TITLE PAGE

Protocol Title: Prospective, Single-Arm, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab in Complement Inhibitor Treatment-Naïve Pediatric and Adult Participants with Atypical Hemolytic Uremic Syndrome (aHUS) in China

Protocol Number: ECU-aHUS-302

Compound: Eculizumab

Study Phase: 3b

Short Title: Single-Arm Study of Eculizumab in Pediatric and Adult Participants with Atypical Hemolytic Uremic Syndrome (aHUS) in China

Sponsor Name: Alexion Europe SAS

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Regulatory Agency Identifier Number(s): Not assigned

Original Protocol: 30 Nov 2021

Protocol Amendment 1: 20 Jun 2022

Protocol Amendment 2: 26 Apr 2023

Sponsor Signatory:

[redacted]

10-May-2023 | 16:57:53 EDT

Date

Alexion Pharmaceuticals, Inc.

Medical Monitor Name and Contact Information can be found in the study contact list.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline 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 amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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Amendment 2

Overall Rationale for the Amendment:

The primary reason for this amendment was to clarify activities to be followed when a change in weight causes a participant to move to a different weight cohort during the study period. Additionally, updates to estimand descriptions for endpoints were also made.

Section # and Title	Description of Change	Brief Rationale
Title Page	Added updated protocol amendment number.	Administrative
Throughout	Updated definition of ED Visit to early discontinuation from the study.	For clarity
1.1 – Synopsis (Objectives, Estimands, and Endpoints) 3 - Objectives, Estimands, and Endpoints 3.1 Primary Estimand	Updated definition of "Population" in "Estimands and Endpoints" for the primary endpoint of efficacy assessment as follows (strikethrough [deleted], bold [added]): **Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria** ~~Participants in the FAS (defined in Section 9.3)~~.	To align the definition of population with ICH E9(R1)
1.1 – Synopsis (Objectives, Estimands, and Endpoints) 3 - Objectives, Estimands, and Endpoints 3.2 - Secondary Estimands	Updated definition of "Population" in "Estimands and Endpoints" for the secondary endpoint of safety assessment as follows (strikethrough [deleted], bold [added]): **Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria**~~Participants in the Safety Set (defined in Section 9.3)~~.	To align the definition of population with ICH E9(R1)

Section # and Title	Description of Change	Brief Rationale
1.1 – Synopsis (Objectives, Estimands, and Endpoints) 3 - Objectives, Estimands, and Endpoints 3.2 - Secondary Estimands	Updated "Population" and "Summary measure" definitions for PK assessment as follows (strikethrough [deleted], bold [added]): Population: **Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria.**~~Participants in the PK Analysis Set (defined in Section 9.3).~~ Summary measure: **Mean serum eculizumab concentrations at all scheduled visits**~~Serum eculizumab concentrations at all available study visits~~.	To align the definition of population with ICH E9(R1).
1.1 – Synopsis (Objectives, Estimands, and Endpoints) 3 - Objectives, Estimands, and Endpoints 3.2 - Secondary Estimands	Updated "Population", "Variable", and "Summary measure" definitions for PD assessment as follows (strikethrough [deleted], bold [added]): Population: **Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria**.~~Participants in the PD Analysis Set (defined in Section 9.3).~~ Variable: ~~Mean c~~**C**hange**s** in serum free and total **C5** ~~complement component 5~~ concentrations over time (Section 3.23.2). Summary measure: **Mean changes in serum free and total C5 concentrations at all scheduled visits**~~Mean change in serum free and total complement component 5 concentrations from baseline over time at all study visits~~.	To align the definition of population with ICH E9(R1).

Section # and Title	Description of Change	Brief Rationale
1.1 – Synopsis (Objectives, Estimands, and Endpoints) 3 - Objectives, Estimands, and Endpoints 3.2 - Secondary Estimands	Updated "Population", "Variable", and "Summary measure" definitions for immunogenicity assessment as follows (strikethrough [deleted], bold [added]): Population: **Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria**.~~Participants in the Safety Set (defined in Section 9.3).~~ Variable: **ADA response category** ~~Proportion of participants who develop ADA and neutralizing antibodies (Section 3.2)~~. Summary measure: **Proportion of ADA positive participants** ~~Proportion of participants at all study visits with ADA positive and neutralizing antibody titers~~.	To align the definition of population with ICH E9(R1).
1.1 - Synopsis (Overall Design) 4.1 - Overall Design	Revised text on prophylactic antibiotics as follows: Participants who are vaccinated less than ~~14 days~~**2 weeks** prior to receiving the first dose of eculizumab will receive treatment with appropriate **prophylactic** antibiotics until ~~14 days~~**2 weeks** after the vaccination.	For internal document consistency.
1.1 - Synopsis (Intervention Groups and Duration) 1.3 - Schedule of Activities (Table 2, Table 3, Table 4, Table 5, and Table 6) 8.11.6 - Study Intervention Administration	Added a footnote to Table 1 and Table 12, and added note for weight assessment in Table 2, Table 3, Table 4, Table 5, and Table 6 to indicate that participants will be weighed prior to dosing at each study visit as eculizumab dosing will be based on the weight assessment at that specific visit. Also added that participants will not need to be weighed at each study visit if eculizumab is permanently discontinued.	To reiterate that weight must be measured prior to other assessments to determine eculizumab dose. To reiterate that if eculizumab is permanently discontinued and the participant remains in the study, for the rest of the scheduled visits, the schedule of activities will not need to be adjusted based on weight.
1.3 - Schedule of Activities (Table 2, Table 4, and Table 6)	Updated Day 0 to Day -1 in the Study Day Visit Window.	For clarity

Section # and Title	Description of Change	Brief Rationale
1.3 - Schedule of Activities (Table 2, Table 4, and Table 6)	Deleted assessment of "LDH isozymes".	Updated as only total LDH is measured in the study and not the individual isoenzymes
1.3 - Schedule of Activities (Table 2, Table 3, Table 4, Table 5, and Table 6)	Added "Dialysis requirement status".	For internal document consistency
1.3 - Schedule of Activities (Table 2, Table 3, Table 4, Table 5, and Table 6)	Added the note "Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line" for "Hematology including coagulation".	For internal document consistency
1.3 - Schedule of Activities (Table 2, Table 3, Table 4, Table 5, and Table 6) 8.11.6 - Study Intervention Administration	Added footnote for "Administration of Study Intervention" and text in "Study Intervention Administration" section to indicate schedule of activities to be followed if a change in weight cohort occurs during the study period. Also added that if eculizumab is permanently discontinued and the participant remains in the study, for the rest of the scheduled visits, the SoA will not need to be adjusted based on weight.	Added to provide clarity on schedule of activities to be followed when a change in weight causes a participant to move to a different weight cohort during the study period.
1.3 - Schedule of Activities (Table 3, Table 5, and Table 6)	Merged table column for "ED" with "Treatment Period".	For clarity
3.1 - Primary Estimand	Added "(composite strategy for intercurrent events)" to the description of the primary estimand.	Added to specify the strategy for handling the intercurrent events.
3.2 - Secondary Estimands	Added "Treatment policy will be applied for the predefined intercurrent events, where all data collected will be used in the analyses as if there is no occurrence of any intercurrent event" to the description of the secondary estimands. Added "For the definition of estimands, the population will be the same as in the primary objective (variables are presented in Table 8); the handling of intercurrent events for main analyses will apply treatment policy strategy, and the summary measures and all the other details will be provided in the SAP."	Added to specify the strategy for handling the intercurrent events.

Section # and Title	Description of Change	Brief Rationale
4.4 - End of Study Definition	Revised definition of end of study for participants who will and will not receive continued access to eculizumab after completing study treatment.	For flexibility and clarity when a change in weight causes a participant to move to a different weight cohort during the study period.
5.1 - Inclusion Criteria	Revised criterion #1 (strikethrough [deleted]): Age - Participants of any age ~~weighing ≥ 5 kg~~.	To reduce redundancy
5.1 - Inclusion Criteria	Revised criterion #2 (strikethrough [deleted], bold [added]): Evaluation of Inclusion Criteria ~~3a~~ **2a** and ~~3b~~ **2b** may be based on local laboratory results within 28 days prior to the start of the Screening Period or laboratory results obtained during the Screening Period from a local or central laboratory. […] If a participant is found to not meet the eligibility criteria for serum creatinine (Inclusion Criterion ~~3c~~**2c**) based on central laboratory results, they must not be enrolled into the study; if the participant has received the first dose of eculizumab, the participant must be withdrawn from the study and may be replaced. A central laboratory result for Inclusion Criterion ~~3c~~ **2c** may not be available prior to first dose; results received after the first dose indicating that eligibility is not satisfied could lead to discontinuation and replacement of the participant. […]	To correct typos
5.1 - Inclusion Criteria	Revised criterion #5 to add reference to Section 6.5.3.	For clarity

Section # and Title	Description of Change	Brief Rationale
6.5.3 - Vaccination	Added the following: • Participants must be administrated prophylactic antibiotics for prevention of meningococcal infection, if study intervention administration occurs before the vaccination administration. • Participants who permanently discontinue study intervention before vaccination against meningococcal infection must be administered prophylactic antibiotics for at least 8 weeks or be vaccinated for meningococcal infection.	To clarify that prophylactic antibiotics must be administered to participants who have started treatment with the study intervention but did not receive the vaccination. To clarify vaccination requirements if there is permanent discontinuation of study intervention.
7.1 - Discontinuation of Study Intervention	Revised text as follows (strikethrough [deleted], bold [added]): If the study intervention is ~~definitively~~ **permanently** discontinued, the participant should**, if at all possible,** remain in the study to be evaluated for ~~safety~~**all assessments described in the SoA (Section 1.3).** If study intervention is ~~definitively~~ **permanently** discontinued~~,~~ **and the participant remains in the study, the participant** should ~~be asked to return for an ED Visit and~~ have ~~a~~ **the** Safety Follow-up Phone Call 8 weeks after the last dose of study intervention. ~~Refer to the SoA (Section 1.3) 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.~~ […] ~~Data collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed are provided in the SoA (Section 1.3).~~	Clarified assessments to be performed when there is permanent discontinuation of study intervention, and the participant remains in the study.

