A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

Unique Protocol ID:	ALXN1210-PNH-303
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Date of Protocol	08 July 2021

TITLE PAGE

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Protocol Number: ALXN1210-PNH-303

Amendment Number: 5

Compound Number: ALXN1210

USAN/INN: Ravulizumab

Short Title: PK Noninferiority Study of Ravulizumab SC Versus Ravulizumab IV

Sponsor Name:
Alexion Pharmaceuticals, Inc.

Sponsor Address:
121 Seaport Boulevard
Boston MA 02210
USA

Regulatory Agency Identifying Number(s):

EudraCT Number: 2017-002370-39

IND Number: 128367

Approval Date: 08 Jul 2021

Sponsor Signatory:

PPD
PPD

Date

Medical monitor contact information can be found in the study contact list distributed to study sites.

24-hour Emergency Contact: PPD

INVESTIGATOR'S AGREEMENT

I have read the ALXN1210-PNH-303 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5 (08 Jul 2021)

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

Overall Rationale for the Amendment

The main rationale for this amendment is addition of secondary efficacy endpoints to align with endpoints indicated in the Statistical Analysis Plan v4.0 and HRQoL and treatment administration satisfaction endpoints to support assessment of patient preference.

Other changes implemented through this protocol amendment constitute the addition of patient preference questionnaire, remote visit options in times of emergency, and COVID-19 risk assessment.

Section/Table	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Patient Preference Questionnaire – Subcutaneous was included under HRQoL and treatment administration satisfaction endpoints.	To support assessment of patient preference
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	The efficacy endpoints of change in clinical manifestations of PNH over time, change in reticulocyte count over time, change in eGFR over time, and change in PNH RBC clone size over time were added in alignment with the endpoints indicated in the Statistical Analysis Plan v.4.0.	To support assessments of disease manifestations and related laboratory parameters
Section 1.1 Synopsis, Section 1.2 Study Schema, Section 4.1 Overall design	Extension Period was corrected from 182 weeks to 172 weeks	To clarify the duration of the Extension Period
Section 1.3 Schedule of Activities, Table 4	Assessment was added for FACIT-Fatigue and EORTC QLQ-C30 on Day 239, and for TASQ-SC on Days 183 and 239.	To align with Statistical Analysis Plan v.4.0 and correct the assessments that were taken out inadvertently in Protocol Amendment 4.
Section 1.3 Schedule of Activities, Table 4 and 5	Years removed in table heading as they did not reflect the timeframe of the table.	Correction
Section 2.4.2 Potential and Identified Risks, Section 10. 8 COVID-19 Risk Assessment	Added text referring reader to coronavirus disease 2019 (COVID-19) considerations and noted that use of immunosuppressants by participants increases risk of serious infections	To conform to EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic and FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, and to advise regarding specific risks to this study population.

Section/Table	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 5	Patient preference questionnaire assessments were added to the Schedule of Activities and a corresponding footnote has been added	To support assessment of patient preference
Section 6.1 Ravulizumab Table, 7	The term "concentrated" was removed from the SC dosage form. Physical description of the Study Drug for SC administration was updated.	Clarified to correctly reflect the physical description of the Study Drug
Section 4.4 Justification of Device Selected and Section 6.2 On-body Delivery System	The time for SC administration of ravulizumab was changed from "in less than" to "in approximately".	To clarify administration time for SC drug delivery and to align with the Instructions for Use for the OBDS.
Section 4.4 Justification of Device Selected and Section 6.3.1 Ravulizumab IV and Ravulizumab SC – In-clinic Administration	Text in Section 4.4 and numbered item 7 in Section 6.3.1 were updated from "device" to "drug-device combination".	To correctly reflect that the OBDS is the drug-device combination.
Section 8.1.6 Quality of Life Questionnaires	Description of the PNH Patient Preference Questionnaire – Subcutaneous was added	To support assessment of patient preference
Section 8.3.6.1 Local and Systemic Reactions	Clarification added for infusion-associated reactions "(infusion-related reactions)".	For clarification
Section 9.4.2.2 Quality of Life and Treatment Administration Satisfaction	Planned analyses of the patient preference questionnaire were described	To support assessment of patient preference
Section 10.1.9 Remote Visit Options in Times of Emergency	Section detailing remote visit options in times of emergency (eg, COVID-19) was added.	To ensure participant safety and treatment continuity.
Section 10.6.4 Patient Preference Questionnaire	Section added to include Patient Preference Questionnaire – Subcutaneous	To support assessment of patient preference
Section 10.10 Protocol Amendment History	Updated to include details of Protocol Amendment 4	To reflect the protocol amendment history

Abbreviations: ADE = adverse device effect; COVID-19 = coronavirus disease 2019; CRF = case report form; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; EORTC = European Organisation for Research and Treatment of Cancer ; FACIT = Functional Assessment of Chronic Illness Therapy; FDA = Food and Drug Administration; GDS = Global Drug Safety; HRQoL = health-related quality of life; IV = intravenous(ly); OBDS = on-body delivery system; PD = pharmacodynamic(s); PNH = paroxysmal nocturnal hemoglobinuria; PK = pharmacokinetic(s); QLQ C30 = Quality of Life Questionnaire-Core 30 Scale; QoL = quality of life; RBC = red blood cell; SC = subcutaneous(ly); TASQ = Treatment Administration Satisfaction Questionnaire.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

Short Title: PK Noninferiority Study of Ravulizumab SC Versus Ravulizumab IV

Rationale: The purpose of this study is to compare the pharmacokinetics (PK) of ravulizumab subcutaneous (SC) administered via an on-body delivery system (OBDS) to ravulizumab intravenous (IV) in patients with paroxysmal nocturnal hemoglobinuria (PNH) who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry. Based on the established relationship between PK exposure and clinical efficacy of ravulizumab IV, the PK noninferiority of ravulizumab SC to ravulizumab IV will enable bridging of efficacy and safety data from ravulizumab IV to ravulizumab SC. The study hypothesis is that Day 71 ravulizumab SC serum C_{trough} will be noninferior compared with Day 71 ravulizumab IV serum C_{trough}.

The study is also intended to demonstrate the safety and tolerability of ravulizumab SC and the ravulizumab OBDS, a drug-device combination product.

Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary PK endpoint**
To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH	Day 71 serum ravulizumab C_{trough}
Secondary	**PK Endpoint**
To characterize PK of ravulizumab SC	C_{trough} over time
	PD Endpoint
To characterize PD of ravulizumab SC	Free serum C5 concentrations over time
	Immunogenicity Endpoint
To characterize immunogenicity of ravulizumab SC	Incidence of treatment-emergent ADAs over time
	HRQoL and Treatment Satisfaction Endpoints
To evaluate HRQoL and treatment satisfaction on ravulizumab SC	• Change in FACIT-Fatigue Scale, Version 4, from Baseline to Day 183 • Change in EORTC QLQ-C30 Version 3.0, from Baseline to Day 183 • Reported treatment administration satisfaction as measured by the TASQ score at Baseline and Day 183 • Reported patient preference as measured by the PPQ-SC score at Day 1093
	Safety Endpoints
To evaluate safety of ravulizumab SC and ravulizumab OBDS	• Change in physical examinations, vital signs, electrocardiograms, and laboratory assessments over time • Incidence of adverse events and serious adverse events

Objectives	Endpoints
	• Incidence of adverse device effects and serious adverse device effects
	Efficacy Endpoints
To evaluate efficacy of ravulizumab SC	• Change over time in LDH • Incidence of breakthrough hemolysis • Achievement of transfusion avoidance • Achievement of stabilized hemoglobin • Change in clinical manifestations of PNH over time • Change in reticulocyte count over time • Change in eGFR over time • Change in PNH RBC clone size over time
	Performance Endpoint
To assess performance of ravulizumab OBDS	• Reported outcome of attempted full-dose administration (including device failure/malfunction)

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; C_{trough} = predose concentration; eGFR = estimated glomerular filtration rate; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; IV = intravenous; LDH = lactate dehydrogenase; OBDS = on-body delivery system; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; PPQ-SC = Patient Preference Questionnaire – Subcutaneous; QLQ-C30 = Quality of Life Questionnaire-Core 30 Scale; RBC = red blood cell; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire.

Study Drug Formulations

Treatment	Formulation	Delivery Mechanism
Ravulizumab IV	10 mg/mL ravulizumab in 10 mM sodium phosphate containing 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection, pH 7.0	Intravenous infusion
Ravulizumab SC	70 mg/mL ravulizumab in 50 mM sodium phosphate containing 25 mM arginine, 5% sucrose, 0.05% polysorbate 80, and water for injection, pH 7.4	Subcutaneous infusion via OBDS

Abbreviations: OBDS = on-body delivery system.

Overall Design:

This is a Phase 3, randomized, open-label, parallel-group, multicenter study to evaluate PK noninferiority of ravulizumab SC administered via an OBDS compared with intravenously administered ravulizumab IV in adult patients with PNH who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry.

The study will consist of an up to a 30-day Screening Period, a 10-week Randomized Treatment Period, and an Extension Period of up to 172 weeks or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first. The study duration for each patient will be up to 3.5 years. Patients will be stratified by weight group (≥ 40 kg to < 60 kg and ≥ 60 kg to < 100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

Ravulizumab IV dosing during the Randomized Treatment Period will be administered in the clinic by a trained member of the site study team. Day 1 of study treatment will occur 12 to 16 days from the patient's last dose of eculizumab. Timing for study drug administration and predose PK sample collection is critical to ensure adequate numbers of patients with evaluable PK data (Table 1). The time for the start of the dose administered on Day 1 is the nominal time for all subsequent doses and PK/PD sample collections. Specifically, all subsequent doses during the Randomized Treatment Period are expected to be administered at the same time of day that the dose was administered on Day 1. The PK samples are expected to be drawn as close as possible to the administration of the dose (or from the nominal time from the start of the Day 1 dose on nondosing days). The PK analysis set population is defined in Section 9.3.

Ravulizumab OBDS will be supplied in a kit, comprising 245 mg of ravulizumab SC in a sterile, single-use, prefilled cartridge assembly copackaged with a single-use injector. Two kits will be used to deliver the full 490 mg dose of ravulizumab SC.

Ravulizumab IV loading and maintenance doses will be based on patient body weight prior to dosing at each dosing visit (Table 1).

During the Randomized Treatment Period, patients assigned to the ravulizumab SC group will receive a loading dose of ravulizumab IV on Day 1, followed by maintenance doses of ravulizumab SC on Day 15 and every week (qw) thereafter through completion of the Randomized Treatment Period. Patients assigned to the ravulizumab IV group will receive a loading dose of ravulizumab IV on Day 1 followed by a maintenance dose of ravulizumab IV on Day 15 (Table 1).

