~~ **1** week~~s~~ apart). Collection of blood (for serum, citrated and K2-EDTA, or P100 plasma) and urine.

4. Schedule of Activities: Tables 3, 4, and 7 footnotes:

   [c] Randomization will occur following confirmation of all eligibility requirements. **Randomization can be performed up to 1 business day prior to Day 1 dosing.**

5. 8.2.2. Vital Signs

   Vital sign measurements will be taken after the participant has been resting in the supine or semi-recumbent position **or preferred position per site standard practice** for at least 5 minutes and will include temperature (tympanic or oral), respiratory rate, ~~supine~~ blood pressure, and pulse. Ideally, the same arm for each participant should be used for BP and pulse measurements. Orthostatic (standing) blood pressure will only be measured at Screening.

6. Schedule of Activities: All Tables footnotes

   - At Screening, supine and standing (orthostatic) blood pressures will be performed. **At all other visits blood pressure can be performed supine or preferred position per site standard practice.**

7. Schedule of Activities: All Tables footnotes

   - If a VOC occurs, samples will be collected as per unscheduled visit**, when feasible.**

Please file this letter and any IRB/EC correspondence with all copies of the protocol in the Investigator Site File and in all pertinent repositories in which the protocol is maintained.

If there are any questions concerning these changes, please contact us. These changes will also be captured in any future protocol amendment.

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**Alexion Pharmaceuticals, Inc.** **14 July 2023**

**Protocol:** ALXN1820-SCD-201 Protocol Amendment 1 (22 August 2022)

**Protocol Title:** A Phase 2a, Randomized, Open-Label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

**Protocol Administrative Change Letter #3**

**Reason for Letter:** Clarify the Safety Follow-up period and intended visit sequence upon a participant meeting criteria (or deciding to) discontinue study drug intervention.

To those sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative changes to the above referenced protocol version.

Protocol Sections below should include additional text noted in **bold** & underlined:

1. **Section 7.1. Discontinuation of Study Drug Intervention**
   In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. **The safety follow-up period should follow the periodicity and assessments defined in the SOA Table 6 from Day 99 through Day 211 and includes any subsequent Complement Activity Follow-up visits. (Cohorts 1 & 2). The safety follow-up period for the optional cohort (Cohort 3) should follow the periodicity and assessments defined in the SOA Table 8 from Day 57 through Day 169 and includes any subsequent Complement Activity Follow-up visits. The first safety follow-up visit, Day 99 for Cohorts 1 & 2 and Day 57 for Cohort 3, must occur 14 days (+/- 3 days) after the patient receives their last dose of ALXN1820.** See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed (Section 1.3).

Please file this letter and any IRB/EC correspondence with all copies of the protocol in the Investigator Site File and in all pertinent repositories in which the protocol is maintained.

If there are any questions concerning these changes, please contact us. These changes will also be captured in any future protocol amendment.

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**Alexion Pharmaceuticals, Inc.** **14 August 2023**

**Protocol:** ALXN1820-SCD-201 Protocol Amendment 1 (22 August 2022)

**Protocol Title:** A Phase 2a, Randomized, Open-Label Study to Evaluate Multiple Dosing Regimens of Subcutaneous ALXN1820 in Adult Patients with Sickle Cell Disease

**Protocol Administrative Change Letter #4**

**Reason for Letter:** Clarify the allowed use of medicines and therapy permitted during the study and provide clarification regarding bilateral tubal ligation as a method of highly effective contraception but not a permanent sterilization method (ie, women who have undergone tubal ligation will be considered of childbearing potential) and remove duplicative text for clarification.

To those sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative changes to the above referenced protocol version.

The Protocol Sections below should include additional text noted in **bold** & underlined and remove the text noted; highlighted in gray and in ~~strikethrough~~:

1. **Section 6.5.1 Allowed Medicine and Therapy**
   Multivitamins, contraceptives, and paracetamol ~~(ie, acetaminophen, at doses of ≤ 2 g/day)~~ are permitted for use during the study at the Investigator's discretion. Topical skin products should not be administered at the site of study drug injection from 24 hours prior until 24 hours following study drug administration.

2. **Section 10.4.1 Women in the Following Categories Are Not Considered WOCBP**
   1. Premenarchal
   2. Premenopausal female with one of the following:
      - Documented hysterectomy
      - Documented ~~bilateral tubal ligation or~~ bilateral salpingectomy
      - Documented bilateral oophorectomy

3. **Section 10.4.2.1 Guidance for Female Participants**
   ~~A highly effective method of contraception, including at least 1 of the following must be used until 6 months after the final dose of ALXN1820.~~
   ~~1. Intrauterine device in place for at least 6 weeks prior to first dose of ALXN1820.~~
   ~~2. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of ALXN1820.~~
   ~~3. Bilateral tubal occlusion for at least 6 weeks prior to first dose of ALXN1820.~~
   ~~4. Progestogen-only hormonal contraception associated with inhibition of ovulation (implantable only) for at least 6 weeks prior to first dose of ALXN1820.~~
   ~~5. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of ALXN1820). Male partner is still required to use condom during heterosexual intercourse.~~
   ~~Female participants must not donate ova from the Day 1 Visit at least until 6 months after their final dose of ALXN1820~~

4. **Schedule of Activities: All Tables footnotes**

   - If a VOC occurs, samples will be collected as per unscheduled visit**, within 7 days of VOC resolution** when feasible.

Please file this letter and any IRB/EC correspondence with all copies of the protocol in the Investigator Site File and in all pertinent repositories in which the protocol is maintained.

If there are any questions concerning these changes, please contact us. These changes will also be captured in any future protocol amendment.

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