Section # and Title	Description of Change	Brief Rationale
7.1 - Discontinuation of Study Intervention	Moved the following paragraph from Section 7.1 to Section 7.2: "If it is determined at any point that a participant's Screening data do not satisfy ADAMTS13 negative testing (< 5% activity, Exclusion Criterion 1) or Shiga toxin negative testing (Exclusion Criterion 2) after receiving at least 1 dose of study intervention, the participant will be discontinued from the study and may be replaced. ED procedures described in the SoA (Section 1.3) will be performed, if possible, on participants who are terminated early from the study, and AEs will be collected through the 8-week Safety Follow-up Phone Call (Section 1.3)."	Updated as the text describes discontinuation from the study.
7.2 Participant Discontinuation/Withdrawal from the Study	Revised text as follows (bold [added]): • At the time of discontinuing from the study, if possible, an ED Visit should be conducted, as shown in the SoA (Section 1.3). **Additionally, participants should have the 8-week Safety Follow-up Phone Call.** 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 8-week Safety Follow-up Phone Call will not be required if a participant withdraws consent.**	To clarify when the 8-week Safety Follow-up Phone Call needs to be performed.
8.2.1 - Physical Examinations	Clarified that weight must be recorded prior to dosing at every study visit, however, if eculizumab is permanently discontinued weight will not need to be measured at each study visit.	For clarity.
8.6 - Pharmacodynamics	Revised text as follows (strikethrough [deleted]): Serum ~~and urine~~ samples will be collected for measurement of C5 ~~(serum)~~ as specified in the SoA (Section 1.3).	Updated as C5 is measured through serum and only serum samples are collected in the study.
8.11.4 - Medical History and aHUS History	Added "emergency room visits" to the documentation of aHUS medical history.	Added as this information is collected in the CRF

Section # and Title	Description of Change	Brief Rationale
8.11.5.1 - Prior Medications	Updated the timeframe for usage of prior medications before the start of Screening or during the Screening Period before the first dose of eculizumab from 30 days to 28 days.	For internal document consistency
9.4.3.1 - PK/PD	Added "total C5" to list of PD data collected. Updated the following statement (strikethrough [deleted], bold [added]): The relationship between PK exposure and PD ~~(serum free C5 concentration) will~~**response may** be explored.	For clarity
10.6 - Protocol Amendment History	Added details on Protocol Amendment 1.	Administrative
Throughout	Headers updated with amendment number and date.	Administrative
Throughout	Corrected grammar, syntax, abbreviations, and formatting.	For clarity and to maintain internal document consistency

Note: […] indicates additional unchanged text.
Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif; AE = adverse event; aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; CRF = case report form; ED = early discontinuation from the study; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; LDH = lactate dehydrogenase; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAP = statistical analysis plan; SoA = Schedule of Activities

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Prospective, Single-Arm, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab in Complement Inhibitor Treatment-Naïve Pediatric and Adult Participants with Atypical Hemolytic Uremic Syndrome (aHUS) in China

Short Title:

Single-Arm Study of Eculizumab in Pediatric and Adult Participants with Atypical Hemolytic Uremic Syndrome (aHUS) in China

Rationale:

Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease characterized by complement-mediated thrombotic microangiopathy (TMA). The annual incidence of aHUS in the United States and European Union is 1 to 2 cases per million. Such published data are not yet available in China; however, case reports from 5 major medical centers in China suggest the estimated annual incidence of aHUS in China is similar. aHUS is associated with sometimes fatal manifestations of the nervous system, cardiovascular, gastrointestinal, and renal systems. TMA in patients with aHUS occurs because of impaired regulation of the alternative complement pathway involving complement component 5 (C5). Eculizumab (SOLIRIS®) is a humanized monoclonal antibody (mAb) that specifically binds to C5 and is the standard of care treatment for aHUS. The therapeutic efficacy and safety of eculizumab in the treatment of aHUS has been demonstrated in 3 pivotal clinical studies for registration and has since been supported by subsequent postmarketing evidence. This postapproval study, agreed as a condition of approval in China, will be conducted in participants with aHUS who are being treated with eculizumab in China.

Objectives, Estimands, and Endpoints

Objectives	Estimands and Endpoints
Primary	
To assess the efficacy of eculizumab in the treatment of participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Complete TMA Response during the 26-week Treatment Period (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All participants who meet response criteria after ICE1 or ICE2 will be considered as nonresponders thereafter. • Summary measure: The proportion of complete TMA responders overall along with 95% CIs.
Secondary	
To characterize the safety and tolerability of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Incidence of TEAEs and SAEs (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be included. • Summary measure: Number and percentage of participants with TEAEs and SAEs and number of events by System Organ Class and Preferred Term.
To characterize the pharmacokinetics of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Serum eculizumab concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean serum eculizumab concentrations at all scheduled visits.
To characterize the pharmacodynamics of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Changes in serum free and total C5 concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean changes in serum free and total C5 concentrations at all scheduled visits.

Objectives	Estimands and Endpoints
To characterize the immunogenicity of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: ADA response category. • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Proportion of ADA positive participants.
Additional Secondary	
To evaluate the efficacy of eculizumab and characterize TMA by additional measures	• Time to Complete TMA Response • Dialysis requirement status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) at all scheduled visits • Chronic kidney disease (CKD) stage classified as improved, stable (no change), or worsened at all scheduled visits compared to baseline • Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin) at all scheduled visits • Increase in hemoglobin of ≥ 20 g/L from baseline through Week 26
To characterize the safety profile of eculizumab by additional safety measures	• Changes from baseline in vital signs and laboratory parameters at scheduled visits

Abbreviations: ADA = antidrug antibody; aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; CI = confidence interval; ICE = intercurrent event; LDH = lactate dehydrogenase; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMA = thrombotic microangiopathy

Overall Design

This is a Phase 3b, open-label, single-arm, multicenter study to evaluate the efficacy and safety of eculizumab in participants with aHUS in China. The study will be conducted in participants of any age who weigh ≥ 5 kg and who previously have not been treated with complement inhibitors. The study consists of an up to 7-day Screening Period and a 26-week Treatment Period. An 8-week Safety Follow-up Phone Call will be required only for participants who discontinue eculizumab treatment during the study or for participants who will not receive continued access to eculizumab after completing study treatment. Approximately 25 eligible participants in China will be enrolled.

After providing informed consent/assent, participants will be screened for eligibility for the study during the 7-day Screening Period. If all inclusion criteria and none of the exclusion criteria are met, participants will be enrolled and vaccinated against *Neisseria meningitidis* if not already vaccinated within the period of active coverage specified by the vaccine manufacturer. Participants who are vaccinated less than 2 weeks prior to receiving the first dose of eculizumab will receive treatment with appropriate prophylactic antibiotics until 2 weeks after the vaccination.

During the 26-week Treatment Period, participants will receive eculizumab by intravenous (IV) administration based on body weight cohorts presented in Table 1.

Participants who discontinue eculizumab treatment at any time during the study will have an Early Discontinuation from Study (ED) Visit at the time of discontinuation and a Safety Follow-up Phone Call 8 weeks after the last dose of eculizumab.

Participants who will not receive continued access to eculizumab after completing the End-of-Study (EOS) Visit will also have an 8-week Safety Follow-up Phone Call.

Participants who complete study treatment and will receive continued access to eculizumab after the study will not have an 8-week Safety Follow-up Phone Call.

Clinical measures and laboratory tests will be performed to assess safety, clinical, and biochemical parameters associated with aHUS.

Disclosure Statement: This is an open-label, single-arm, treatment study.

Number of Participants: Approximately 25 participants will be enrolled and treated.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent/assent process and satisfying inclusion/exclusion criteria. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Eculizumab will be administered by IV infusion according to body weight as described in Table 1.

Table 1: Eculizumab Induction and Maintenance Dosing by Weight Cohort[a]

Body Weight	Induction	Maintenance
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Day 29; then 1200 mg every 2 weeks
30 to <40 kg	600 mg weekly × 2 doses	900 mg at Day 15; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Day 15; then 600 mg every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 2 weeks
5 to < 10 kg	300 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 3 weeks

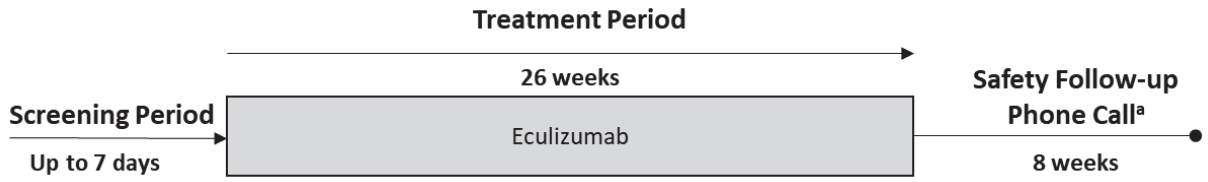
[a] Participants will be weighed at each study visit as eculizumab dosing will be based on the weight assessment.

The total duration of study participation for each participant will be up to 35 weeks, including the Screening Period (up to 7 days), Treatment Period (26 weeks), and Safety Follow-up Phone Call (8 weeks).

Data Monitoring Committee: No.

1.2. Schema

Figure 1: ECU-aHUS-302 Study Design Schematic



[a] The Safety Follow-up Phone Call is required for any participant who discontinues eculizumab early or for any participant who will not receive continued access to eculizumab after completing study treatment.

1.3. Schedule of Activities

Table 2: Schedule of Activities: Screening and Treatment Period, Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Study Period	**Screening**	**Treatment Period[a]**										**Notes**
Study Day **Visit Window (days)**	**-7 to -1**	**1**	**8** **± 1**	**15** **± 1**	**22** **± 1**	**29** **± 1**	**43** **± 2**	**57** **± 2**	**71** **± 2**	**85** **± 2**	**99** **± 2**	
End of Week	**-1**	**Day 1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	
General Assessments/Procedures												
Informed consent/assent	X											Refer to Section 8.11.1.
Inclusion/exclusion	X	X										Refer to Section 8.11.3.
Demographics	X											Refer to Section 8.11.2.
Medical and aHUS history	X											Refer to Section 8.11.4.
Prior medications	X											Refer to Section 8.11.5.
Weight	X	X	X	X	X	X	X	X	X	X	X	Participants must be weighed prior to dosing as eculizumab dosing will be based on the weight assessment at each visit. Participant will not need to be weighed at each study visit if eculizumab is permanently discontinued.
Height[b]	X	X	X	X	X	X	X	X	X	X	X	
Confirmation or administration of meningococcal vaccination	X											Participants must be vaccinated against meningococcal infection and revaccinated during the study if needed (Section 6.5.3).
Hib and *Streptococcus pneumoniae* vaccination	X											For pediatric participants only. Refer to Section 6.5.3.
HIV test	X											Test includes HIV-1 and HIV-2. Refer to Section 8.2.4.
Direct Coombs test[c]	X											Refer to Section 8.2.4.
ADAMTS13 test	X											Refer to Section 8.2.4.
ST-HUS test	X											Refer to Section 8.2.4.
Pregnancy test[d]	X	X			X		X		X		X	Female participants of childbearing potential only (Section 8.2.5).
Follicle-stimulating hormone	X											Postmenopausal females only (Section 8.2.4 and Section 10.4.1).
Safety and Efficacy Assessments												
Full physical examination	X											Refer to Section 8.2.1.
Abbreviated physical examination		X			X		X		X		X	Refer to Section 8.2.1.

Table 2: Schedule of Activities: Screening and Treatment Period, Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Study Period	**Screening**	**Treatment Period[a]**										**Notes**
Study Day **Visit Window (days)**	**-7 to -1**	**1**	**8** **± 1**	**15** **± 1**	**22** **± 1**	**29** **± 1**	**43** **± 2**	**57** **± 2**	**71** **± 2**	**85** **± 2**	**99** **± 2**	
End of Week	**-1**	**Day 1**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.2.
ECG	X											Refer to Section 8.2.3.
Chemistry	X	X			X		X		X		X	Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Dialysis requirement status	X	Continuous monitoring										Refer to Section 8.1.2.
Hematology including coagulation	X	X			X		X		X		X	Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Urinalysis and urine chemistry	X	X			X		X		X		X	Refer to Section 8.2.4.
Participant Safety Card[e]		X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Concomitant medications		Continuous monitoring										Refer to Section 8.11.5.
Adverse events		Continuous monitoring										Refer to Section 8.3.
PK/PD/ADA Assessments												
PK/PD sampling[f]		B/P	T/P			T/P				T/P		Refer to Section 8.5 and Section 8.6.
ADA/NAb blood sample		B								T		Refer to Section 8.9.
Administration of Study Intervention[g]												
Eculizumab infusion (mg) 20 to < 30 kg		600	600	600	NA	600	600	600	600	600	600	Administered after all other required tests/procedures. Refer to Section 8.11.6.
Eculizumab infusion (mg) 30 to < 40 kg		600	600	900	NA	900	900	900	900	900	900	Administered after all other required tests/procedures. Refer to Section 8.11.6.
Eculizumab infusion (mg) ≥ 40 kg		900	900	900	900	1200	1200	1200	1200	1200	1200	Administered after all other required tests/procedures. Refer to Section 8.11.6.