Table 1: Study Drug Dosing

<table>
<tr><th>Treatment Group</th><th colspan="2">Randomized Treatment Period (10 weeks)</th><th>Extension Period (up to 172 weeks)</th></tr>
<tr><td>Ravulizumab SC</td><td rowspan="2">Loading Dose on Day 1:
Ravulizumab IV 2400 mg[a] or Ravulizumab IV 2700 mg[b]</td><td>SC Doses on Days 15, 22, 29, 36, 43, 50, 57, and 64:
Ravulizumab SC 490 mg[c] (2 ravulizumab OBDS kits per weekly dose)</td><td rowspan="2">Maintenance Doses on Day 71 and qw through Day 1275:
Ravulizumab SC 490 mg[d] (2 ravulizumab OBDS kits per weekly dose)</td></tr>
<tr><td>Ravulizumab IV</td><td>Maintenance Dose on Day 15:
Ravulizumab IV 3000 mg[a]
or
Ravulizumab IV 3300 mg[b]</td></tr>
</table>

[a] Weight group ≥ 40 to < 60 kg.
[b] Weight group ≥ 60 to < 100 kg.
[c] On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration. On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab dosing can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic at these visits.

[d] Self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.

Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

Day 71 is the end of the Randomized Treatment Period and the beginning of the Extension Period. All Day 71 assessments completed prior to dosing are considered part of the Randomized Treatment Period. Dosing on Day 71 is the start of the Extension Period. During the Extension Period:

- Patients who had been randomized to the ravulizumab SC group will continue to receive 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)
- Patients who had been randomized to the ravulizumab IV group will switch to 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)

Ravulizumab SC dosing during the Extension Period can be self-administered by the patient at home with the following exceptions where ravulizumab SC will be administered in the clinic:

- For patients who had been randomized to the ravulizumab IV group, ravulizumab SC 490 mg dose on Day 71 will be self-administered by the patient in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.
- For all patients, doses that coincide with study visits specified in the Schedule of Activities (SoA, Section 1.3) will be self-administered by the patient in the clinic with oversight by trained study site personnel.
- With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits (with oversight by trained study site personnel).

The end of the study for each patient occurs when the safety follow-up is completed. The safety follow-up consists of a phone call 30 days after the last dose. Data collection during the safety follow-up is limited to reporting adverse events and concomitant medications. If a patient discontinues treatment, but does not discontinue from the study, the end of study for such a patient will be their last visit as long as that visit is more than 30 days from their last dose. The end of the study is defined as the date of the last patient visit or safety follow up, whichever occurs later.

Number of Patients:

Approximately 105 patients (70 patients in the ravulizumab SC group and 35 patients in the ravulizumab IV group) will be enrolled in the study. An interim analysis for sample size re-estimation will be conducted and the sample size may be increased to a maximum of 144 patients Section 9.5).

Inclusion Criteria

Patients must meet all inclusion and no exclusion criteria. Patients who fail study eligibility may be rescreened once based on discussion and agreement between the Investigator and the Medical Monitor.

Patients are eligible to be included in the study only if they fulfill all of the following criteria:

Age

1. Patients must be at least 18 years of age at the time of signing the informed consent.

Patient and Disease Characteristics

2. Treated with eculizumab according to the labeled dosing recommendation for PNH (900 mg every 14 days ± 2 days) for at least 3 months prior to study entry with no missed doses within 2 months prior to study entry and no more than 2 doses outside of the visit window.
3. Lactate dehydrogenase levels ≤ 1.5 × ULN (upper limit of normal), according to central laboratory, at Screening. Sample must be obtained within 24 hours of or immediately prior to a scheduled eculizumab dose administration (ie, at trough eculizumab level).
4. Documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010).
5. Vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug to reduce the risk of meningococcal infection (*N meningitidis*).

Weight

6. Body weight ≥ 40 to < 100 kg, and in the opinion of the Investigator, are likely to remain within this body weight range for the duration of the study.

Contraception

7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified contraception guidance while on treatment and for at least 8 months after last dose of study drug.

Informed Consent

8. Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including self-administration of ravulizumab SC doses, and the use of any data collection device(s) to directly record patient data.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met:

Medical Conditions

1. More than 1 LDH value > 2 × ULN within the 3 months prior to study entry.
2. Major adverse vascular event (MAVE) in the 6 months prior to study entry.
3. Platelet count < 30,000/mm^3 (30 × 10^9/L) at Screening.

4. Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.
5. History of bone marrow transplantation.
6. History of *N meningitidis* infection.
7. History of unexplained infections.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
9. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
10. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
11. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
12. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient's participation in an investigational clinical study.
13. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Day 1, coexisting chronic anemia unrelated to PNH) that would make patients unlikely to tolerate the requirements of the protocol).
14. History of hypersensitivity to any ingredient contained in the study drug including hypersensitivity to murine proteins.
15. Female patients who plan to become pregnant or are currently pregnant or breastfeeding.
16. Female patients who have a positive pregnancy test result at screening or on Day 1.
17. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose an additional risk for the patient, or confound the outcome of the study.
18. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to Screening.
19. Inability to complete the requirements for SC self-administration.
20. Inability to travel to the clinic for specified visits during the Randomized Treatment Period or fulfil the logistic requirements of study drug.

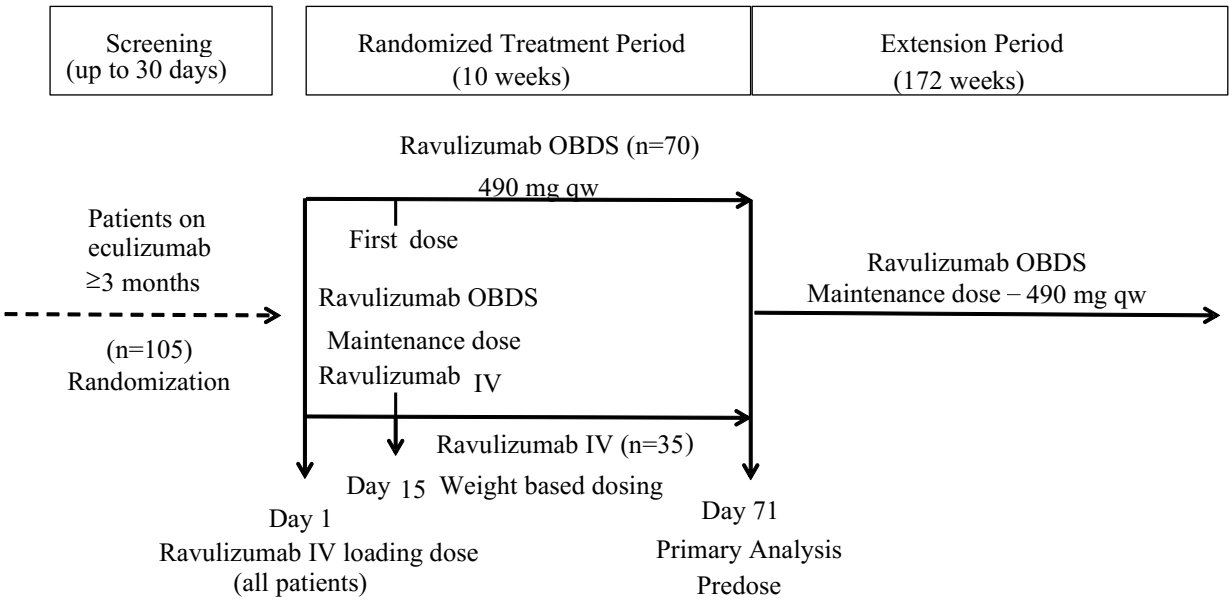
Prior/Concomitant Therapy

21. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to study entry.

Prior/Concurrent Clinical Study Experience

22. Participation in another study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater (except for participation in observational studies [eg, PNH Registry]).
23. Received any other experimental C5 antagonist at any time.

1.2. Study Schema



Ravulizumab SC dosage: Day 1 loading dose (IV) = 2400 mg for patients weighing ≥ 40 kg to < 60 kg and 2700 mg for patients weighing ≥ 60 kg to < 100 kg; Day 15 and all subsequent SC doses = 490 mg qw for all patients.
Ravulizumab IV dosage: Day 1 loading dose (IV) = 2400 mg for patients weighing ≥ 40 mg to < 60 kg and 2700 mg for patients weighing ≥ 60 kg to < 100 kg; Day 15 maintenance dose (IV) = 3000 mg for patients weighing ≥ 40 kg to < 60 kg, 3300 mg for patients weighing ≥ 60 kg to < 100 kg.
Extension Period maintenance doses (SC) = 490 mg qw for all patients.
Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

1.3. Schedule of Activities

The SoA for Screening and the Randomized Treatment Period is provided for the ravulizumab SC group in Table 2 and for the ravulizumab IV group in Table 3 . Day 71 is the end of the Randomized Treatment Period. All assessments for Day 71 will be performed prior to dosing. On Day 15, a qualified member of the site study team will train patients randomized to ravulizumab SC on self-administration of ravulizumab SC using the OBDS kits prior to self-administration by the patient. The patient will self-administer the Day 15 dose of ravulizumab SC in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab SC can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on these days (with oversight by trained study site

personnel). On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel.

The SoA for the Extension Period is provided in Table 4 and Table 5 . Dosing on Day 71 is the start of the Extension Period. The first dose of ravulizumab SC for patients who had been randomized to ravulizumab IV during the Randomized Treatment Period will be on Day 71. On Day 71, a qualified member of the site study team will train patients who had been randomized to ravulizumab IV on self-administration of ravulizumab SC using the OBDS kits prior to self-administration by the patient. The patient will self-administer the Day 71 dose of ravulizumab SC in the clinic with oversight by trained study site personnel. For patients who had been randomized to ravulizumab SC, dosing on Day 71 will be by self-administration during the in-clinic visit. For the remainder of the Extension Period, weekly dosing of ravulizumab SC for all patients can be by self-administration by the patient at home or in the clinic at visits specified in Table 4 and Table 5 . With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits (with oversight by trained study site personnel).

Procedures conducted as part of the patient's routine clinical management (eg, hematology assessments) and obtained before signing of the informed consent form (ICF) may be utilized for screening purposes provided the procedures meet protocol-specified criteria and were performed within the time frame specified in the SoA.

Quality of life assessments will be administered and recorded on paper throughout the study. Data associated with ravulizumab SC dosing when it is administered in the home setting during the Extension Period will be recorded in a patient e-diary.

The site will monitor self-administration of ravulizumab SC by the patient via telephone calls with the patient on scheduled at-home dosing days during the Randomized Treatment Period (patients randomized to ravulizumab SC) to ensure that the patient is queried about study drug dose administered and device condition. During the Extension Period, the site will contact patients by telephone on Day 78 to query the patient on study drug administration and completion of the patient e-diary. After Day 78, sites will monitor self-administration of ravulizumab SC via the patient e-diary.

Laboratory specimen handling and processing instructions will be provided in the study laboratory manual. Blood samples should not be collected from a heparinized line. Post IV dose (Day 1 for both cohorts, and also Day 15 for the ravulizumab IV cohort) blood samples should be collected from the contralateral arm.