[a] An ED Visit and Safety Follow-up Phone Call are required for any participant who discontinues the study during the Treatment Period. Refer to Table 3 for assessments at the ED Visit and Safety Follow-up Phone Call.
[b] For adult participants (≥ 18 years of age), height will be collected only at Screening.
[c] Eligibility may be determined using results from test carried out as standard of care for the treatment of the current TMA prior to a participant giving informed consent/assent. In these cases, informed consent/assent will be provided prior to collecting the data for the study.
[d] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.
[e] Instruct the participant to carry safety card at all times and bring to scheduled visits.

[f] PK/PD baseline (B) and trough (T) samples are to be taken within 90 minutes before eculizumab infusion. Peak (P) samples are to be taken within 90 minutes after completion of eculizumab infusion.

[g] Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from the previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the criteria described in Section 8.11.6.

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; B = baseline; ECG = electrocardiogram; ED = early discontinuation from the study; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; NA = not applicable; NAb = neutralizing antibody; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; ST-HUS = Shiga toxin-related hemolytic uremic syndrome; T = trough; TMA = thrombotic microangiopathy

Table 3: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Study Period or Visit	Treatment Period								Notes
Study Day Visit Window (days)	113 ± 2	127 ± 2	141 ± 2	155 ± 2	169/ EOT ± 2	183/ EOS[a] ± 2	ED[b]	Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3	
End of Week	16	18	20	22	24	26			
General Assessments/Procedures									
Weight	X	X	X	X	X	X	X		Participants must be weighed prior to dosing as eculizumab dosing will be based on the weight assessment at each visit. Participant will not need to be weighed at each study visit if eculizumab is permanently discontinued.
Height[d]	X	X	X	X	X	X	X		
Pregnancy test[e]		X		X		X	X		Female participants of childbearing potential only (Section 8.2.5).
Safety and Efficacy Assessments									
Abbreviated physical examination	X	X		X		X	X		Refer to Section 8.2.1.
Vital signs	X	X	X	X	X	X	X		Refer to Section 8.2.2.
ECG						X	X		Refer to Section 8.2.3.
Chemistry	X	X		X		X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Dialysis requirement status	X	Continuous monitoring							Refer to Section 8.1.2.
Hematology including coagulation	X	X		X		X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Urinalysis and urine chemistry	X	X		X		X	X		Refer to Section 8.2.4.
Review safety card[f]	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Concomitant medications	Continuous monitoring						X	X	Refer to Section 8.11.5.
Adverse events	Continuous monitoring						X	X	Refer to Section 8.3.
PK/PD/ADA Assessments									

Table 3: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

Study Period or Visit	Treatment Period								Notes
Study Day Visit Window (days)	113 ± 2	127 ± 2	141 ± 2	155 ± 2	169/ EOT ± 2	183/ EOS[a] ± 2	ED[b]	Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3	
End of Week	**16**	**18**	**20**	**22**	**24**	**26**			
PK/PD sampling[g]			T/P			T	X		Refer to Section 8.5 and Section 8.6. PK/PD sample at an ED Visit may be collected at any time.
ADA/NAb blood sample						T	X		Refer to Section 8.9. ADA sample at an ED Visit may be collected at any time.
Administration of Study Intervention[h]									
Eculizumab infusion (mg) 20 to < 30 kg	600	600	600	600	600				Administered after all other required tests/procedures. Refer to Section 8.11.6.
Eculizumab infusion (mg) 30 to < 40 kg	900	900	900	900	900				Administered after all other required tests/procedures. Refer to Section 8.11.6.
Eculizumab infusion (mg) ≥ 40 kg	1200	1200	1200	1200	1200				Administered after all other required tests/procedures. Refer to Section 8.11.6.

Table 3: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg

[a] For weight cohorts ≥ 40 kg, 30 to < 40 kg, and 20 to < 30 kg, the Day 183 Visit will be the EOS Visit for participants who complete study treatment and who will receive continued access to eculizumab after the study. Refer to the Safety Follow-up Phone Call (footnote c) for participants who complete study treatment but who will not receive continued access to eculizumab after the study.

[b] An ED Visit is required at the time of withdrawal for any participant who discontinues the study during the Treatment Period. Also refer to the Safety Follow-up Phone Call (footnote c).

[c] The Safety Follow-up Phone Call is required for any participant who discontinues eculizumab early during the Treatment Period; the Safety Follow-up Phone Call will be the EOS Visit for participants who discontinue eculizumab early. The Safety Follow-up Phone Call is also required for any participant who has completed the Day 183 Visit but who will not receive continued access to eculizumab after the study; the Safety Follow-up Phone Call will be the EOS Visit for these participants. The Safety Follow-up Phone Call should occur 8 weeks after the last dose of eculizumab. Other means of verbal communication, such as videoconferencing, are acceptable for the Safety Follow-up Phone Call.

[d] For adult participants (≥ 18 years of age), height will be collected only at Screening.

[e] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

[f] Instruct the participant to carry safety card at all times and bring to scheduled visits.
[g] PK/PD Trough (T) samples are to be taken within 90 minutes before eculizumab infusion. Peak (P) samples are to be taken within 90 minutes after completion of eculizumab infusion.
[h] Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from the previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the criteria described in Section 8.11.6.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation from the study; EOS = end of study; EOT = end of treatment; NAb = neutralizing antibody; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; T = trough

Table 4: Schedule of Activities: Screening and Treatment Period, Weight Cohort 10 to < 20 kg

Study Period	**Screening**	**Treatment Period[a]**										**Notes**
Study Day **Visit Window (days)**	**-7 to -1**	**1**	**8** **± 1**	**22** **± 2**	**36** **± 2**	**50** **± 2**	**64** **± 2**	**78** **± 2**	**92** **± 2**	**106** **± 2**	**120** **± 2**	
End of Week	**-1**	**Day 1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	
General Assessments/Procedures												
Informed consent/assent	X											Refer to Section 8.11.1.
Inclusion/exclusion	X	X										Refer to Section 8.11.3.
Demographics	X											Refer to Section 8.11.2.
Medical and aHUS history	X											Refer to Section 8.11.4.
Prior medications	X											Refer to Section 8.11.5.
Weight	X	X	X	X	X	X	X	X	X	X	X	Participants must be weighed prior to dosing as eculizumab dosing will be based on the weight assessment at each visit. Participant will not need to be weighed at each study visit if eculizumab is permanently discontinued.
Height[b]	X	X	X	X	X	X	X	X	X	X	X	
Confirmation or administration of meningococcal vaccination	X											Participants must be vaccinated against meningococcal infection and revaccinated during the study if needed (Section 6.5.3).
Hib and *Streptococcus pneumoniae* vaccination	X											For pediatric participants only. Refer to Section 6.5.3.
HIV test	X											Test includes HIV-1 and HIV-2. Refer to Section 8.2.4.
Direct Coombs test[c]	X											Refer to Section 8.2.4.
ADAMTS13 test	X											Refer to Section 8.2.4.
ST-HUS test	X											Refer to Section 8.2.4.
Pregnancy test[d]	X	X		X		X		X		X		Female participants of childbearing potential only (Section 8.2.5).
Follicle-stimulating hormone	X											Postmenopausal females only (Section 8.2.4 and Section 10.4.1).
Safety and Efficacy Assessments												
Full physical examination	X											Refer to Section 8.2.1.
Abbreviated physical examination		X		X		X		X		X		Refer to Section 8.2.1.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.2
ECG	X											Refer to Section 8.2.3

Table 4: Schedule of Activities: Screening and Treatment Period, Weight Cohort 10 to < 20 kg

Study Period	**Screening**	**Treatment Period**[a]										**Notes**
Study Day **Visit Window (days)**	**-7 to -1**	**1**	**8** **± 1**	**22** **± 2**	**36** **± 2**	**50** **± 2**	**64** **± 2**	**78** **± 2**	**92** **± 2**	**106** **± 2**	**120** **± 2**	
End of Week	**-1**	**Day 1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	
Chemistry	X	X		X		X		X		X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Dialysis requirement status	Continuous monitoring											Refer to Section 8.1.2.
Hematology including coagulation	X	X		X		X		X		X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Urinalysis and urine chemistry	X	X		X		X		X		X		Refer to Section 8.2.4.
Participant Safety Card[e]		X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Concomitant medications		Continuous monitoring										Refer to Section 8.11.5.
Adverse events		Continuous monitoring										Refer to Section 8.3.
PK/PD/ADA Assessments												
PK/PD sampling[f]		B/P	T/P		T/P				T/P			Refer to Section 8.5 and Section 8.6.
ADA/NAb blood sample		B							T			Refer to Section 8.9.
Administration of Study Intervention[g]												
Eculizumab infusion (mg) 10 to < 20 kg		600	300	300	300	300	300	300	300	300	300	Administered after all other required tests/procedures. Refer to Section 8.11.6.

[a] An ED Visit and Safety Follow-up Phone Call are required for any participant who discontinues the study during the Treatment Period. Refer to Table 5 for assessments at the ED Visit and Safety Follow-up Phone Call.

[b] For adult participants (≥ 18 years of age), height will be collected only at Screening.

[c] Eligibility may be determined using results from test carried out as standard of care for the treatment of the current TMA prior to a participant giving informed consent/assent. In these cases, informed consent/assent will be provided prior to collecting the data for the study.

[d] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

[e] Instruct the participant to carry safety card at all times and bring to scheduled visits.

[f] PK/PD baseline (B) and trough (T) samples are to be taken within 90 minutes before eculizumab infusion. Peak (P) samples are to be taken within 90 minutes after completion of eculizumab infusion.

[g] Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from the previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the criteria described in Section 8.11.6.

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; B = baseline; ECG = electrocardiogram; ED = early discontinuation from the study; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; NAb = neutralizing antibody; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; ST-HUS = Shiga toxin-related hemolytic uremic syndrome; T = trough; TMA = thrombotic microangiopathy

Table 5: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohort 10 to < 20 kg

Study Period or Visit	**Treatment Period**							**Notes**
Study Day **Visit Window (days)**	**134** **± 2**	**148** **± 2**	**162** **± 2**	**176/ EOT** **± 2**	**190/ EOS[a]** **± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose)** ± 3	
End of Week	**19**	**21**	**23**	**25**	**27**			
General Assessments/Procedures								
Weight	X	X	X	X	X	X		Participants must be weighed prior to dosing as eculizumab dosing will be based on the weight assessment at each visit. Participant will not need to be weighed at each study visit if eculizumab is permanently discontinued.
Height[d]	X	X	X	X	X	X		
Pregnancy test[e]	X		X		X	X		Female participants of childbearing potential only (Section 8.2.5).
Safety and Efficacy Assessments								
Abbreviated physical examination	X		X		X	X		Refer to Section 8.2.1.
Vital signs	X	X	X	X	X	X		Refer to Section 8.2.2.
ECG					X	X		Refer to Section 8.2.3.
Chemistry	X		X		X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Dialysis requirement status	Continuous monitoring							Refer to Section 8.1.2.
Hematology including coagulation	X		X		X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Urinalysis and urine chemistry	X		X		X	X		Refer to Section 8.2.4.
Review safety card[f]	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Concomitant medications	Continuous monitoring					X	X	Refer to Section 8.11.5.
Adverse events	Continuous monitoring					X	X	Refer to Section 8.3.
PK/PD/ADA Assessments								

Table 5: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohort 10 to < 20 kg

Study Period or Visit	Treatment Period							Notes
Study Day **Visit Window (days)**	**134** **± 2**	**148** **± 2**	**162** **± 2**	**176/ EOT** **± 2**	**190/ EOS[a]** **± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose)** ± 3	
End of Week	**19**	**21**	**23**	**25**	**27**			
PK/PD sampling[g]		T/P		T		X		Refer to Section 8.5 and Section 8.6. PK/PD sample at an ED Visit may be collected at any time.
ADA/NAb blood sample				T		X		Refer to Section 8.9. ADA sample at an ED Visit may be collected at any time.
Administration of Study Intervention[h]								
Eculizumab infusion (mg) 10 to < 20 kg	300	300	300	300				Administered after all other required tests/procedures. Refer to Section 8.11.6.

[a] For weight cohort 10 to < 20 kg, the Day 190 Visit will be the EOS Visit for participants who complete study treatment and who will receive continued access to eculizumab after the study. Refer to the Safety Follow-up Phone Call (footnote c) for participants who complete study treatment but who will not receive continued access to eculizumab after the study.

[b] An ED Visit is required at the time of withdrawal for any participant who discontinues the study during the Treatment Period. Also refer to the Safety Follow-up Phone Call (footnote c).

[c] The Safety Follow-up Phone Call is required for any participant who discontinues eculizumab early during the Treatment Period; the Safety Follow-up Phone Call will be the EOS Visit for participants who discontinue eculizumab early. The Safety Follow-up Phone Call is also required for any participant who has completed the Day 190 Visit but who will not receive continued access to eculizumab after the study; the Safety Follow-up Phone Call will be the EOS Visit for these participants. The Safety Follow-up Phone Call should occur 8 weeks after the last dose of eculizumab. Other means of verbal communication, such as videoconferencing, are acceptable for the Safety Follow-up Phone Call.

[d] For adult participants (≥ 18 years of age), height will be collected only at Screening.

[e] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

Table 5: Schedule of Activities: Treatment Period (Continued) to End of Study, Weight Cohort 10 to < 20 kg

[f] Instruct the participant to carry safety card at all times and bring to scheduled visits.

[g] PK/PD Trough (T) samples are to be taken within 90 minutes before eculizumab infusion. Peak (P) samples are to be taken within 90 minutes after completion of eculizumab infusion.

[h] Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from the previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the criteria described in Section 8.11.6.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation from the study; EOS = end of study; EOT = end of treatment; NAb = neutralizing antibody; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; T = trough

Table 6: Schedule of Activities: Screening, Treatment Period, and End of Study, Weight Cohort 5 to < 10 kg

Study Period or Visit	**Screening**	**Treatment Period**													**Notes**
Study Day Visit Window (days)	**-7 to -1**	**1**	**8 ± 1**	**29 ± 2**	**50 ± 2**	**71 ± 2**	**92 ± 2**	**113 ± 2**	**134 ± 2**	**155 ± 2**	**176/ EOT ± 2**	**197/ EOS[a] ± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3**	
End of Week	**-1**	**Day 1**	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**			
General Assessments/Procedures															
Informed consent/assent	X														Refer to Section 8.11.1.
Inclusion/exclusion	X	X													Refer to Section 8.11.3.
Demographics	X														Refer to Section 8.11.2.
Medical and aHUS history	X														Refer to Section 8.11.4.
Prior medications	X														Refer to Section 8.11.5.
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		Participants must be weighed prior to dosing as eculizumab dosing will be based on the weight assessment at each visit. Participant will not need to be weighed at each study visit if eculizumab is permanently discontinued.
Height[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Confirmation or administration of meningococcal vaccination	X														Participants must be vaccinated against meningococcal infection and

Table 6: Schedule of Activities: Screening, Treatment Period, and End of Study, Weight Cohort 5 to < 10 kg

Study Period or Visit	**Screening**	**Treatment Period**													**Notes**
Study Day Visit Window (days)	**-7 to -1**	**1**	**8 ± 1**	**29 ± 2**	**50 ± 2**	**71 ± 2**	**92 ± 2**	**113 ± 2**	**134 ± 2**	**155 ± 2**	**176/ EOT ± 2**	**197/ EOS[a] ± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3**	
End of Week	**-1**	**Day 1**	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**			
															revaccinated during the study if needed (Section 6.5.3).
Hib and *Streptococcus pneumoniae* vaccination	X														For pediatric participants only. Refer to Section 6.5.3.
HIV test	X														Test includes HIV-1 and HIV-2. Refer to Section 8.2.4.
Direct Coombs test[e]	X														Refer to Section 8.2.4.
ADAMTS13 test	X														Refer to Section 8.2.4.
ST-HUS test	X														Refer to Section 8.2.4.
Pregnancy test[f]	X	X		X	X	X	X	X	X	X	X	X	X		Female participants of childbearing potential only (Section 8.2.5).
Follicle-stimulating hormone	X														Postmenopausal females only (Section 8.2.4 and Section 10.4.1).
Safety and Efficacy Assessments															
Full physical examination	X														Refer to Section 8.2.1.
Abbreviated physical examination		X	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.2.1.

Table 6: Schedule of Activities: Screening, Treatment Period, and End of Study, Weight Cohort 5 to < 10 kg

Study Period or Visit	**Screening**	**Treatment Period**													**Notes**
Study Day Visit Window (days)	**-7 to -1**	**1**	**8 ± 1**	**29 ± 2**	**50 ± 2**	**71 ± 2**	**92 ± 2**	**113 ± 2**	**134 ± 2**	**155 ± 2**	**176/ EOT ± 2**	**197/ EOS[a] ± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3**	
End of Week	**-1**	**Day 1**	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.2.2
ECG	X											X	X		Refer to Section 8.2.3
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line (Section 8.2.4).
Dialysis requirement status	Continuous monitoring														Refer to Section 8.1.2.
Hematology including coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X		Clinical laboratory measurements will be collected predose on dosing days and not from a heparinized line. Refer to Section 8.2.4.
Urinalysis and urine chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.2.4.
Participant Safety Card[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 8.2.6.
Concomitant medications		Continuous monitoring											X	X	Refer to Section 8.11.5.
Adverse events		Continuous monitoring											X	X	Refer to Section 8.3.
PK/PD/ADA Assessments															
PK/PD blood samples[h]		B/P				T/P				T/P			X		Refer to Section 8.5 and Section 8.6.

Table 6: Schedule of Activities: Screening, Treatment Period, and End of Study, Weight Cohort 5 to < 10 kg

Study Period or Visit	**Screening**	**Treatment Period**												**Notes**
Study Day Visit Window (days)	**-7 to -1**	**1**	**8 ± 1**	**29 ± 2**	**50 ± 2**	**71 ± 2**	**92 ± 2**	**113 ± 2**	**134 ± 2**	**155 ± 2**	**176/ EOT ± 2**	**197/ EOS[a] ± 2**	**ED[b]**	**Safety Follow-up Phone Call/EOS[c] (8 weeks after last dose) ± 3**	
End of Week	**-1**	**Day 1**	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**			
															PK/PD sample at an ED Visit may be collected at any time.
ADA/NAb blood sample		B								T			X		Refer to Section 8.9. ADA sample at an ED Visit may be collected at any time.
Administration of Study Intervention[i]															
Eculizumab infusion (mg)		300	300	300	300	300	300	300	300	300	300				Administered after all other required tests/procedures. Refer to Section 8.11.6.

[a] For weight cohort 5 to < 10 kg, the Day 197 Visit will be the EOS Visit for participants who complete study treatment and who will receive continued access to eculizumab after the study. Refer to the Safety Follow-up Phone Call (footnote c) for participants who complete study treatment but who will not receive continued access to eculizumab after the study.

[b] An ED Visit is required at the time of withdrawal for any participant who discontinues the study during the Treatment Period. Also refer to the Safety Follow-up Phone Call (footnote c).

[c] The Safety Follow-up Phone Call is required for any participant who discontinues eculizumab early during the Treatment Period; the Safety Follow-up Phone Call will be the EOS Visit for participants who discontinue eculizumab early. The Safety Follow-up Phone Call is also required for any participant who has completed the Day 197 Visit but who will not receive continued access to eculizumab after study participation; the Safety Follow-up Phone Call will be the EOS Visit for these participants. The Safety Follow-up Phone Call should occur 8 weeks after the last dose of eculizumab. Other means of verbal communication, such as videoconferencing, are acceptable for the Safety Follow-up Phone Call.

[d] For adult participants (≥ 18 years of age), height will be collected only at Screening.

Table 6: Schedule of Activities: Screening, Treatment Period, and End of Study, Weight Cohort 5 to < 10 kg

[e] Eligibility may be determined using results from test carried out as standard of care for the treatment of the current TMA prior to a participant giving informed consent/assent. In these cases, informed consent/assent will be provided prior to collecting the data for the study.

[f] For female participants of childbearing potential, a serum pregnancy test should be performed at Screening and the last study visit, and at other timepoints as determined by the Investigator. A urine pregnancy test should be performed at all other timepoints.

[g] Instruct the participant to carry the safety card at all times and bring to scheduled visits.

[h] PK/PD baseline (B) and trough (T) samples are to be taken within 90 minutes before eculizumab infusion. Peak (P) samples are to be taken within 90 minutes after completion of eculizumab infusion.

[i] Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from the previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the criteria described in Section 8.11.6.

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; B = baseline; ECG = electrocardiogram; ED = early discontinuation from the study; EOS = end of study; EOT = end of treatment; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; NAb = neutralizing antibody; P = peak; PD = pharmacodynamics; PK = pharmacokinetics; ST-HUS = Shiga toxin-related hemolytic uremic syndrome; T = trough; TMA = thrombotic microangiopathy

2. INTRODUCTION

2.1. Study Rationale

Eculizumab has been approved in China for the treatment of aHUS in children and adult patients. The therapeutic efficacy and safety of eculizumab has been demonstrated in 3 global pivotal clinical trials conducted at study sites outside of China for registration and has since been supported by subsequent postmarketing evidence (Socié, 2019). This postapproval study, agreed as a condition of approval in China, will be conducted in Chinese participants with aHUS being treated in China.

In addition to safety and efficacy evaluation, the study is intended to characterize the population pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity of eculizumab in this patient population. Drug safety information will be collected continuously to support the safety profile.

2.2. Background

aHUS is TMA most often caused by mutations in genes encoding proteins involved in the alternative pathway of complement (APC) or by autoantibodies against APC regulatory proteins (Noris, 2010), although pathologic gene mutations or autoantibodies are only identified in at most 50% to 60% of patients (Fakhouri, 2017; Schaefer, 2018). Patients with aHUS are at risk for life-threatening manifestations of disease resulting from endothelial damage, including thrombocytopenia, intravascular hemolysis, acute renal failure, and extrarenal tissue damage. Importantly, approximately 20% of patients experience extrarenal manifestations of disease, including central nervous system, cardiac, gastrointestinal, distal extremity, and severe systemic organ involvement (Brodsky, 2015; Loirat, 2011).

aHUS is a rare and life-threatening disease with an annual incidence in the United States and European Union of 1 to 2 cases per million (Constantinescu, 2004; Salvadori, 2013).

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

Eculizumab is a humanized mAb that specifically binds to C5 and is the standard of care treatment for aHUS. Before the availability of eculizumab, mortality rates among patients with aHUS were as high as 15% during the acute progressing phase of the disease (Noris, 2010; Sellier-Leclerc, 2007). Up to 50% of patients progressed to end-stage kidney disease (ESKD), often within a year of disease onset, and required dialysis or kidney transplant to sustain life.