Unscheduled visits that occur outside the protocol-specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments conducted during unscheduled visits will be performed at the discretion of the Investigator.

If breakthrough hemolysis is suspected, LDH, PK, PD, and antidrug antibody (ADA) samples must be collected for analysis at the central laboratory. If the suspected event of breakthrough hemolysis occurs outside of a scheduled visit, the patient is expected to return to the site for an Unscheduled Visit for evaluation and collection of the required LDH, PK, PD, and ADA samples. For purposes of defining breakthrough hemolysis, assessment of LDH must be based on a central laboratory value.

Table 2: Ravulizumab Subcutaneous Treatment Group: Schedule of Study Visits and Activities – Screening Through End of Randomized Treatment Period

Study Day	**Screening –30 to –1**	**1**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**[a]
Study Week			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Site visit (V) or at-home dosing of ravulizumab SC (H)		**V**	**V**	**H**	**V**	**H**	**V**	**H**	**V**	**V**	**V**
Dose window (nominal time in hours from the start of the first dose on Day 1)[b]			**± 1**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 1**	**± 1**	**± 1**
Informed consent	X										
Inclusion/exclusion	X	X									
Medical history and demographics	X										
Confirmation or administration of meningococcal vaccination[c]	X	X									
HIV testing	X										
PNH clone size[d]	X	X									X
Height	X										
Weight	X	X	X		X		X		X	X	X
Pregnancy test[e]	X	X	X								X
Randomization		X									
Ravulizumab IV loading dose administration[f]		X									
Ravulizumab SC administration[g]			X[h]	X[i]	X[h]	X[i]	X[h]	X[i]	X[h]	X[h]	
Patient training on dose administration[j]			X								
Scheduled telephone call[k]				X		X		X			
Infusion site evaluation[l]		X	X		X		X		X	X	
PK/PD sampling (within 30 minutes predose)[m]		X	X						X	X	X
Postdose PK/PD sampling (within 30 minutes postdose)		X									
Immunogenicity (ADA) (within 30 minutes predose)[m]		X									X
PNH symptomatology	X	X	X				X				X
FACIT-Fatigue	X	X					X				X
EORTC QLQ-C30	X	X					X				X
TASQ-IV[n]	X	X	X								
TASQ-SC[o]							X				X
Vital signs[p]	X	X	X		X		X		X	X	X
Safety 12-lead ECG	X										X
Chemistry, including LDH[q]	X	X	X		X		X		X		X
Hematology, including coagulation	X	X	X		X		X		X		X
Urinalysis and urine chemistry	X	X	X		X		X		X		X
Physical examination	X										
Abbreviated physical examination[r]		X	X		X		X		X		X

Table 2: Ravulizumab Subcutaneous Treatment Group: Schedule of Study Visits and Activities – Screening Through End of Randomized Treatment Period

Study Day	**Screening –30 to –1**	**1**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**[a]
Study Week			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Site visit (V) or at-home dosing of ravulizumab SC (H)		**V**	**V**	**H**	**V**	**H**	**V**	**H**	**V**	**V**	**V**
Dose window (nominal time in hours from the start of the first dose on Day 1)[b]			**± 1**	**± 6**	**± 6**	**± 6**	**± 6**	**± 6**	**± 1**	**± 1**	**± 1**
Review safety card		X	X		X		X		X	X	X
Breakthrough hemolysis[s]		←Monitor continuously→									
Adverse events/adverse device effects	←Monitor continuously→										
Concomitant medications	←Monitor continuously→										
Record transfusions and transfusion parameters	←Monitor continuously→										

[a] Day 71 assessments for the Randomized Treatment Period must be performed predose on Day 71.
[b] Dosing **must** be administered on the visit day indicated during the Randomized Treatment Period. Doses after Day 1 are expected to be administered at the same nominal time as the dose on Day 1.
[c] All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug.
[d] White blood cell (granulocyte and monocyte) and red blood cell clone size measured by high-sensitivity flow cytometry at Screening and Day 1; red blood cell clone size only on Day 71.
[e] Female patients of childbearing potential only: serum pregnancy test at Screening and Day 71; urine pregnancy test at all other required time points. A negative urine test result is required prior to administering ravulizumab to female patients of childbearing potential at the indicated visits.
[f] Ravulizumab IV weight-based dosing on Day 1 (2400 mg for patients ≥ 40 to < 60 kg and 2700 mg for patients ≥ 60 to < 100 kg) is to be administered after Day 1 assessments are performed.
[g] Ravulizumab SC 490 mg qw maintenance dose on Day 15 and thereafter.
[h] Ravulizumab SC self-administered in the clinic.
[i] Ravulizumab SC self-administered at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on these days (with oversight by trained study site personnel).
[j] A qualified member of the site study team will provide initial (and ongoing as appropriate) training on how to properly self-administer ravulizumab SC using the 2 required OBDS kits.
[k] Site will contact patient via telephone at scheduled dosing times to ensure patient is queried about study drug dose administration and device condition.
[l] New or worsening abnormalities should be reported as AEs
[m] The timing for PK sample collection is critical to the primary endpoint for this study. Serum samples for PK/PD/ADA analyses are to be collected as close as possible, but no more than 30 minutes prior to dosing. Day 71 dosing is included in the Extension Period (Table 4). Samples should be collected from the contralateral arm used for IV dosing. Samples should not be collected from a heparinized line.
[n] At screening, patients complete TASQ-IV within 24 hours of receiving their eculizumab dose.
[o] Patients randomized to ravulizumab SC group complete TASQ-IV at Screening, Day 1 and Day 15 and then complete TASQ-SC at Day 43 and Day 71.
[p] On dosing days, vital signs will be obtained before study drug administration.
[q] Follicle stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.

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

[s] If a suspected event of breakthrough hemolysis occurs, blood samples for LDH, PK, PD, and ADA parameters will be collected and sent to the central laboratory for analysis. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required blood samples.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; H = at-home dosing; HIV = human immunodeficiency virus; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; qw = every week; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire; V = site visit.

Table 3: Ravulizumab Intravenous Treatment Group: Schedule of Study Visits and Activities – Screening Through End of Randomized Treatment Period

Study Day	**Screening –30 to –1**	**1**	**15**	**29**	**43**	**57**	**71[a]**
Study Week			**2**	**4**	**6**	**8**	**10**
Site visit (V)		**V**	**V**	**V**	**V**	**V**	**V**
Dose window (nominal time in hours from the start of first dose on Day 1)[b]			**± 1**				**± 1**
Informed consent	X						
Inclusion/Exclusion	X	X					
Medical history and demographics	X						
Confirmation or administration of meningococcal vaccination[c]	X	X					
HIV testing	X						
PNH clone size[d]	X	X					X
Height	X						
Weight	X	X	X				X
Pregnancy test[e]	X	X	X				X
Randomization		X					
Ravulizumab IV loading dose administration[f]		X					
Ravulizumab IV administration[g]			X				
Infusion site evaluation[h]		X	X				
PK/PD sampling (within 30 minutes predose)[i]		X	X				X
Postdose PK/PD sampling (within 30 minutes postdose)		X	X			X[j]	
Immunogenicity (ADA) (within 30 minutes predose)[i]		X					X
PNH symptomatology	X	X	X		X		X
FACIT-Fatigue	X	X			X		X
EORTC QLQ-C30	X	X			X		X
TASQ-IV	X[k]	X			X		X
Vital signs[l]	X	X	X	X	X	X	X
Safety 12-Lead ECG	X						X
Chemistry, including LDH[m]	X	X	X	X	X	X	X
Hematology, including coagulation	X	X	X	X	X	X	X
Urinalysis and urine chemistry	X	X	X	X	X	X	X
Physical examination	X						
Abbreviated physical examination[n]		X	X	X	X	X	X
Review safety card		X	X	X	X	X	X
Breakthrough hemolysis[o]		←Monitor continuously→					
Adverse events	←Monitor continuously→						
Concomitant medications	←Monitor continuously→						
Record transfusions and transfusion parameters		←Monitor continuously→					

[a] Day 71 assessments for the Randomized Treatment Period must be performed predose on Day 71.
[b] Dosing must be administered on the visit day indicated during the Randomized Treatment Period. Doses after Day 1 are expected to be administered at the same nominal time as the dose on Day 1.
[c] All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug.
[d] White blood cell (granulocyte and monocyte) and red blood cell clone size measured by high-sensitivity flow cytometry at Screening and Day 1; red blood cell clone size only on Day 71.
[e] Female patients of childbearing potential only. Serum pregnancy test at Screening and Day 71; urine pregnancy test at all other required time points. A negative urine test result is required prior to administering ravulizumab to female patients of childbearing potential at the indicated visits.
[f] Ravulizumab IV weight-based loading dose on Day 1 (2400 mg for patients weighing ≥ 40 to < 60 kg and 2700 mg for patients weighing ≥ 60 to < 100 kg) is to be administered after Day 1 assessments are performed.
[g] Ravulizumab weight-based maintenance dosing on Day 15 is: 3000 mg for patients weighing ≥ 40 to < 60 kg and 3300 mg for patients weighing ≥ 60 to < 100 kg.
[h] New or worsening abnormalities should be reported as AEs
[i] The timing for PK sample collection is critical to the primary endpoint for this study. Serum samples for PK/PD/ADA analyses are to be collected as close as possible but no more than 30 minutes prior to dosing. Day 71 dosing is included in the Extension Period (Table 4). Samples should be collected from the contralateral arm used for IV dosing. Samples must not be collected from a heparinized line.
[j] There is no dose of ravulizumab administered on Day 57; sample to be collected anytime during the assessments on Day 57.
[k] During Screening, patients complete TASQ-IV within 24 hours of receiving a dose of eculizumab.
[l] On dosing days, vital signs will be obtained before study drug administration.
[m] Follicle stimulating hormone levels will be measured during Screening only in order to confirm postmenopausal status.
[n] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated physical examination.
[o] If a suspected event of breakthrough hemolysis occurs, blood samples for LDH, PK, PD, and ADA parameters will be collected and sent to the central laboratory. If the suspected event of breakthrough does not occur at a scheduled visit, an Unscheduled Visit should occur for evaluation of the patient and collection of the required blood samples.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HIV = human immunodeficiency virus; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; TASQ = Treatment Administration Satisfaction Questionnaire; V = site visit.