Eculizumab has no known off-target interactions with other proteins in vitro or in vivo. In addition, eculizumab is predicted to be effectorless, having no detectable binding to complement C1q or most Fcγ receptors (FcγR I, IIb/c IIIa, IIIb) and more than 10-fold weaker binding than an immunoglobulin G1 (IgG1) isotype to FcγR IIa. Upon binding to the complement protein C5,

eculizumab blocks cleavage to C5a and C5b by C5 convertase, which prevents generation of C5b-9. These attributes underlie the established safety and therapeutic efficacy profile of eculizumab as demonstrated in the clinical studies and supported by subsequent postmarketing experiences.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of eculizumab may be found in the Soliris Package Insert.

2.3.1. Risk Assessment

Table 7: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified Risks		
Meningococcal infection	The use of eculizumab is known to increase the patient's susceptibility to *Neisseria meningitidis* infection.	Participants must be vaccinated against all available serotypes of *N meningitidis* (A, C, Y, W135, and B if available). Prophylactic antibiotics will be required for participants (if initiated on eculizumab less than 2 weeks after the start of vaccination series). Each participant will be provided with a Participant Safety Card with signs and symptoms of meningococcal infection, instructions on when to contact a healthcare provider, and relevant contact information. The Participant Safety Card will be reviewed at each visit (Schedule of Activities, Section 1.3).
Other infections	Children treated with eculizumab may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).	Participants < 18 years of age must also be vaccinated against Hib and *S pneumoniae* according to national and local vaccination schedule guidelines, prior to, or at the time of, receiving the first dose of eculizumab.
Infusion-related reaction	As with all therapeutic proteins, administration of eculizumab may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. Most infusion reactions that occurred in patients receiving eculizumab were nonserious and did not required discontinuation of eculizumab.	Participants with known hypersensitivity to eculizumab, murine proteins, or to any of the excipients will be excluded. Treatment with eculizumab will be discontinued in participants who experience serious hypersensitivity reactions (see Section 7).
Potential Risks		
Immunogenicity	Therapeutic proteins, including humanized monoclonal antibodies like eculizumab, may be associated with immunogenicity responses. Infrequent antibody responses have	Presence of antidrug antibodies will be assessed. Blood samples will be collected to test for presence and titer of antidrug antibodies to eculizumab in serum prior to study intervention

Table 7: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	been detected in eculizumab-treated patients across all clinical studies. In paroxysmal nocturnal hemoglobinuria placebo-controlled studies, low antibody responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).	administration as indicated in the Schedule of Activities (Section 1.3).

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this original protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19 (see Section 10.5).

2.3.2. Benefit Assessment

Eculizumab is a recombinant, humanized mAb that binds to complement protein C5 and delivers rapid, sustained, and specific inhibition of C5 activation and the terminal complement cascade. Eculizumab has been shown to be an effective therapy for the treatment of aHUS.

Five single-arm studies (4 prospective studies: C08-002A/B [NCT00844545 and NCT00844844], C08-003A/B [NCT00838513 and NCT00844428], C10-003 [NCT01193348], and C10-004 [NCT01194973] and 1 retrospective study C09-001r [NCT01770951]) evaluated the safety and efficacy of eculizumab for the treatment of aHUS. Reduction in terminal complement activity was observed after commencement of eculizumab. Eculizumab reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline.

2.3.3. Overall Benefit: Risk Conclusion

Eculizumab has a cumulative patient-year exposure of 62341 at the time of this original protocol and has been well tolerated. Considering the measures taken to minimize risk to participants who will take part in this study, the potential risks identified in association with eculizumab are balanced by the anticipated benefits that may be afforded to participants with aHUS. In addition, eculizumab remains the standard of care for aHUS.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Mapping of objectives to estimands and endpoints is provided in Table 8.

Table 8: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
Primary	
To assess the efficacy of eculizumab in the treatment of participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Complete TMA Response during the 26-week Treatment Period (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All participants who meet response criteria after ICE1 or ICE2 will be considered as nonresponders thereafter. • Summary measure: The proportion of complete TMA responders overall along with 95% CIs.
Secondary	
To characterize the safety and tolerability of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Incidence of TEAEs and SAEs (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention; o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be included. • Summary measure: Number and percentage of participants with TEAEs and SAEs and number of events by System Organ Class and Preferred Term.
To characterize the pharmacokinetics of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Serum eculizumab concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean serum eculizumab concentrations at all scheduled visits.

Table 8: Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
To characterize the pharmacodynamics of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: Changes in serum free and total C5 concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean changes in serum free and total C5 concentrations at all scheduled visits.
To characterize the immunogenicity of eculizumab in participants with aHUS	• Population: Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. • Variable: ADA response category (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Proportion of ADA positive participants.
Additional Secondary	
To evaluate the efficacy of eculizumab and characterize TMA by additional measures	• Time to Complete TMA Response • Dialysis requirement status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) at all scheduled visits • Chronic kidney disease (CKD) stage classified as improved, stable (no change), or worsened at all scheduled visits compared to baseline • Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin) at all scheduled visits • Increase in hemoglobin of ≥ 20 g/L from baseline through Week 26
To characterize the safety profile of eculizumab by additional safety measures	• Changes from baseline in vital signs and laboratory parameters at scheduled visits

Abbreviations: ADA = antidrug antibody; aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; CI = confidence interval; ICE = intercurrent event; LDH = lactate dehydrogenase; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMA = thrombotic microangiopathy

3.1. Primary Estimand

The primary objective of the study is to assess the efficacy of eculizumab in the treatment of participants with aHUS in China.

The estimand corresponding to the primary objective is defined as follows:

The proportion of participants with Complete TMA Response during the 26-week Treatment Period without premature discontinuation of study intervention or the initiation of disallowed therapy or medicine (composite strategy for intercurrent events). Population for this analysis includes Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria.

3.2. Secondary Estimands

Secondary objectives of the study are to characterize the safety and tolerability of eculizumab, PK and PD of eculizumab, and immunogenicity of eculizumab in participants with aHUS in China during the 26-week Treatment Period.

The estimands corresponding to these secondary objectives are as follows. Populations for analysis are Chinese participants with aHUS who are eligible to be enrolled in the study, based on the inclusion and exclusion criteria. Treatment policy will be applied for the predefined intercurrent events, where all data collected will be used in the analyses as if there is no occurrence of any intercurrent event.

- Number and percentage of participants in the Safety Set with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) and number of events.
- Mean serum eculizumab concentrations at all scheduled visits.
- Mean changes in serum free and total C5 concentrations at all scheduled visits.
- Proportion of antidrug antibody (ADA) positive participants.

Additional secondary objectives are presented in Table 8. For the definition of estimands, the population will be the same as in the primary objective (variables are presented in Table 8); the handling of intercurrent events for main analyses will apply treatment policy strategy, and the summary measures and all the other details will be provided in the Statistical Analysis Plan (SAP).

3.3. Tertiary/Exploratory Estimands

Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3b, open-label, single-arm, multicenter study to evaluate the efficacy and safety of eculizumab in participants with aHUS in China. The study will be conducted in participants of any age who weigh ≥ 5 kg and who previously have not been treated with complement inhibitors. Up to 25 eligible participants in China will be enrolled.

The study consists of an up to 7-day Screening Period and a 26-week Treatment Period. An 8-week Safety Follow-up Phone Call will be required only for participants who discontinue eculizumab treatment during the study or for participants who will not receive continued access to eculizumab after completing study treatment. The study schematic is provided in Section 1.2.

After providing informed consent/assent, participants will be screened for eligibility for the study during the 7-day Screening Period. If all inclusion criteria and none of the exclusion criteria are met, participants will be enrolled and vaccinated against *N meningitidis* if not already vaccinated within the period of active coverage specified by the vaccine manufacturer. Participants who are vaccinated less than 2 weeks prior to receiving the first dose of eculizumab will receive treatment with appropriate prophylactic antibiotics until 2 weeks after the vaccination.

During the 26-week Treatment Period, participants will receive eculizumab by IV administration based on body weight cohorts presented in Table 12.

Participants who discontinue eculizumab treatment at any time during the study will have an ED Visit at the time of discontinuation from the study and a Safety Follow-up Phone Call 8 weeks after the last dose of eculizumab.

Participants who will not receive continued access to eculizumab after completing the EOS Visit will also have a Safety Follow-up Phone Call 8 weeks after the last dose of eculizumab.

Participants who complete study treatment and will receive continued access to eculizumab after the study (see Section 6.7) will not have an 8-week Safety Follow-up Phone Call.

Clinical measures and laboratory tests will be performed to assess safety, clinical, and biochemical parameters associated with aHUS.

4.2. Scientific Rationale for Study Design

This postapproval study has been designed to assess the efficacy and safety of eculizumab in pediatric and adult participants with aHUS in China. Eculizumab is currently the standard of care for aHUS. The safety and effectiveness of eculizumab for the treatment of aHUS have been established in pediatric patients.

Based on past human experience and cumulative clinical study safety data of eculizumab in paroxysmal nocturnal hemoglobinuria, aHUS, myasthenia gravis, and neuromuscular optica syndrome, eculizumab has been shown to be well tolerated and safe, and exposure to eculizumab in humans has not raised any unexpected safety concerns. The use of eculizumab in pediatric patients for this indication is supported by evidence from 4 adequate and well-controlled clinical studies assessing the safety and effectiveness of eculizumab for the treatment of aHUS. The

assessments included in this protocol are consistent with those used in other studies with eculizumab.

4.3. Justification for Dose

The weight-based dosages of eculizumab in this study (Section 6.1) are based on label recommendations (Soliris Package Insert) and have been well established in global pivotal Phase 3 studies. The selection of the eculizumab dose regimen for patients with aHUS is based on targeting immediate, complete, and sustained inhibition of terminal complement in patients with aHUS.

4.4. End of Study Definition

Participants who will receive continued access to eculizumab after completing study treatment:

- A participant is considered to have completed the study if the participant completes the last scheduled procedure in their last recorded weight cohort as shown in the Schedule of Activities (SoA; Section 1.3).

Participants who will NOT receive continued access to eculizumab after completing study treatment:

- A participant is considered to have completed the study if the participant completes the last scheduled procedure in their last recorded weight cohort and completes the Safety Follow-up Phone Call shown in the SoA (Section 1.3).

A participant is considered to have terminated early from the study if the participant is discontinued from the study after enrollment (defined as completion of the informed consent/assent process and satisfying inclusion/exclusion criteria) and prior to completing the study, as specified above. A participant who terminates the study during the Treatment Period will complete the ED Visit and the Safety Follow-up Phone Call as shown in the SoA (Section 1.3).

The end of the study is defined as the date the last participant completes the last visit (including follow-up) 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

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants of any age.

Type of Patient and Disease Characteristics

2. Complement treatment naïve with evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:
   a. Platelet count < 150000/μL during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
   b. Lactate dehydrogenase (LDH) ≥ 1.5 × upper limit of normal (ULN) during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin ≤ lower limit of normal (LLN) for age and gender during the Screening Period or ≤ 28 days prior to the start of the Screening Period, **and**
   c. Serum creatinine level ≥ ULN in adults (≥ 18 years of age), or ≥ 97.5th percentile for age (Section 8.11.3) at Screening in children (< 18 years of age) (participants who require dialysis for < 3 months are also eligible)

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

3. Among participants with a kidney transplant:
   a. Known history of aHUS prior to current kidney transplant, **or**
   b. If no known history of aHUS, persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (eg, suspending or reducing the dose) of calcineurin inhibitor (CNI; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor (mTORi; eg, sirolimus, everolimus)
4. Among participants with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.

5. To reduce the risk of meningococcal infection (*N meningitidis*), all participants must be vaccinated against *N meningitidis* if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer. Participants must be vaccinated at least 14 days prior to receiving the first dose of eculizumab or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination (Refer to Section 6.5.3).
6. Participants < 18 years of age must have been vaccinated against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* according to local vaccination schedule guidelines.
7. In participants receiving treatment with medications known to cause TMA, persistent evidence of TMA at least 4 days after modifying the excluded medication (eg, gemcitabine, CNI [eg, cyclosporine, tacrolimus], or mTORi [eg, sirolimus, everolimus]).