Table 4: Schedule of Study Visits and Activities – Extension Period Through Day 365

Study Day	**71**	**78**	**85**	**99**	**127**	**183**	**239**	**295**	**365**
Study Week	**10**		**12**	**14**	**18**	**26**	**34**	**42**	**52**
Site visit (V) or at-home dosing of ravulizumab SC (H)	**V**	**H**	**V**	**V**	**V**	**V**	**V**	**V**	**V**
Visit Window (± Day)	**NA**		**1**	**1**	**1**	**1**	**1**	**1**	**1**
Dose window (nominal time in hours from the start of first dose on Day 1)[a]	**± 1**								
Patient training on dose administration[b]	X								
Ravulizumab SC administration	X	X	X	X	X	X	X	X	X
Telephone call check		X[c]							
Infusion site evaluation[d]	X		X	X	X	X	X	X	X
PK/PD sampling[e]	X		X	X	X	X	X	X	X
Immunogenicity (ADA)[e]			X	X	X	X	X	X	X
PNH symptomatology				X	X	X		X	X
FACIT-Fatigue		X		X		X	X	X	X
EORTC QLQ-C30		X		X		X	X	X	X
TASQ-SC			X			X	X		X
Vital signs[f]			X	X	X	X	X	X	X
Chemistry, including LDH			X	X	X	X	X	X	X
Hematology, including coagulation			X	X	X	X	X	X	X
Urinalysis and urine chemistry			X	X	X	X	X	X	X
Pregnancy test[g]			X	X	X	X	X	X	X
Weight			X	X	X	X	X	X	X
Abbreviated physical examination[h]			X	X	X	X	X	X	X
Review safety card			X	X	X	X	X	X	X
Treatment adherence monitoring by e-diary		←At every weekly dose→							
Breakthrough hemolysis[i]	←Monitor continuously→								
Record transfusions and transfusion parameters	←Monitor continuously→								
Concomitant medications	←Monitor continuously→								
Adverse events	←Monitor continuously→								

[a] Day 71 dosing is the beginning of the Extension Period. The Day 71 dose is expected to be administered at the same nominal time as the dose on Day 1. The ravulizumab SC 490 mg dose on Day 71 will be self-administered in the clinic. For patients who had been randomized to the ravulizumab IV group, this will be part of the required training program.

[b] For patients who had been randomized to the ravulizumab IV group, a qualified member of the site study team will provide initial (and ongoing as appropriate) training on how to properly self-administer ravulizumab SC using the 2 required OBDS kits. For all patients, doses that coincide with study visit days will be self-administered in the clinic with

oversight by trained study site personnel. All other doses can be self-administered at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits (with oversight by trained study site personnel).

[c] Site will contact patients by telephone to query the patient on ravulizumab SC administration and completion of the patient e-diary.

[d] New or worsening abnormalities should be reported as AEs.

[e] Serum samples for PK/PD/ADA analyses will be collected predose (Day 71 included; see Table 2 and Table 3). Samples should not be collected from a heparinized line.

[f] Vital signs will be obtained before study drug administration.

[g] For female patients of childbearing potential only. A negative urine test result is required prior to administering ravulizumab to female patients of childbearing potential at the indicated visits.

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

[i] If a suspected event of breakthrough hemolysis occurs, blood samples for LDH, PK, PD, and ADA parameters will be collected and sent to the central laboratory for analysis. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required blood samples.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; H = at-home dosing; LDH = lactate dehydrogenase; NA = not applicable; OBDS = on-body delivery system; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire; V = site visit.

Table 5: Schedule of Study Visits and Activities – Extension Period, Day 421 Through Day 1275

Study Day	**421**	**477**	**533**	**589**	**645**	**701**	**757**	**813**	**869**	**925**	**981**	**1037**	**1093**	**1149**	**1205**	**1275/ ET**	**Safety Follow-up**
Study Week	**60**	**68**	**76**	**84**	**92**	**100**	**108**	**116**	**124**	**132**	**140**	**148**	**156**	**164**	**172**	**182**	
Site Visit Window (± Day)	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	
Ravulizumab SC administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call check																	X[b]
PK/PD sampling[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity (ADA)[c]		X		X		X		X		X		X		X		X	
FACIT-Fatigue							X						X			X	
EORTC QLQ-C30							X						X			X	
TASQ-SC							X						X			X	
PPQ-SC													X			X[d]	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety 12-Lead ECG																X	
Chemistry, including LDH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, including coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis and urine chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Abbreviated physical examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination																X	
Review safety card	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment adherence monitoring by e-diary	←At every weekly dose→																
Breakthrough hemolysis[h]	←Monitor continuously→																
Record transfusions and transfusion parameters	←Monitor continuously→																
Concomitant medications	←Monitor continuously→																
Adverse events	←Monitor continuously→																

[a] For all patients, doses that coincide with study visit days can be self-administered in the clinic with oversight by trained study site personnel. All other doses can be self-administered at home.
[b] A follow-up phone call is to be conducted 30 days after the last dose of study drug and is limited to adverse event and concomitant medication monitoring.
[c] Serum samples for PK/PD/ADA analyses will be collected predose. Samples should not be collected from a heparinized line.
[d] PPQ-SC will be collected only once for each patient; at Day 1093 or at ET for patients who discontinue the study prior to Day 1093. PPQ-SC will not be collected at Day 1275.
[e] Vital signs will be obtained before study drug administration.
[f] For female patients of childbearing potential only. Serum pregnancy test at ET only; urine pregnancy test at all other time points. A negative urine test result is required prior to administering ravulizumab to female patients of childbearing potential at the indicated visits.
[g] Abbreviated physical examination consists of a body system relevant examination based upon Investigator (or designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated physical examination.
[h] If a suspected event of breakthrough hemolysis occurs, blood samples for LDH, PK, PD, and ADA parameters will be collected and sent to the central laboratory for analysis. If the suspected event of breakthrough does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the required blood samples.

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; H = at-home dosing; LDH = lactate dehydrogenase; NA = not applicable; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; PPQ-SC = Patient Preference Questionnaire - Subcutaneous; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire; V = site visit.

2. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare and life-threatening acquired hemolytic disorder caused by uncontrolled activation of the terminal complement pathway (Brodsky, 2014; Brodsky, 2015). Chronic, uncontrolled complement component 5 (C5) cleavage and release of C5a and C5b-9 lead to red blood cell (RBC) hemolysis. Hemolysis results in the release of intracellular free hemoglobin and lactate dehydrogenase (LDH) into circulation; irreversible binding to and inactivation of nitric oxide (NO) by hemoglobin and inhibition of NO synthesis; vasoconstriction and tissue-bed ischemia due to absence of vasodilatory NO as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction; platelet activation; and a proinflammatory and prothrombotic state (Brodsky, 2014; Hill, 2013). A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension (Brodsky, 2014; Hill, 2013; Hill, 2012; Hillmen, 2010). Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system (Brodsky, 2014). Secondary effects in addition to the risk of major end organ damage from thrombosis include abdominal pain, extreme or unrelenting fatigue, difficulties in concentrating or thinking, and reduced activities of daily living (ADL).

The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block intravascular hemolysis and thereby prevent thrombosis. Prior to ravulizumab, the only approved treatment for PNH that blocks terminal complement activity was eculizumab (Soliris®), a humanized monoclonal antibody (mAb) derived from the murine anti-human C5 antibody m5G1.1 and specifically binds to the complement protein C5 with high affinity. Eculizumab is administered by intravenous (IV) infusion every other week.

2.1. Ravulizumab

Ravulizumab (IV formulation; Ultomiris®) was approved by the FDA on 21 Dec 2018 for the treatment of PNH. Ravulizumab (ALXN1210) is a humanized mAb that binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b. Ravulizumab was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain (Sheridan, 2018). These changes extend the half-life of ravulizumab relative to eculizumab, while preserving the high degree of specificity and selectivity for binding to C5 of eculizumab (Sahelijo, 2015).

There is extensive clinical experience with ravulizumab administered IV in completed Phase 1 studies and ongoing Phase 1b, 2, and 3 clinical studies. Detailed information about the pharmacokinetics (PK), mechanism of action, known and expected benefits, risks, and reasonably anticipated adverse events (AEs) with ravulizumab IV administration is provided in the Investigator's Brochure (IB).

A Phase 1 study of ravulizumab administered SC was conducted in healthy volunteers (Study ALXN1210-SC-101). This Phase 1 study evaluated the safety, tolerability, PK, pharmacodynamics (PD), and immunogenicity of a single 400-mg dose of ravulizumab SC compared with a single 400-mg dose of ravulizumab IV. In this study, ravulizumab was

administered subcutaneously by a trained member of the study team at clinical sites. Administration of ravulizumab 400 mg SC was generally safe and well tolerated.

2.2. On-body Delivery System

The ravulizumab on-body delivery system (OBDS) is a drug-device combination product comprised of a prefilled cartridge containing ravulizumab SC copackaged with an on-body injector. The device is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, microprocessor controlled), investigational medical device with a 29-gauge integrated needle (manufactured by West Pharmaceuticals, Inc.) designed to be used together with a prefilled stoppered Crystal Zenith® cartridge with a piston and telescopic screw assembly (TSA) (Figure 1).

The OBDS cartridge and on-body injector used in ravulizumab OBDS kits is the same platform currently approved for use with evolocumab (Repatha®) as a combination agent in the United States and CE marked in the European Union as a class IIa Medical Device.

There is no clinical experience with the ravulizumab OBDS in patients with PNH.

Figure 1: Diagram of the On-body Delivery System

Abbreviation: CZ = Crystal Zenith.

2.3. Study Rationale

The purpose of this study is to compare the PK, specifically predose serum concentration (C_{trough}), of ravulizumab SC administered via an OBDS versus ravulizumab IV administration in patients who are clinically stable and have been treated with eculizumab for at least 3 months prior to study entry. Based on the established relationship between PK exposure and clinical response in patients with PNH treated with IV ravulizumab that has shown maximal efficacy (terminal complement inhibition and LDH suppression effect) at the C_{trough} achieved in the registration study, demonstration of noninferior C_{trough} for ravulizumab SC compared with ravulizumab IV will enable bridging of the efficacy and tolerability data from ravulizumab IV registration studies.

The study hypothesis is that Day 71 C_{trough} for ravulizumab SC will be noninferior to that for ravulizumab IV. A noninferiority, rather than a bioequivalence, design was selected for the comparison between treatments for the following reasons:

- A noninferiority outcome on Day 71 C_{trough} will ensure similar efficacy between SC and IV.
- Ravulizumab is tolerated at higher PK exposures following IV administration than those expected in this study from either the SC group or the IV group, thus noninferior and higher SC ravulizumab C_{trough} compared with IV ravulizumab C_{trough} will represent similar tolerability.

Following the clinical development of ravulizumab administered IV once every 8 weeks (q8w), the availability of treatment with ravulizumab SC every week (qw) provides an additional treatment option for patients that may reduce the burdens associated with chronic IV treatment regimens. To simplify self-administration for patients, the use of an OBDS to deliver ravulizumab SC has been selected, and is based on a "user friendly" drug-device combination product (Section 6.2).

Subcutaneous administration will also provide patients the option to self-administer with increased flexibility that may improve their health-related quality of life (HRQoL). This study will assess safety and HRQoL relative to the current standard of care (eculizumab administered as a biweekly IV infusion). In addition, ravulizumab IV has a well-tolerated safety profile even at higher doses, thus PK parameters for ravulizumab SC that are higher than corresponding parameters for ravulizumab IV (ie, C_{trough}) are expected to have similar tolerability.