Weight

8. Body weight ≥ 5 kg.

Sex

9. Male and/or female.
10. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance as described in Section 10.4.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. Known familial or acquired ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency (activity < 5%). (Note: Participants with pending ADAMTS13 test results who meet all other criteria may be enrolled and allowed to receive the Day 1 dose. If results return positive for activity < 5%, the participant will be withdrawn [Section 7.2]).
2. Shiga toxin-related hemolytic uremic syndrome (ST-HUS) as demonstrated by local guidelines. (Note: Participants with pending ST-HUS test results who meet all other criteria may be enrolled and allowed to receive the Day 1 dose. If results return positive, the participant will be withdrawn [Section 7.2]).
3. Positive direct Coombs test which, in the judgment of the Investigator, is indicative of a clinically significant immune-mediated hemolysis not due to aHUS.
4. Known human immunodeficiency virus (HIV) infection.
5. Unresolved meningococcal disease.

6. Confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics.
7. Presence or suspicion of active and untreated systemic infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.
8. Heart, lung, small bowel, pancreas, or liver transplant.
9. Among participants with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection according to Banff 2013 criteria.
10. Among participants without a kidney transplant, history of kidney disease other than aHUS, such as:
    a. Known kidney biopsy finding suggestive of underlying disease other than aHUS
    b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg, small kidneys for age)
    c. Known family history and/or genetic diagnosis of noncomplement-mediated genetic renal disease (eg, focal segmental glomerulosclerosis)
11. Identified drug exposure-related HUS.
12. History of malignancy within 5 years of Screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. Bone marrow transplant/hematopoietic stem cell transplant within 6 months prior to the start of Screening.
14. HUS related to vitamin B12 deficiency.
15. HUS related to known genetic defects of cobalamin C metabolism.
16. Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome.
17. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD for >3 months).
18. Prior use of eculizumab or other complement inhibitors.
19. Use of tranexamic acid within 7 days prior to the start of Screening.

Prior/Concomitant Therapy

20. Other immunosuppressive therapies such as acute steroids (within 28 days prior to the start of Screening), chronic steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless:
    a. Part of an established post-transplant antirejection regimen, **or**
    b. Participant has confirmed anticomplement factor antibodies requiring immunosuppressive therapy, **or**
    c. Steroids are being used for a condition other than aHUS (eg, asthma), **or**

d. Participant is experiencing an acute aHUS relapse immediately after transplant (see Section 6.5.1)

21. Receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening; or single dose of rituximab within 7 days prior to the start of Screening.
22. Received vasopressors or inotropes within 7 days prior to Screening.
23. Previously or currently treated with a complement inhibitor.

Prior/Concurrent Clinical Study Experience

24. Has participated in another interventional treatment study or used any experimental therapy within 30 days before initiation of study intervention on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater.

Diagnostic Assessments

25. Female participants who have a positive pregnancy test at Screening or Day 1.

Other Exclusions

26. Hypersensitivity to any excipient in eculizumab, including hypersensitivity to murine proteins.
27. Pregnant, breastfeeding, or intending to conceive during the course of the study.
28. Any medical or psychological condition that, in the opinion of the Investigator, could increase the risk to the participant by participating in the study or confound the outcome of the study.

Laboratory results for Exclusion Criterion 1 and/or Exclusion Criterion 2 may not be available prior to first dose. Later results for Exclusion Criterion 1 and/or Exclusion Criterion 2 could lead to discontinuation of study intervention and replacement of the participant (refer to Section 7.1 for study intervention discontinuation and replacement details).

5.3. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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.

Individuals who do not meet the criteria for participation in this study (eg, screen failure) due to a reason that is expected to resolve or has resolved may be rescreened once after the reason for

screen fail has resolved or is expected to resolve prior to rescreening and after discussion and agreement between the Investigator and the Medical Monitor. Any abnormal laboratory parameter results outside of the reference range at Screening may be retested once within the Screening window at the Investigator's discretion and after discussing with Alexion's Medical Monitor for the purpose of 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.

6.1. Study Intervention Administered

In this study, participants will receive open-label eculizumab during the Treatment Period. Specific details of the study intervention are provided in Table 9.

Table 9: Study Intervention

Study Intervention Name	Eculizumab		
Type	Monoclonal antibody		
Dose Formulation	Sterile liquid		
Unit Dose Strength(s)	300 mg/30 mL (10 mg/mL) as a clear, colorless solution in a single-dose vial		
Dosage Level(s)	Dosing is based on body weight as follows:		
	Body weight	Induction	Maintenance
	≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Day 29; then 1200 mg every 2 weeks
	30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Day 15; then 900 mg every 2 weeks
	20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Day 15; then 600 mg every 2 weeks
	10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 2 weeks
	5 to < 10 kg	300 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 3 weeks
Route of Administration	Intravenous infusion		
Use	Experimental		
IMP and NIMP	IMP		
Sourcing	Provided centrally by Alexion or contracted manufacturing organization		
Packaging and Labeling	Eculizumab will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Eculizumab will be supplied in kits and labeled as required per country requirement.		

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product

6.1.1. Study Intervention(s) Packaging and Labeling

Study intervention will be labeled according to the country's regulatory requirements. At a minimum, the container will be labeled with:

- The protocol number
- Lot number/expiry date
- Alexion name and address
- Instructions for use and storage

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study intervention at the study site, the study intervention kits should be removed from the shipping container and immediately stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. The study intervention should not be frozen.

Prior to administration, the study intervention solution should be visually inspected for particulate matter and discoloration. The study intervention solution should be clear and colorless.

Infusions of study intervention should be prepared using aseptic technique.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention 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 Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
4. 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

This is an open-label study. All participants, site personnel, and Alexion staff will be unblinded to participant treatment.

6.4. Study Intervention Compliance

When participants are dosed at the investigational site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine 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 with any questions regarding concomitant or prior therapy.

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria (Section 5.2) and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the participant takes or undergoes within 28 days prior to the start of Screening until the first dose of study intervention, will be recorded in the participant's eCRF. In addition, history of meningococcal vaccination must be collected prior to first dose of study intervention.

All medications and therapies or procedures undertaken during the study will be recorded in the participant's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for aHUS. Concomitant medications will be recorded from the first infusion of study intervention through 8 weeks after the participant's last dose of study intervention. Any changes in concomitant medications also will be recorded in the participant's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the participant's standard of care during the study, or for the treatment of any AE, along with the allowed medications described below may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the participant's source document/medical chart and eCRF.

6.5.1. Allowed Medicine and Therapy

The following concomitant medications are allowed if the following conditions apply, and dose adjustments are not expected during the Treatment Period:

- Erythropoietin, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Immunosuppressants, if the participant has been receiving a stable dose for at least 8 weeks before Screening.
- Corticosteroids, if the participant has been receiving a stable dose for at least 4 weeks before Screening.
- Vitamin K antagonists (eg, warfarin), if the participant has had a stable international normalized ratio (INR) level (per Investigator's discretion) for at least 4 weeks before Screening.

- Iron supplements or folic acid, if the participant has been receiving a stable dose for at least 4 weeks before Screening.

Adjustments in the frequency or dose level in any of the above medications can be made if the Medical Monitor or Investigator deems it is in the best interest of the participant.

The following concomitant medications and therapy during the study are allowed under certain circumstances and restrictions:

- Other immunosuppressive therapies such as steroids, mTOR inhibitors, or tacrolimus are allowed under the following circumstances ONLY IF:
  - Part of an established post-transplant antirejection regime and dose of such medications must have been unchanged for at least 4 weeks prior to screening, or
  - Participant has confirmed anticomplement factor antibodies requiring immunosuppressive therapy and dose of such medications must have been unchanged for at least 4 weeks prior to Screening
  - Steroids are being used for a condition other than aHUS (eg, asthma)
  - Participant is experiencing an acute aHUS relapse immediately after transplant. In addition, a stable dose of these medications must be maintained during the Treatment Period unless there is a discussion and agreement between the Investigator and Alexion.

The Medical Monitor should be contacted with any questions regarding concomitant or prior therapy.

6.5.2. Disallowed Medicine and Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 terminal half-lives (whichever is longer) before the start of study intervention until completion of the Safety Follow-up Phone Call, unless, in the opinion of the Investigator and Alexion, the medication will not interfere with the study.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

Participants are prohibited from receiving any of the following medications and procedures at any time after the first dose of study intervention (including participants who discontinue eculizumab treatment but remain in study) until completion of the study or early termination of the participant from the study:

- Use of any other investigational drug or device as part of a clinical study
- Use of any other complement inhibitor
- IVIg (unless for an unrelated medical need, eg, hypogammaglobinemia)
- Rituximab
- Plasma exchange/plasma infusion

- Traditional Chinese herbal preparations that in the opinion of the Investigator or Alexion might confound the assessment of the participant

A participant who receives the above prohibited medications and/or procedures after the first dose of study intervention will be withdrawn from the study.

6.5.3. Vaccination

As with any terminal complement antagonist, the use of eculizumab increases a participant's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all participants must be vaccinated against meningococcal infection if not already vaccinated within the period of active coverage specified by the vaccine manufacturer.

- Participants who initiate study intervention less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
- Participants must be administrated prophylactic antibiotics for prevention of meningococcal infection, if study intervention administration occurs before the vaccination administration.
- Participants who permanently discontinue study intervention before vaccination against meningococcal infection must be administered prophylactic antibiotics for at least 8 weeks or be vaccinated against meningococcal infection.
- Participants must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).
- Vaccines against serotypes A, C, Y, W135 are required, plus B where available, to prevent common pathogenic meningococcal serotypes.
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given per official guidance and local practice on the appropriate use of antibacterial agents.
- All participants should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

Pediatric participants (< 18 years of age) are required to be vaccinated against Hib and *S pneumoniae* according to local vaccination schedule guidelines.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the participants during the course of the study, participants will be provided a safety card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at specific timepoints as part of the review of the safety card and throughout the study as described in the SoA (Section 1.3).

6.6. Dose Modification

Dose modification is not permitted.

6.7. Intervention After the End of the Study

Participants who complete the study and show clinical benefit will be offered continued access to eculizumab as permitted by regulations until eculizumab is commercially available.

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 permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for all assessments at the scheduled visits described in the SoA (Section 1.3).

If study intervention is permanently discontinued and the participant remains in the study, the participant should have the Safety Follow-up Phone Call 8 weeks after the last dose of study intervention.

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

- Serious hypersensitivity reaction
- Pregnancy or planned pregnancy (Section 10.4.3)
- Severe uncontrolled infection
- Use of disallowed medication (defined in Section 6.5.2)
- Alexion or Investigator deems it necessary for the participant

7.1.1. Temporary Discontinuation

In the event of a need for temporary discontinuation, the Investigator is encouraged to discuss the circumstances with the Medical Monitor in all cases. Temporary or permanent discontinuation of study intervention should be considered in the case of moderate to severe infections. For permanent discontinuation, refer to Section 7.1.

7.2. 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 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 activity is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an ED Visit should be conducted, as shown in the SoA (Section 1.3). Additionally, participants should have the 8-week Safety Follow-up Phone Call. 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 intervention and from the study at that time.
  - If it is determined at any point that a participant's Screening data do not satisfy ADAMTS13 negative testing (< 5% activity, Exclusion Criterion 1) or Shiga toxin negative testing (Exclusion Criterion 2) after receiving at least 1 dose of study intervention, the participant will be discontinued from the study and may be replaced. ED procedures described in the SoA (Section 1.3) will be performed, if possible, on participants who are terminated early from the study, and AEs will be collected through the 8-week Safety Follow-up Phone Call (Section 1.3).

- The 8-week Safety Follow-up Phone Call will not be required if a participant withdraws consent.
- 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, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 to reschedule the missed visit as soon as possible, 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, 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 lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

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 study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 informed consent/assent form 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 (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests.
- Repeat or unscheduled samples may be obtained for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Laboratory Assessments for Efficacy Estimands/Endpoints

Laboratory assessments (platelets, LDH, and estimated glomerular filtration rate [eGFR]) to determine Complete TMA Response, hematologic response, and renal response will be performed according to the SoA (Section 1.3) and will be assessed based on the predetermined criteria for Complete TMA Response as defined below.

The primary efficacy endpoint is Complete TMA Response during the 26-week Treatment Period. The criteria for Complete TMA Response are the following:

1. Normalization of platelet count (defined as platelet count ≥ 150000/μL)
2. Normalization of LDH (defined as LDH ≤ ULN)
3. ≥ 25% improvement in serum creatinine from baseline

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

8.1.2. Kidney Function Parameters

eGFR will be calculated from serum creatinine. The eGFR calculation will be based on the Modification of Diet in Renal Disease (MDRD) formula according to demographics.

Proteinuria will be determined from the urine protein to creatinine ratio on a spot urine test at select target days as specified in the SoA (Section 1.3).

Dialysis requirement status will be collected prior to Screening, during Screening, and during the Treatment Period as specified in the SoA (Section 1.3).

8.1.3. Other Disease-related Laboratory Parameters

Blood and urine samples will be collected at the times indicated in the SoA (Section 1.3).

The response of increase in hemoglobin of ≥ 20 g/L from baseline through Week 26 is defined as follows:

Participants must meet the criteria of increase in hemoglobin of ≥ 20 g/L from baseline at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, to be classified as having achieved the response.

Chronic kidney disease (CKD) stage classification (Table 10) will include improved (excluding participants with Stage 1 at baseline as they cannot improve), worsened (excluding participants with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 will be considered the worst category, while Stage 1 will be considered the best category.

Table 10: Estimated Glomerular Filtration Rate Category/Stage in Chronic Kidney Disease

eGFR Category/Stage	eGFR (mL/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60 - 89	Mildly decreased[a]
G3a	45 - 59	Mildly to moderately decreased
G3b	30 – 44	Moderately to severely decreased
G4	15 – 29	Severely decreased
G5	< 15	Kidney failure

Note: In the absence of evidence of kidney damage, neither eGFR category/stage G1 nor G2 fulfill the criteria for CKD.
[a] Relative to the adult level.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate
Source: Levin, 2013

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal system. Height and weight will also be measured and recorded.
- An abbreviated physical examination will include a body-system relevant examination based on Investigator judgment and participant symptoms.

- Height will be measured recorded at Screening for all participants. Weight will be measured and recorded at every visit for all participants. Weight must be recorded prior to dosing at every study visit. Weight will not need to be measured at each study visit if eculizumab is permanently discontinued.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body temperature (°C or °F), pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed.
- Blood pressure and pulse measurements will be assessed seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- On dosing days, vital sign measurements will be taken before study intervention administration.

8.2.3. Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be conducted as outlined in the SoA (Section 1.3) to obtain heart rate, PR, QRS, QT, and QTc intervals.
- Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and to determine the clinical significance of the results. These assessments will be indicated on the eCRF. For any clinically significant abnormal ECG results, the Investigator must contact the Medical Monitor to discuss the participant's continued eligibility to participate in this study.

8.2.4. Clinical Safety Laboratory Assessments

- 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 or within 8 weeks after the final dose of study intervention 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 collected in accordance with the Laboratory Manual and the SoA (Section 1.3).
- Laboratory assessments performed at the institution's local laboratory that require a change in participant management or are considered clinically significant by the Investigator must be recorded in the AE or SAE eCRF. When possible, parameter value outside of the reference range should be entered in a free-text field.

8.2.5. Pregnancy

- Pregnancy data from female participants of childbearing potential and female spouses/partners of male participants will be collected from the first dose of study intervention through 5 months after the final dose of study intervention. Any female participant who becomes pregnant during the study should be considered for discontinuation from the study intervention and withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.3.

8.2.6. Participant Safety Card

Before the first dose of study intervention, a Participant Safety Card will be provided to participants to carry with them at all times until 3 months after the final dose of study intervention. The card is provided to increase participant awareness of the risk of meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform participants on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card.

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 informed consent form (ICF) at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion 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 nonleading 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 7.3). 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 toward 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)/Independent Ethics Committees (IECs), and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required.
- 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 Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Adverse Events of Special Interest (AESI)

Meningococcal infections are considered to be AESIs.

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.

Alexion does not recommend specific treatment for an 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/Treating Physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a plasma sample for PK 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

- Serum samples will be collected for measurement of concentrations of eculizumab as specified in the SoA (Section 1.3).
- 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. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected at any time that day.
- Samples will be used to evaluate the PK of eculizumab. PK samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Full details of the analytical method used will be described in a separate bioanalytical report.

8.6. Pharmacodynamics

- Serum samples will be collected for measurement of C5 as specified in the SoA (Section 1.3).

- 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 eculizumab. PD samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Full details of the analytical method used will be described in a separate bioanalytical report.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Serum samples for ADA and neutralizing antibody analysis will be collected at timepoints according to SoA (Section 1.3). All efforts will be made to obtain the immunogenicity samples at the exact nominal time relative to dosing. Out-of-window protocol deviation capture for immunogenicity samples follows that specified for PK sample collection (Section 8.5).

8.9.1. ADA Variables

ADA variables include ADA response category incidence and titer over the duration of the study as follows. ADA response category definitions and titer thresholds will be provided in the SAP.

ADA response categories

- ADA negative
- ADA positive

Participants that are ADA positive will be categorized as follows:

- Pre-existing immunoreactivity
- Treatment-emergent ADA responses
  - Persistent treatment-emergent responses
  - Transient treatment-emergent responses
  - Indeterminate treatment-emergent responses
- Treatment-boosted ADA responses
- Neutralizing antibody positive

8.10. Health Economics Data and/or Medical Resource Utilization

Medical resource utilization and/or health economics data will not be collected during this study.

8.11. Other Assessments and Procedures

8.11.1. Informed Consent

The Investigator or qualified designee must obtain signed and dated informed consent and assent, where applicable, from each participant or legally authorized representative prior to conducting any study procedures. All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.

8.11.2. Demographics

A review of demographic parameters, including age, gender, race, and ethnicity will be performed.

8.11.3. Inclusion and Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the participant qualifies for study participation.

The 97.5th percentile serum creatinine reference intervals by age are presented in Table 11.

Table 11: 97.5th Percentile Serum Creatinine Reference Intervals

Age (Gender) Group	97.5th Percentile Value (mg/dL)	97.5th Percentile Value (µmol/L)
2 months to < 1 year of age	0.39	34
1 to < 3 years of age	0.35	31
3 to < 5 years of age	0.42	37
5 to < 7 years of age	0.48	42
7 to < 9 years of age	0.55	48
9 to < 11 years of age	0.64	57
11 to < 13 years of age	0.71	63
13 to < 15 years of ag	0.81	72
15 to adult (males)	1.18	104
15 to adult (females)	1.02	90

Source: Adapted from Ceriotti, 2008

8.11.4. Medical History and aHUS History

The participant's aHUS medical history, including onset of first aHUS symptom, date of diagnosis, and emergency room visits, will be documented at the Screening Visit. The participant's medical history, including prior and concomitant conditions/disorders, will be recorded at the Screening Visit. Medication use (prescription or over-the-counter, including vitamins and/or herbal supplements) within 28 days prior to the start of Screening will also be recorded. Participants must be complement inhibitor treatment naïve to enroll in the study.

8.11.5. Prior and Concomitant Medications Review

8.11.5.1. Prior Medications

Prior medications (including vitamins, herbal preparations, and those discussed in the exclusion criteria [Section 5.2]), vaccines, and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) that the participant takes or undergoes within 28 days before the start of Screening or during the Screening Period before the first dose of eculizumab, as well as any meningococcal vaccine administered, will be recorded in the participant's eCRF. Additionally, all medications or therapies ever used for treatment of aHUS before the first dose of eculizumab must be collected.

8.11.5.2. Concomitant Medications

Use of concomitant medications and nondrug therapies (Section 6.5) will be evaluated during the study. At each visit (specified in the SoA [Section 1.3]), participants should be questioned about any new medication or nondrug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and nondrug therapies should be recorded in the source documents and the participant's eCRF.

8.11.6. Study Intervention Administration

This section describes the dosage regimen of study intervention. At the scheduled dosing visits (Section 1.3), study intervention administration should be performed after all other tests and procedures have been completed, excluding the postdose blood sampling for PK and serum free C5.

Based on the result of weight assessment prior to dosing, a participant may be attributed to a different weight cohort from previous visit due to weight gain or weight loss. The schedule of activities from this point on will follow the below criteria:

1. If the current visit is a scheduled visit for both the updated and previous weight cohorts, then all the activities to be performed at this visit should follow the plan for the updated weight cohort (the criteria for hematology and clinical chemistry can be overruled by bullet #3 mentioned below). For all future visits, the schedule should be based on the updated weight cohort unless further change of weight cohort occurs.
2. If the current visit is NOT a scheduled visit for the updated weight cohort (eg, a participant in the 5 to < 10 kg cohort has a scheduled visit at Day 71/Week 10 and is weighed above 10 kg at the visit, then under the new weight cohort of 10 to < 20 kg, Day 71/Week 10 is NOT a scheduled visit), then the activities to be performed at this visit should follow the plan of the most recent past scheduled visit under the updated weight cohort (eg, the participant mentioned above is now in the 10 to < 20 kg cohort, and at Day 71/Week 10, this participant will follow the scheduled activity of Day 64/Week 9), (the criteria for hematology and clinical chemistry can be overruled by bullet #3 mentioned below). For all future visits, the schedule should be based on the updated weight cohort unless further change of weight cohort occurs.
3. Regardless of the schedule for the updated weight cohort (either current visit day/week is a scheduled visit or not), if under the previous weight cohort the participant is scheduled

to take any assessment related to efficacy (hematology and clinical chemistry) at the current visit, then these assessments will still be performed at the current visit (eg, a participant who is originally in the 5 to < 10 kg weight cohort comes for the Day 71/Week 10 visit and weighs 10 to < 20 kg, per the above criteria, this participant will follow the schedule of Day 64/Week 9, except that clinical chemistry and hematology will still be assessed). This criterion overrules the previous 2 criteria for efficacy assessments.

If eculizumab is permanently discontinued and the participant remains in the study, for the rest of the scheduled visits, the SoA will not need to be adjusted based on weight.

Refer to Section 6 for additional information about study intervention including preparation, handling, storage, and accountability. For detailed instructions, refer to the Pharmacy Manual.

Eculizumab is supplied for clinical studies as a sterile, preservative-free 10 mg/mL solution in single-use vials and designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion. **Eculizumab must NOT be administered as an IV push or bolus injection.**

Eculizumab will be administered by IV infusion according to body weight as presented in Table 12.