2.4. Benefit/Risk Assessment

Please refer to the ravulizumab Investigator's Brochure and the Ravulizumab OBDS Device Investigator's Brochure for a complete description.

2.4.1. Potential Benefits

The main objective of effective PNH treatment with targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to block hemolysis and prevent thrombosis.

The recommended dosing of the currently approved therapy for patients with PNH (eculizumab, Soliris) administered by IV infusion, begins with an induction regimen of 600 mg administered IV once weekly for 4 weeks followed by maintenance dosing of 900 mg in the fifth week and every 2 weeks (q2w) (14 ± 2 days) thereafter. The requirement for biweekly IV infusions administered by a health care professional may significantly impact patients' QoL, many of whom have to miss days of work, as well as may require travel to clinical sites to accommodate treatment.

In the Phase 3 Study ALXN1210-PNH-302, ravulizumab IV (n = 97) was shown to be noninferior to eculizumab IV (n = 98) for the treatment of patients with PNH who were clinically stable and had received eculizumab for at least 3 months prior to study entry, based on the primary endpoint of percent change in LDH levels, a direct marker of complement-mediated hemolysis in PNH. All efficacy endpoints were consistently in favor of ravulizumab, with fewer

and less frequent breakthrough hemolysis events in patients treated with ravulizumab. A similar safety profile was observed for ravulizumab and eculizumab.

Self-administered SC treatment for PNH offers the potential for increased independence over treatment by IV infusion and may reduce the burdens and risks associated with chronic IV treatment regimens while increasing patient adherence (Ingersoll, 2008).

Therapies that can be delivered SC are desirable, particularly for patients with chronic diseases such as PNH who currently only have IV options available commercially. Therefore, it is important to evaluate the ravulizumab on-body injector as a potential option for self-administration at home through short-duration SC infusions, which could result in a more convenient way of dosing.

2.4.2. Potential and Identified Risks

2.4.2.1. *Neisseria meningitidis* Infections

Increased susceptibility to infection with *Neisseria meningitidis* is a known risk associated with terminal complement inhibition. Similar to eculizumab, the main risk associated with ravulizumab is the risk of meningococcal infections.

Specific risk mitigation measures are in place to address this risk (Section 8.3.5).

2.4.2.2. Immunogenicity

Administration of any therapeutic protein, including ravulizumab, may induce an immunogenic response potentially resulting in ADAs. The spectrum of potential clinical consequences may include severe hypersensitivity-type reactions and decrease in efficacy (PK and/or PD neutralization) due to development of neutralizing ADA (Casadevall, 2002; Li, 2001).

Of the 261 patients with PNH who were treated with ravulizumab in the ravulizumab IV clinical studies, 1 patient developed a treatment-emergent ADA. Treatment-emergent ADAs have been observed in 3 healthy subjects treated with ravulizumab SC and 1 healthy subject treated with ravulizumab IV in Study ALXN1210-SC-101, and in 4 healthy Japanese subjects in Study ALXN1210-HV-104. All ADA positive titer values were low and negative for eculizumab cross-reactivity. There was no apparent impact of immunogenicity on the PK or PD of ravulizumab.

In studies of patients with atypical hemolytic uremic syndrome (aHUS), only 1 treatment-emergent ADA has been reported with ravulizumab.

Monitoring of immunogenicity for this study will be conducted as described in Section 1.3 and Section 8.2.6.3.

2.4.2.3. Local and Systemic Reactions

Protein therapies administered either SC or IV have the potential risk of causing local (infusion-site reactions) and systemic reactions (infusion-associated reactions). Infusion-site reactions are those localized to the site of SC or IV drug administration and may include reactions such as erythema, pruritus, and bruising. Infusion-associated reactions are those systemic in nature which may be immune or non immune-mediated generally occurring within hours of drug administration. Immune-mediated reactions may include allergic reactions (eg,

anaphylaxis), while non immune-mediated reactions are nonspecific (eg, headache, dizziness, nausea). Monitoring for these reactions will be conducted as part of routine safety assessments for this study (Section 8.3.6.1).

2.4.2.4. Pregnancy Exposure

No studies of ravulizumab have been conducted in pregnant women.

Pregnant or nursing female patients will be excluded from the clinical study. Patients enrolled in the study, and their spouses/partners, will use a highly effective or acceptable method of contraception as required in Section 10.5 (Appendix 5). In the event of a pregnancy, the patient will be discontinued from study drug (Section 7.1).

2.4.2.5. Potential Device-Related Risks

There is no clinical experience with the ravulizumab OBDS. It is considered an investigational medical device and as such bears some potential risks resulting from device deficiencies or user error. Risk management activities (risk control and mitigation measures) have been conducted per ISO14971. Please refer to the Ravulizumab OBDS Investigator's Brochure for a more complete description of the device and potential benefit/risk.

Data supporting the development of the ravulizumab OBDS include the data from the healthy volunteer study using the SmartDose device, that showed the device was well tolerated and safe to use. A risk management study was performed on the ravulizumab OBDS by Alexion and West Pharmaceutical Services, Inc. and risk analyses were performed in accordance with EN ISO 14971:2012. The results of these risk assessments show that all residual risks fall under the low/acceptable or medium/investigate risk category. Control strategies are in place to further mitigate the medium/investigate category risks. Therefore, it is considered that these potential risks are balanced by the opportunity to develop ravulizumab OBDS as an alternative and more convenient way of drug administration in patients requiring chronic treatment.

2.4.2.6. Considerations for Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.8.

2.4.3. Conclusion

The efficacy of ravulizumab IV was shown to be noninferior to eculizumab in Phase 3 clinical studies in complement inhibitor-naïve patients and in patients who had previously received treatment with eculizumab. Ravulizumab (IV formulation; Ultomiris) was approved by the FDA on 21 Dec 2018 for the treatment of PNH. Ravulizumab SC may provide additional benefit by reducing the treatment burden associated with chronic IV dosing. The safety of ravulizumab SC via an OBDS in patients with PNH at the doses specified in this protocol is supported by data from clinical studies of ravulizumab IV and SC in healthy volunteers and clinical studies of ravulizumab IV in patients with PNH, in addition to postmarketing data on the West SmartDose Platform used with other approved therapies. The benefit/risk of ravulizumab SC administration to patients with PNH is anticipated to be favorable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary PK endpoint**
To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH	Day 71 serum ravulizumab C_{trough}
Secondary	**PK Endpoint**
To characterize PK of ravulizumab SC	C_{trough} over time
	PD Endpoint
To characterize PD of ravulizumab SC	Free serum C5 concentrations over time
	Immunogenicity Endpoint
To characterize immunogenicity of ravulizumab SC	Incidence of treatment-emergent ADAs over time
	HRQoL and Treatment Satisfaction Endpoints
To evaluate HRQoL and treatment satisfaction on ravulizumab SC	• Change in FACIT-Fatigue Scale, Version 4, from Baseline to Day 183 • Change in EORTC QLQ-C30 Version 3.0, from Baseline to Day 183 • Reported treatment administration satisfaction as measured by the TASQ score at Baseline and Day 183 • Reported patient preference as measured by the PPQ-SC score at Days 1093
	Safety Endpoints
To evaluate safety of ravulizumab SC and ravulizumab OBDS	• Change in physical examinations, vital signs, electrocardiograms, laboratory assessments over time • Incidence of adverse events and serious adverse events • Incidence of adverse device effects and serious adverse device effects
	Efficacy Endpoints
To evaluate efficacy of ravulizumab SC	• Change over time in LDH • Incidence of breakthrough hemolysis • Achievement of transfusion avoidance • Achievement of stabilized hemoglobin • Change in clinical manifestations of PNH over time • Change in reticulocyte count over time • Change in eGFR over time • Change in PNH RBC clone size over time
	Performance Endpoint
To assess performance of ravulizumab OBDS	• Reported outcome of attempted full-dose administration (including device failure/malfunction)

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; C_{trough} = predose concentration; eGFR = estimated glomerular filtration rate; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; IV = intravenous; LDH = lactate dehydrogenase; OBDS = on-body delivery system; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; PPQ-SC = Patient Preference Questionnaire – Subcutaneous; QLQ-C30 = Quality of Life Questionnaire-Core 30 Scale; RBC = red blood cell; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, open-label, parallel-group, multicenter study to evaluate PK noninferiority of ravulizumab SC administered via an OBDS compared with intravenously administered ravulizumab IV in adult patients with PNH who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry. This study is planned to be conducted at up to 60 centers globally.

The study will consist of an up to a 30-day Screening Period, a 10-week Randomized Treatment Period, and an Extension Period of up to 172 weeks or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first (Section 1.2). The study duration for each patient will be up to 3.5 years. Study entry is defined as the date when informed consent is provided. Patients will be stratified by weight groups (≥ 40 to < 60 kg and ≥ 60 to < 100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

All IV dosing during the Randomized Treatment Period will be administered in the clinic by a trained member of the site study team. Day 1 of study treatment will occur 12 to 16 days from the patient's last dose of eculizumab. Timing for study drug administration and predose PK sample collection is critical to ensure adequate numbers of patients with evaluable PK data (Table 6). The time for the start of the dose administered on Day 1 is the nominal time for all subsequent doses and PK/PD sample collections. Specifically, all subsequent doses during the Randomized Treatment Period are expected to be administered at the same time of day that the dose was administered on Day 1. The PK samples are expected to be drawn as close as possible to the administration of the dose (or from the nominal time from the start of the Day 1 dose on nondosing days). The PK analysis set population is defined in Section 9.3.

The study will enroll at least 105 patients (70 patients in the ravulizumab SC group; 35 patients in the ravulizumab IV group). An interim analysis for sample size re-estimation will be conducted and the sample size may be increased to a maximum of 144 patients (Section 9.5).

Ravulizumab OBDS will be supplied in a kit, comprising 245 mg of ravulizumab SC in a sterile, single-use, prefilled cartridge assembly copackaged with a single-use injector. Two kits will be used to deliver the full 490 mg dose of ravulizumab SC.

Ravulizumab IV loading and maintenance doses will be based on patient body weight at the last recorded study visit.

Patients randomly assigned to the ravulizumab SC group will receive a loading dose of ravulizumab IV on Day 1 followed by maintenance doses of ravulizumab SC on Day 15 and qw thereafter for a total of 10 weeks of study treatment. Two ravulizumab OBDS kits will be used to deliver the full maintenance dose of ravulizumab SC. Patients randomly assigned to the ravulizumab IV group will receive a loading dose of ravulizumab IV on Day 1 followed by a maintenance dose of ravulizumab IV on Day 15 (Table 6).