Table 12: Eculizumab Induction and Maintenance Dosing by Weight Cohort[a]

Body Weight	Induction	Maintenance
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Day 29; then 1200 mg every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Day 15; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Day 15; then 600 mg every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 2 weeks
5 to < 10 kg	300 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 3 weeks

[a] Participants will be weighed at each study visit as eculizumab dosing will be based on the weight assessment.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2. Sample Size Determination

Approximately 25 eligible participants will be enrolled. Based on the adult (Study C10-004) and pediatric (Study C10-003) studies, 65% of participants are expected to achieve Complete TMA Response. Twenty-five participants would yield a 95% confidence interval (CI) for the proportion of response with a half-width of approximately 20%.

9.3. Populations for Analyses

Efficacy analyses will be performed on the Full Analysis Set (FAS). Safety analyses will be performed on the Safety Set. PK analyses will be performed on the PK Analysis Set. The populations are defined in Table 13.

Table 13: Populations for Analyses

Population	Description
Full Analysis Set	All participants who receive at least 1 dose of study intervention and have at least 1 efficacy assessment post first dose.
Safety Set	All participants who receive at least 1 dose of study intervention.
Pharmacokinetic Analysis Set	All participants who receive at least 1 dose of study intervention and have evaluable pharmacokinetic data.
Pharmacodynamic Analysis Set	All participants who receive at least 1 dose of study intervention and have evaluable pharmacodynamic data.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate SAP before database lock and analysis, including procedures for accounting for missing data. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary or secondary objectives or the study conduct. Any other change to the data analysis methods described in the protocol or SAP, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data may be conducted as deemed appropriate.

All data collected will be presented using summary tables, figures, and data listings. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. Continuous variables will be summarized using descriptive statistics, including the number of observations, and mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and the percentage of participants. All summaries and statistical analysis will be stratified by age group (< 18 years and ≥ 18 years), if appropriate, and overall.

Analyses will be performed using the SAS® software version 9.4 or higher.

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Estimand(s) and Endpoint

The primary endpoint is Complete TMA Response during the 26-week Treatment Period.

The estimand corresponding to the analysis for this endpoint will consist of estimating the proportion of complete TMA responders in the FAS. This will be performed by calculating the point estimate and a 95% CI for the proportion of complete TMA responders in eculizumab-treated participants. The CI will be based on exact confidence limits using the Clopper-Pearson method. Complete TMA Response will also be analyzed by subgroups based on age (< 18 years and ≥ 18 years), if appropriate.

9.4.1.2. Analyses of Secondary Efficacy Estimand(s) and/or Endpoint(s)

9.4.1.2.1. Time to Complete TMA Response

For this endpoint, a Kaplan-Meier cumulative distribution curve will be generated along with a 2-sided 95% CI. The corresponding summary table will present the cumulative distribution function estimate, the number of participants at risk, the number of participants responding, and the number of participants censored at each postbaseline timepoint. The table will also present first quartile, median, and third quartile, along with corresponding 2-sided 95% CI of time to Complete TMA Response.

9.4.1.2.2. Increase in Hemoglobin

The response of increase in hemoglobin of > 20 g/L from baseline through Week 26 will be analyzed in the same manner as the primary efficacy endpoint.

9.4.1.2.3. Other Efficacy Endpoints

eGFR will be measured at select target days as specified in the SoA (Section 1.3) and CKD stage assessed by eGFR (Table 10) will be classified as improved, stable (no change), or worsened compared to baseline. The eGFR will be calculated for all visits at which serum chemistry values are collected using the MDRD formula in participants ≥ 18 years of age and MDRD Schwartz formula in participants < 18 years of age.

Observed values and changes from baseline in eGFR and hematologic parameters (platelets, LDH, hemoglobin), CKD classification, and dialysis requirement status will be summarized over time at all scheduled visits.

For participants requiring dialysis within 5 days prior to Day 1, the proportion of participants no longer requiring dialysis will be summarized over time. A 2-sided 95% CI for the proportion of participants receiving dialysis will be provided.

9.4.1.3. Multiplicity Adjustment

This section is not applicable, as all analyses are descriptive, and p-values will not be provided.

9.4.1.4. Analyses of Exploratory Estimand(s) and/or Endpoint(s)

Not applicable.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set.

The following definitions will be used for AEs:

- Pretreatment AEs: Any AE that starts after providing informed consent/assent but before the first infusion of study intervention.
- TEAE: Any AE that starts during or after the first infusion of study intervention.

The incidence of TEAEs, TEAEs leading to withdrawal from the study, TEAEs leading to study intervention discontinuation, study intervention-related TEAEs, TEAEs during study intervention administration, severe TEAEs, treatment-emergent serious adverse events (TESAEs), and AESI will be summarized. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and will be summarized by System Organ Class and Preferred Term.

Hematology, blood chemistry and urinalysis results will be summarized (actual values as well as change from baseline) by visit using summary statistics (n, mean, median, standard deviation, minimum and maximum) for continuous variables and shift tables for categorical variables.

9.4.3. Other Analyses

Other analyses will be described in the SAP.

9.4.3.1. PK/PD

PK and PD analyses will be described in the SAP (or PK analysis plan, as applicable), and finalized before database lock. Individual serum eculizumab (PK), free, and total C5 concentration-time data will be listed, plotted, and summarized with descriptive statistics, with mean concentration-time data plotted.

The PK data in this study might be pooled with other studies to conduct a population-PK modelling analyses. The potential impact of participant characteristics (covariates) on PK will be evaluated. The relationship between PK exposure and PD response may be explored. The population-PK analysis will be described in a separate SAP. The results of population-PK analysis will be presented in a separate report.

9.4.3.2. Immunogenicity

For assessment of immunogenicity, the presence 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.

All ADA analyses will be performed on the Safety Set using the ADA variables included in Section 8.9.1. Additional details will be provided in the SAP.

9.5. Interim Analyses

An interim analysis will not be performed.

9.6. Data Monitoring Committee

This study will not include a Data Monitoring Committee.

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion 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 substantial amendments to the protocol will require IRB/IEC and regulatory/health authority 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, Directive 2001/20/EC, 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 and assent, where applicable, from all study participants, or the participant's legally authorized representative, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee 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 assent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent or assent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent or assent must also sign the informed consent or assent form(s).
- Participants must be reconsented or reassented to the most current version of the informed consent or assent form(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent or assent 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. Original 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 outside of the Screening window (Section 1.3) are required to sign a new ICF (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 individual 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. 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on the 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 electronically signing the eCRF.
- 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 after study completion per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. 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. eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. 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 investigational 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.

10.1.8. Study and Site Start and Closure

The study start date is the date of the first signed ICF.

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 EOS or ED Visit and Safety Follow-up Phone Call if applicable, all data have been collected and entered into the electronic data capture (EDC) 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 causes. 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.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication 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 engagement 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 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 Coordinating 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 Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.10. 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 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 intervention for shipment to the site.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- Women of childbearing potential (WOCBP) should only be enrolled after a negative serum pregnancy test. Additional pregnancy testing (urine or serum) should be performed per the timepoints specified in the SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report.

Table 14: Protocol-Required Safety Laboratory Assessments

Hematology	**Clinical Chemistry**
Free hemoglobin	Alanine aminotransferase
Haptoglobin	Albumin
Hematocrit	Alkaline phosphatase
Hemoglobin	Amylase
Mean corpuscular hemoglobin	Aspartate aminotransferase
Platelet count	Bicarbonate
RBC count	Blood urea nitrogen
RBC distribution width	C-reactive protein
RBC mean corpuscular volume	Calcium
Reticulocyte count	Chloride
WBC count	Creatinine
WBC differential	Gamma-glutamyltransferase
	Glucose
Coagulation Panel	Lactate dehydrogenase
International normalized ratio	Magnesium
Partial thromboplastin time	Phosphorus
Prothrombin time	Potassium
	Sodium
Urine Chemistry	Total bilirubin (direct and indirect)
Microalbumin	Total protein
Creatinine	Uric acid
Total protein	Coombs
Urinalysis	**Virus Serology**
Albumin	HIV-1
Appearance	HIV-2
Bilirubin	
Blood	**Other**
Color	ADA
Creatinine	ADAMTS13 activity
Glucose	Beta human chorionic gonadotropin (*females of childbearing potential only*)
Ketone	
Nitrite	Serum free and total C5
pH	Pharmacokinetic assay
Protein	Shiga toxin-related HUS screen (eg, Shiga toxin enzyme immunoassay/PCR in stool/stool culture)
Specific gravity	
Urobilinogen	Serum follicle-stimulating hormone (*postmenopausal females only*)

Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 3; C5 = complement component 5; HIV = human immunodeficiency virus; HUS = hemolytic uremic syndrome; PCR = polymerase chain reaction; RBC = red blood cell; WBC = white blood cell

Investigators must document their review of each laboratory safety report.

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. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

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

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.
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

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- 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:

- 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.
- 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.
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.

SUSARs 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.

Recording of AE and/or SAE

- 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 Common Terminology Criteria for Adverse Events (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 he/she has 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 Alexion with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- 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.
- The primary mechanism for reporting an SAE to Alexion will be the EDC system.
- 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.
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- The site will enter the SAE data into the EDC system as soon as it becomes available.
- 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.
- After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.
  - 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.

10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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 more than one FSH measurement may be required. 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 serum pregnancy test as required by local regulations before the first dose of study intervention. Additional requirements for pregnancy testing during and after dosing with study intervention 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 study intervention.

Female participants of childbearing potential must use a highly effective method of contraception, including at least 1 of the following until at least 5 months after the final dose of study intervention.

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
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 study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
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 study intervention). 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 5 months after the final dose of study intervention.

Other methods of contraception that are not considered as highly effective for female participants, but are acceptable birth control methods that result in a failure rate of more than 1% per year include:

1. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
2. Male or female condom with or without spermicide
3. Cap, diaphragm, or sponge with spermicide
4. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods)

The following methods are considered unacceptable (ie, are not allowed) 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 study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose study intervention and those who have not had a vasectomy must use a condom with or without spermicide during heterosexual intercourse for at least 5 months after their final dose of study intervention.

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 with or without 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 5 months (generally 5.5 terminal half-lives) after their final dose of study intervention.

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from the first dose of study intervention through 5 months after the final dose of study intervention. Any female participant who becomes pregnant during

the study should be considered for discontinuation from the study intervention and withdrawn from the study. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study intervention during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention 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.

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 study intervention.
- 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

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The information will be recorded on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the 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.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.5. COVID-19 Risk Assessment

aHUS is a life-threatening disease 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. In this particular case, the fact that the study is open-label and every participant is treated with the study intervention also contributes to the potential benefit a participant may derive from participating in the study. Given that treatment for aHUS does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in participants not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study participant 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 15.

Table 15: 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 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform nonurgent 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 the sites have the resourcing and capabilities to implement the study 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. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. 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. 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. 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

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

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

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

10.6. Protocol Amendment History

The Protocol Amendment Summary of Changes table for the current amendment is located directly after the Table of Contents.

DOCUMENT HISTORY		
Document	**Date**	**Summary of Key Changes in the Amendment**
Protocol Amendment 1	20 Jun 2022	This amendment was initiated mainly to update exclusion criteria and pregnancy language
Original Protocol	30 Nov 2021	Not applicable

10.7. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 16: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
APC	alternative pathway of complement
C5	complement component 5
C5b-9	terminal complement complex
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CNI	calcineurin inhibitor
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation from the study
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
EOS	end of study
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
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
IgG1	immunoglobulin G1
INR	international normalized ratio

Table 16: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
IRB	Institutional Review Board
IV	intravenous
IVIg	intravenous immunoglobulin
LDH	lactate dehydrogenase
LLN	lower limit of normal
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mTORi	mammalian target of rapamycin inhibitors
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
ST-HUS	Shiga toxin-related hemolytic uremic syndrome
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMA	thrombotic microangiopathy
ULN	upper limit of normal
WOCBP	women of childbearing potential

11. REFERENCES

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