On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration. Once training has been completed, the patient

will be able to self-administer ravulizumab SC. On Days 29, 43, 57, and 64, patients can self-administer ravulizumab SC in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab SC can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On days that ravulizumab SC is self-administered at home, the site will contact the patient via telephone at scheduled times to ensure patient is queried about study drug dose administration and device condition.

Table 6: Dosing

<table>
<tr><th>Treatment Group</th><th colspan="2">Randomized Treatment Period (10 weeks)</th><th>Extension Period (up to 172 weeks)</th></tr>
<tr><td>Ravulizumab SC</td><td rowspan="2">Loading Dose on Day 1:
Ravulizumab IV
2400 mg[a] or
Ravulizumab IV
2700 mg[b]</td><td>SC Doses on Days 15, 22, 29, 36, 43, 50, 57, and 64:
Ravulizumab SC 490 mg[c]
(2 ravulizumab OBDS kits per weekly dose)</td><td rowspan="2">Maintenance Doses on Day 71 and qw through Day 1275:
Ravulizumab SC 490 mg[d]
(2 ravulizumab OBDS kits per weekly dose)</td></tr>
<tr><td>Ravulizumab IV</td><td>Maintenance Dose on Day 15:
Ravulizumab IV 3000 mg[a]
or
Ravulizumab IV 3300 mg[b]</td></tr>
</table>

[a] Weight group ≥ 40 to < 60 kg.
[b] Weight group ≥ 60 to < 100 kg.
[c] On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for self-administration at home. On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab SC can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits.
[d] Self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.
Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

Day 71 is the end of the Randomized Treatment Period and the beginning of the Extension Period. All Day 71 assessments completed prior to dosing are considered part of the Randomized Treatment Period. Dosing on Day 71 is the start of the Extension Period. During the Extension Period:

- Patients who had been randomized to the ravulizumab SC group will continue to receive 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)
- Patients who had been randomized to the ravulizumab IV group will switch to 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)

Ravulizumab SC dosing during the Extension Period will be self-administered by the patient at home with the following exceptions where ravulizumab SC must be administered in the clinic:

- For patients who had been randomized to the ravulizumab IV group, the ravulizumab SC 490-mg dose on Day 71 will be self-administered by the patient in the clinic with oversight by trained study site personnel as part of the required training program for at home self-administration
- For all patients, doses that coincide with study visits specified in the SoA (Section 1.3) will be self-administered by the patient in the clinic with oversight by trained study site personnel.
- With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits (with oversight by trained study site personnel).
- An additional follow-up phone call will occur 30 days following the last dose of ravulizumab (SC or IV) and is limited to AE and concomitant medication monitoring.

4.2. Scientific Rationale for Study Design

The purpose of this study is to compare the PK, specifically serum C_{trough}, of ravulizumab SC administered via an OBDS versus ravulizumab IV in patients with PNH who are clinically stable and have been treated with eculizumab for at least 3 months prior to study entry.

This study is designed to bridge the efficacy data generated during the studies supporting registration of ravulizumab IV to ravulizumab SC on the basis of PK noninferiority principles. The scientific rationale for the use of PK noninferiority principles is as follows:

1. There is an established relationship between PK exposure and clinical efficacy that underscores a direct link between drug concentration and complement inhibition.
2. There is an established clinical relevance of a PK target concentration for efficacy. Specifically, clinical efficacy can be achieved by complete and sustained complement inhibition through ensuring serum ravulizumab C_{trough} remains above the PK target concentration at all times. In the Phase 3 studies, steady state therapeutic serum concentrations were achieved immediately following the initial dose of ravulizumab and were sustained with q8w maintenance.
3. To bridge the efficacy of the reference IV product to the follow-on SC product by establishing PK C_{trough} noninferiority comparison, where the comparison is performed using the standard regulatory framework of demonstrating the lower bound of a 2-sided 90% CI of the geometric mean ratio for C_{trough} (SC/IV) being greater than the prespecified noninferiority boundary of 0.8.

In the proposed study, the test (ravulizumab SC) and the reference (ravulizumab IV) groups are expected to maintain ravulizumab C_{trough} concentrations above the PK target concentration for efficacy from the start of study treatment. The noninferiority PK assessment is planned on Day 71 (at the time of the C_{trough} following the first maintenance IV dose) and the Sponsor plans to collect safety and tolerability data for up to 3.5 years) or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first.

The safety parameters being evaluated are commonly used in clinical studies per International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

4.3. Justification for Dose

The doses of ravulizumab IV intended for administration in this study are standardized in the clinical development program of ravulizumab IV. Full details are available in the Ravulizumab OBDS Investigator's Brochure.

A single dose of ravulizumab SC 400 mg, administered consecutively as 4 separate 100-mg injections, has been evaluated in a Phase 1 healthy volunteer study and preliminary data indicate ravulizumab SC 400 mg was generally well-tolerated and without any safety concerns.

The proposed weekly dosing regimen of ravulizumab SC 490 mg to be evaluated in this study was identified by integrating the available Phase 1 PK data from Study ALXN1210-SC-101 and from the ravulizumab IV clinical development program using a modelling and simulation framework. A fixed SC maintenance dose of 490 mg for patients weighing ≥ 40 to < 100 kg starting 2 weeks following an IV loading dose is expected to maintain serum drug concentrations above the target concentration needed for complete inhibition of terminal complement in all adult patients weighing ≥ 40 to < 100 kg from the start of the treatment.

4.4. Justification for Device Selected

Ravulizumab SC is intended to be self-administered via SC infusion for maintenance dosing using the ravulizumab OBDS in the clinic or home setting. The ravulizumab OBDS kit consists of ravulizumab SC in a sterile, single-use, prefilled cartridge and is copackaged with a single-use on-body injector.

The drivers for the SC device selection were dose volume capability, demonstrated reliability, and patient-centered usability requirements including ease of use with minimal steps, minimal discomfort, hidden needle, as well as the ability to move about and perform moderate physical activities during the infusion such as walking, reaching, and bending. The West SmartDose Gen 1 device platform meets these criteria.

The ravulizumab OBDS is a disposable, single-use drug-device combination that is configured to deliver a fixed dose of ravulizumab via SC infusion in approximately 10 minutes (2 devices are required for each weekly dose). The device is designed to be easy to use, with a single button to initiate dosing, visual and auditory cues of the device readiness and dose completion, and a safety lock that prevents accidental initiation of dose delivery until the device is attached to the body via an adhesive patch. The small gauge needle in the device and route of administration may carry a reduced risk of systemic infection and other complications compared with IV infusions. Please refer to the Ravulizumab OBDS Investigator's Brochure for a more complete description of the device.

4.5. Regulatory Status and Approval Strategy

Ravulizumab (IV formulation; Ultomiris®) has been approved in the US, Japan, and the EU for the treatment of PNH. Ravulizumab SC has not received marketing authorization in any country.

The West SmartDose device platform is used for a currently marketed product (evolocumab 420 mg). It is the first delivery system with a regulatory approval track record and proven performance compared with other delivery systems under development with similar functionality

and user interface profile. However, it is considered an investigational medical device for the intended use with ravulizumab.

Following clinical evaluation in this study, the ravulizumab OBDS is planned to be registered for its intended use with ravulizumab according to local regulations.

4.6. End of Study Definition

The end of the study for each patient occurs when the safety follow-up is completed. The safety follow-up consists of a telephone call 30 days after the last dose. Data collection during the safety follow-up is limited to reporting adverse events and concomitant medications. If a patient discontinues treatment, but does not discontinue from the study, the end of study for such a patient will be their last visit as long as that visit is more than 30 days from their last dose. The end of the study is defined as the date of the last patient visit or safety follow up, whichever occurs later.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients must meet all inclusion and no exclusion criteria. Patients who fail any of the eligibility criteria may be rescreened once based on discussion and agreement between the Investigator and the Medical Monitor.

Patients are eligible to be included in the study only if they fulfill all of the following criteria:

Age

1. Patients must be at least 18 years of age at the time of signing the informed consent.

Patient and Disease Characteristics

2. Treated with eculizumab according to the labeled dosing recommendation for PNH (900 mg every 14 days ± 2 days) for at least 3 months prior to study entry with no missed doses within 2 months prior to study entry and no more than 2 doses outside of the visit window.
3. Lactate dehydrogenase levels ≤ 1.5 × ULN (upper limit of normal), according to central laboratory, at Screening. Sample must be obtained within 24 hours of or immediately prior to a scheduled eculizumab dose administration (ie, at trough eculizumab level).
4. Documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010).
5. Vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug to reduce the risk of meningococcal infection (*N meningitidis*).

Weight

6. Body weight ≥ 40 to < 100 kg, and in the opinion of the Investigator, are likely to remain within this body weight range for the duration of the study.

Contraception

7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified contraception guidance (Section 10.5 [Appendix 5]) while on treatment and for at least 8 months after last dose of study drug.

Informed Consent

8. Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including self-administration of ravulizumab SC doses, and the use of any data collection device(s) to directly record patient data.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met:

Medical Conditions

1. More than 1 LDH value > 2 × ULN within the 3 months prior to study entry.

2. Major adverse vascular event (MAVE) in the 6 months prior to study entry.
3. Platelet count < 30,000/mm^3 (30×10^9/L) at Screening.
4. Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.
5. History of bone marrow transplantation.
6. History of *N meningitidis* infection.
7. History of unexplained infections.
8. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
9. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
10. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
11. History of malignancy within 5 years of Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
12. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precludes the patient's participation in an investigational clinical study.
13. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Day 1, coexisting chronic anemia unrelated to PNH) that would make patients unlikely to tolerate the requirements of the protocol).
14. History of hypersensitivity to any ingredient contained in the study drug including hypersensitivity to murine proteins.
15. Female patients who plan to become pregnant or are currently pregnant or breastfeeding.
16. Female patients who have a positive pregnancy test result at screening or on Day 1.
17. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might interfere with the patient's full participation in the study, pose an additional risk for the patient, or confound the outcome of the study.
18. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to Screening.
19. Inability to complete the requirements for SC self-administration.
20. Inability to travel to the clinic for specified visits during the Randomized Treatment Period or fulfil the logistic requirements of study drug.

Prior/Concomitant Therapy

21. Concomitant use of anticoagulants is prohibited if not on a stable regimen for at least 2 weeks prior to study entry.

Prior/Concurrent Clinical Study Experience

22. Participation in another study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater (except for participation in observational studies [eg, PNH Registry]).
23. Received any other experimental C5 antagonist at any time.

5.3. Lifestyle Considerations

Not applicable for this study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to treatment.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY DRUG AND MEDICAL DEVICE

6.1. Ravulizumab

Ravulizumab SC is formulated at pH 7.4 and is supplied in 3.5-mL single-use cartridges. Each cartridge of ravulizumab SC contains 245 mg of ravulizumab (70 mg/mL) in 50 mM sodium phosphate, 25 mM arginine, 5% sucrose, 0.05% polysorbate 80, and water for injection.

Ravulizumab IV is formulated at pH 7.0 and is supplied in 30-mL single-use vials. Each vial of ravulizumab IV contains 300 mg of ravulizumab (10 mg/mL) in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80, and water for injection.

Both ravulizumab SC and ravulizumab IV formulations are suitable for human use and manufactured under current Good Manufacturing Practices.

Details regarding ravulizumab SC and ravulizumab IV formulations are presented in Table 7 . The dosing reference charts for ravulizumab SC and ravulizumab IV groups are presented in Table 8 and Table 9 , respectively.

Table 7: Study Drug Administered

	Ravulizumab SC (Test Therapy)	Ravulizumab IV (Reference Therapy)
Dosage Form	Sterile, preservative-free aqueous solution (70 mg/mL) in single-use, 3.5-mL prefilled cartridge designed for use in a single-use on-body delivery system	Concentrated sterile, preservative-free aqueous solution (10 mg/mL) in single-use 30-mL vials
Route of Administration	SC infusion via the ravulizumab OBDS [a]	IV infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia)
Packaging and Supply	Ravulizumab primary container closure is cyclic olefinic polymer crystal zenith cartridge stoppered with butyl rubber stopper and a telescopic screw assembly. The ravulizumab OBDS will be supplied in kits copackaged with the prefilled cartridge and device.	The US Pharmacopeia/European Pharmacopeia Type 1 borosilicate glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits.
Physical Description of Study Drug	Translucent clear to yellowish color, practically free from particles	Clear to translucent, slight whitish color, practically free from particles
Manufacturer	Alexion or contracted manufacturing organization	Alexion or contracted manufacturing organization

[a] The ravulizumab OBDS is a drug-device combination product of a prefilled cartridge containing ravulizumab and the West SmartDose device that will be copackaged for SC administration.

Abbreviations: IV = intravenous; OBDS = on-body delivery system; SC = subcutaneous.

Table 8: Dosing Reference Chart for Ravulizumab Subcutaneous Group

Dose Type	Body Weight (kg)[a]	Dose (mg)	Ravulizumab Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Minimum Infusion Duration minutes (hours)	Maximum Infusion Rate (mL/hour)
Loading (IV)	≥ 40 to < 60	2400[a]	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700[a]	270	270	540	102 (1.7)	318
Maintenance (SC)	≥ 40 to < 100	490	3.5 mL × 2	NA	7.0 mL	9 minutes (0.15)[b]	23.3

Note: Additional dose preparation instructions are provided in the pharmacy manual.
[a] Ravulizumab IV dose will be based on the body weight at the last recorded study visit.
[b] The rate of the SC infusion is preprogrammed into the device. Nine minutes is an approximate based on the instructions for use.
Abbreviations: IV = intravenous; NA = not applicable; SC = subcutaneous.

Table 9: Dosing Reference Chart for Ravulizumab Intravenous Group

Dose Type	Body Weight (kg)[a]	Dose (mg)	Ravulizumab Volume (mL)	Saline Volume (mL)	Total Volume (mL)	Minimum Infusion Duration minutes (hours)	Maximum Infusion Rate (mL/hour)
Loading (IV)	≥ 40 to < 60	2400	240	240	480	114 (1.9)	253
	≥ 60 to < 100	2700	270	270	540	102 (1.7)	318
Maintenance (IV)	≥ 40 to < 60	3000	300	300	600	140 (2.4)	250
	≥ 60 to < 100	3300	330	330	660	120 (2.0)	330
Extension (SC)	≥ 40 to < 100	490	3.5 mL × 2	NA	7.0 mL	9 minutes (0.15)[b]	23.3

Note: Additional dose preparation instructions are provided in the pharmacy manual.
[a] Ravulizumab IV dose will be based on the body weight at the last recorded study visit.
[b] The rate of the SC infusion is preprogrammed into the device. Nine minutes is an approximate based on the instructions for use.
Abbreviations: IV = intravenous; NA = not applicable; SC = subcutaneous.

6.1.1. Study Drug Preparation and Administration

Ravulizumab IV will be prepared and administered by a trained member of the site study team. Ravulizumab SC can be self-administered by patients who have completed the required training for self-administration of ravulizumab SC. Study drug is to be dispensed only to enrolled patients who are confirmed eligible for participation.

6.1.1.1. Ravulizumab Subcutaneous

On Day 15 during the Randomized Treatment Period (for patients randomized to ravulizumab SC) and Day 71 during the Extension Period (for patients randomized to ravulizumab IV), a qualified member of the site study team will provide initial (and ongoing as appropriate) training on how to properly self-administer ravulizumab SC using the 2 required OBDS kits. Following completion of required training, all patients will self-administer their weekly SC infusions at home or in the clinic (with oversight by trained study site personnel), on days specified in the

SoA (Section 1.3). With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits.

The patient is required to follow the instructions for use (IFU) as written. Detailed instructions regarding self-administration of the study drug are provided in the IFU.

In the event of OBDS malfunction where no dose or a partial dose is delivered, the patient should use a new OBDS to ensure that the patient receives at least 490 mg of ravulizumab SC. Please refer to Section 10.4 (Appendix 4), Investigational Medical Product or Device Complaints.

6.1.1.2. Ravulizumab Intravenous

Ravulizumab IV must NOT be administered as an IV push or bolus injection.

Infusions of ravulizumab IV should be prepared using aseptic technique. The patient's required dose of ravulizumab will be further diluted as specified in Table 7 and Table 8 . Once the dosing solution is prepared for a patient, it can only be administered to that patient. Drug will be administered using an IV tubing set via an infusion pump. Use of a 0.2-micron filter is required during infusion of ravulizumab IV. Vials of study drug are for one time use only and any drug product remaining in the vial should not be used for another patient.

The in-use shelf life of the dosing solution is 6 hours at ambient temperature. The expiration date and time of the dosing solution is calculated from breach of the first vial. The dose must be administered within the expiration date and time.

Additional details on preparation and dose administration of study drug are provided in the pharmacy manual.

6.1.1.3. Special Treatment Considerations

Infusion of other MAbs has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. Refer to Section 10.7 (Appendix 7) for guidance on identifying and managing potential drug infusion reactions.

6.1.2. Packaging and Labeling

6.1.2.1. Ravulizumab SC

Ravulizumab SC will be packaged as described in Section 6.2.1.

6.1.2.2. Ravulizumab Intravenous

The primary packaging of ravulizumab IV consists of a 30-mL vial (Type I borosilicate glass) with a stopper and a seal. The secondary packaging consists of a single vial carton. Both primary (vial) and secondary (carton) packaging include a booklet label with relevant information.

6.2. On-body Delivery System

The ravulizumab OBDS drug-device combination product consists of a prefilled cartridge containing ravulizumab SC and an on-body injector. The ravulizumab OBDS is a compact, sterile, single-use, electro-mechanical, wearable infusion device that administers a fixed dose of ravulizumab from a prefilled cartridge assembly into an SC tissue at a fixed rate via a stainless

steel 29-gauge needle. The device is a sterile, single use, surgically invasive active medical device for transient use as per definitions from Medical Device Directive 93/42/EEC. The device contains non removable batteries and includes a biocompatible adhesive patch. The device with adhesive is removed from the skin following completion of the dose.

The primary container closure (cartridge) consists of a 5-mL CZ cartridge with a chlorobutyl elastomeric septum, a chlorobutyl elastomeric piston, and a TSA that is threaded into the piston. The prefilled CZ cartridge is copackaged with the on-body injector in a 2-compartment blister tray. The prefilled cartridge assembly is loaded into the device immediately prior to use by the patient. The device is designed for use only with the provided 3.5-mL prefilled cartridge.

After loading the cartridge into the device, adhering the device to the skin, and device activation the 3.5-mL dose will be delivered in approximately 10 minutes.

Following the completion of training on the use of the device by a qualified member of the site study team, all patients will self-administer ravulizumab SC doses as specified in the SoA. Additional instructions will be provided in the IFU. Additional details on the device are located in the Ravulizumab OBDS Investigator's Brochure.

6.2.1. Packaging and Labeling

The ravulizumab OBDS drug-device combination consists of 2 parts: a prefilled cartridge containing ravulizumab and the on-body injector. The prefilled cartridge and device constituent parts are copackaged in a thermoformed blister pack with a Tyvek lid over the compartment containing the device to provide a sterile barrier. The secondary packaging consists of a blank carton containing the blister pack and a booklet label with relevant instructions.

An identification trace label is attached to the Tyvek covered blister, a serial number label attached to the side of the device, and a single panel label is affixed to each cartridge.

6.2.2. Anticipated Risks, Contraindications, Warnings

Refer to the Ravulizumab OBDS Device Investigator's Brochure for anticipated risks, contraindications, and warnings.

6.3. Handling, Storage, Accountability, and Administration

Details regarding preparation, handling, storage, accountability, and administration of the study drug (ravulizumab IV and ravulizumab SC as part of the ravulizumab OBDS kits), whether administered in the clinic or self-administered at home are discussed below. Additional guidance is provided in the pharmacy manual and the IFU.

6.3.1. Ravulizumab IV and Ravulizumab SC – In-clinic Administration

1. Study drug kits will be released to each site upon receipt of all required documentation based upon applicable regulations.
2. Upon arrival of the study drug kits at the study site, the pharmacist or designee should promptly remove the study drug kits from the shipping cooler and store them in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light.

3. Ravulizumab IV admixed drug product and ravulizumab OBDS kits should be at ambient temperature prior to administration. The material must not be heated (eg, by using a microwave or other heat source).
4. Only authorized site staff may supply or administer study drug at times noted in Section 1.3. The patient will undergo training, by a qualified member of the site study team, to self-administer using the ravulizumab OBDS on Day 15 (patients randomized to ravulizumab SC) and on Day 71 during the Extension Period (patients who had been randomized to ravulizumab IV). After completion of training, ravulizumab SC can be self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel at times noted in Section 1.3. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
5. The Investigator, institution, pharmacist, or the head of the medical institution (if applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
6. Unless institutional procedures require immediate destruction of used ravulizumab IV study drug, accountability will be performed on used and unused IV study drug vials.
7. The ravulizumab OBDS is a single-use drug-device combination that will be immediately disposed in a biological waste container after drug administration. Accountability will be performed on used and unused cartridges and devices.
8. At the end of the study, a final reconciliation must be performed between the amount of study drug kits supplied, dispensed, and subsequently destroyed or returned to Alexion.

6.3.2. Ravulizumab SC – At-home Administration

Ravulizumab OBDS kits for self-administration will be provided to patients in accordance with regional and local requirements.

Upon receipt of the ravulizumab OBDS kits the patient is expected to promptly store them in accordance with the IFU.

Patients are expected to follow the training instructions and IFU on each dosing day to ensure appropriate administration of their ravulizumab dose. The study site personnel will monitor self-administration of ravulizumab SC via telephone calls with the patient on scheduled at-home dosing days during the Randomized Treatment Period to ensure that the patient is queried about study drug dose administered and device condition. During the Extension Period, ravulizumab SC will be self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.

A biological waste container will be supplied to each patient for at-home disposal of used ravulizumab OBDS. Unused kits should be returned to the site.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Measures implemented to reduce potential bias include stratification and randomization. Following stratification by weight (≥ 40 to < 60 kg or ≥ 60 to < 100 kg) each patient will be randomly assigned to a treatment group in a 2:1 ratio using a centralized interactive voice- or web response system.

6.5. Study Drug Compliance

At in-clinic visits, ravulizumab IV will be administered in a controlled setting under the oversight of the Investigator or designee, thereby ensuring compliance with study drug administration. At scheduled in-clinic visits, ravulizumab SC will be self-administered by the patient in a controlled setting with oversight by trained study site personnel, thereby ensuring compliance with study drug administration. Prior to self-administration, all patients are required to complete training for proper use of the ravulizumab OBDS kits by a qualified member of the site study team. When patients are self-administering the required ravulizumab SC doses at home, compliance will be monitored by the site via telephone calls with the patient on scheduled at-home dosing days during the Randomized Treatment Period to ensure that the patient is queried about study drug dose administered and device condition. During the Extension Period, the site will contact patients by telephone on Day 78 to query the patient on study drug administration and completion of the patient e-diary. After Day 78, sites will monitor self-administration of ravulizumab SC via the patient e-diary.

6.6. Prior and Concomitant 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 patient takes or undergoes within 28 days prior to the start of Screening until the first dose of study drug, will be recorded in the patient's electronic case report forms (eCRF). In addition, history of meningococcal vaccination must be collected for the 3 years prior to first dose of study drug.

Transfusions of packed red blood cells received within 1 year prior to first study drug administration will be recorded in the patient's eCRF.

All medication use and procedures undertaken during the study will be recorded in the patient's source document/medical chart and eCRF. This record will include all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications for PNH. Concomitant medications will be recorded from the first infusion of study drug through 30 days after the patient's last dose of study drug, unless the patient transitions to an alternate treatment for PNH. Any changes in concomitant medications also will be recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care during the study, or for the treatment of any AE, along with the allowed medications described below may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

Concomitant use of anticoagulants is prohibited if not on a stable dose regimen for at least 2 weeks prior to study entry.

Use of complement inhibitors other than the patient's assigned study treatment is prohibited.

6.7. Dose or Treatment Group Modification

Patients who received ravulizumab IV during the Randomized Treatment Period will switch to ravulizumab SC 490 mg qw at the start of the Extension Period and continue with this treatment for the duration of the study.

During the Randomized Treatment Period, if any patient administered ravulizumab IV reaches a body weight ≥ 100 kg before Day 71, the patient's data will be excluded from the primary endpoint analysis and the patient will be discontinued from the study as described in Section 7.1. If the patient's body weight is ≥ 100 kg on Day 71, the patient's data will be included in the primary analysis. The patient will be discontinued from the study following completion of Day 71 predose assessments.

During the Randomized Treatment Period, if any patient administered ravulizumab SC reaches a body weight ≥100 kg, the patient will be discontinued from treatment. The patient's data will not be included in the primary endpoint analysis, unless the first observation of such a weight for this patient was at the Day 71 assessment. The patient will be discontinued from the study as described in Section 7.1.

If any patient administered ravulizumab SC reaches a body weight ≥ 100 kg, the patient will be discontinued from treatment.

No other dose or treatment group modification is permitted in the study.

6.8. Treatments After the End of the Study

Upon completion of the last study visit, patients will return to the care of their treating physician.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Patient Discontinuation/Withdrawal From the Study

A patient 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. If a patient discontinues treatment from the study, the Investigator will attempt to perform (if the patient agrees) assessments specified for the Early Termination (ET) Visit (SoA, Section 1.3). The Sponsor and site monitor will be notified as soon as possible. If a patient is withdrawn from the study or withdraws consent no further data will be collected. Patients who withdraw from the study will not be replaced.

Patients should be discontinued from study drug if any of the following occur during the study:

- Serious hypersensitivity reactions (such as bronchospasm with wheezing or requiring ventilator support or symptomatic hypotension, refer to Section 10.7) or serum sickness-like reactions manifesting 1 to 14 days after drug administration;
- Severe uncontrolled infection;
- Patient body weight increase to ≥ 100 kg;
- Pregnancy or planned pregnancy; or
- If the Sponsor's Medical Monitor or the Investigator deems it is in the best interest of the patient.

It is expected that the Investigator will contact the Medical Monitor prior to discontinuing a patient's study drug. If a patient is discontinued from study drug the patient may remain in the clinical study. In this case the patient should be encouraged to return for the remainder of his or her protocol-scheduled visits until starting a different complement-targeted therapy.

The reason for the treatment discontinuation (patient discontinues study drug, but may continue to be present for protocol-required assessments) or study discontinuation (patient discontinues study drug and ends participation in the study) will be recorded in the eCRF.

If a patient is withdrawn from the study with an ongoing AE or an unresolved laboratory abnormality that, in the opinion of the Investigator, is outside of the reference range and clinically significant (Section 8.2.6), the Investigator will attempt to provide follow-up until the laboratory abnormality or AE has resolved or stabilized.

A patient whose body weight increases to 100 kg or more will be discontinued from the study and will return to the care of the patient's treating physician.

If a female patient is permanently discontinued from study drug due to pregnancy, the Investigator will attempt to follow up until the outcome of the pregnancy is known Section 10.5 (Appendix 5).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use all data collected before such a withdrawal of consent.

If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records as well as inform the site monitor and Sponsor.

7.2. Lost to Follow-Up

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

The following actions must be taken if a patient fails to return to the clinic for a required study visit or if the patient is unable to be contacted by telephone on days that are scheduled for at-home self-administration of ravulizumab SC:

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

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

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

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

Should the study be terminated early, the Sponsor or designee will notify the health authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local requirements. Additionally, the Investigators and site monitors will be informed about study termination and applicable next steps.

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. However, under exceptional circumstances, the Investigator may also need to deviate from the protocol to eliminate an immediate hazard to a trial subject and this needs to be discussed as soon as possible with medical monitor.

8.1. Efficacy Assessments

8.1.1. Lactate Dehydrogenase and Other Disease-Related Laboratory Parameters

Blood and urine samples will be collected at the time points indicated in the SoA (Section 1.3). The following disease-related laboratory parameters will be measured during the study:

- Lactate dehydrogenase
- Reticulocyte count
- Paroxysmal nocturnal hemoglobinuria RBC clone size evaluated by high-sensitivity flow cytometry (Borowitz, 2010)
- Estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula)

8.1.2. Transfusion Avoidance

Achievement of transfusion avoidance is defined as patients who remained transfusion free and did not require a transfusion after the first dose of study drug.

8.1.3. Breakthrough Hemolysis

Breakthrough hemolysis is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2 \times$ ULN as assessed by the central laboratory.

8.1.4. Stabilized Hemoglobin

Stabilized hemoglobin is defined as the avoidance of a ≥ 2 g/dL decrease in hemoglobin level from Baseline in the absence of transfusion from Baseline to the end of the period of interest.

8.1.5. Paroxysmal Nocturnal Hemoglobinuria Symptomatology

The Investigator or designee will assess each patient for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria.

8.1.6. Quality of Life Questionnaires

Two validated HRQoL scales will be administered to patients before study drug administration and at the time points specified in the SoA (Section 1.3).

- The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, Version 4.0, is a collection of HRQoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. Patients will score each item on a 5-point scale: 0 (not at all) to 4 (very much). Total scores range from 0 to 52 with higher score indicating better HRQoL.
- The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, is a questionnaire developed to assess the HRQoL of cancer patients. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions are related to HRQoL, with the first 28 questions scored on a 4-point scale (1 = not at all to 4 = very much) and the final 2 questions that probe the patient's overall health and HRQoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0% to 100%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning, but a high score for a symptom scale represents a high level of symptomatology/problem.

Treatment administration satisfaction and patient preference questionnaires will also be assessed at the time points specified in the SoA (Section 1.3).

- The Treatment Administration Satisfaction Questionnaire (TASQ) is a validated questionnaire that will assess patients' perceptions and satisfaction with prior eculizumab IV or ravulizumab SC treatment (Theodore-Oklota, 2016). The TASQ scores treatment administration satisfaction through 5 domains: physical impact, psychological impact, impact on ADL, convenience, and satisfaction. Each domain offers up to 5 response options with lower scores indicating a more positive response. Scoring is completed by summing each of the 5 domains. NOTE: Any safety data generated from this questionnaire will be documented as an AE on the AE eCRF as per the Investigator's medical judgement.
- The PNH Patient Preference Questionnaire-Subcutaneous (PNH-PPQ-SC [PPQ-SC]) was developed to evaluate patient preference for ravulizumab administered subcutaneously versus eculizumab administered intravenously. The questionnaire contains 13 questions, including 1 overall preference question; 1 question evaluating preference for eculizumab or ravulizumab according to 13 treatment characteristics (eg, "Frequency of treatment", "Time required to receive treatment") and 1 write-in option; 1 question asking patients to indicate which treatment characteristic was most important for their overall medication preference; 5 questions evaluating aspects of treatment with eculizumab; and 5 questions evaluating those same aspects of treatment with ravulizumab administered subcutaneously. The overall preference question asks patients to indicate which of the 2 medications they prefer based upon their experience with the 2 treatments. Patients may also select "I do not have a

preference". Question 1 is scored such that "Soliris (eculizumab) via infusion" = -1, "Ultomiris SC (ravulizumab) via subcutaneous injection" = 1, and "I do not have a preference" = 0. Question 2, which assesses preference on 13 treatment characteristics, uses a 5-point scale ("Strongly Prefer Soliris (eculizumab)" = -2; "Somewhat Prefer Soliris (eculizumab)" = -1; "I do not have a Preference" = 0; "Somewhat Prefer Ultomiris SC (ravulizumab)" = 1; "Strongly Prefer Ultomiris SC (ravulizumab)" = 2). The 10 questions that elicit patient evaluation of each drug use a 5-point scale ("Not at all" = 0; "A little bit" = 1; "Somewhat" = 2; "Quite a bit" = 3; "Very much" = 4). Of these 10 questions, 2 (Questions 6 and 11) will be reverse scored so that high scores in the patient evaluation section of the questionnaire represent a more favorable evaluation of the drug in consideration.

The FACIT-Fatigue, EORTC QLQ-C30, TASQ-IV/TASQ-SC, and PPQ-SC will be administered and recorded on paper. Examples of these QoL assessment tools are provided in Appendix 6 (Section 10.6.1, Section 10.6.2, Section 10.6.3, and Section 10.6.4, respectively).

8.2. Safety Assessments

The Investigator or designee will meet with the patients to discuss the potential safety risks of ravulizumab SC, ravulizumab OBDS, and ravulizumab IV to give the Investigator the opportunity to address any of the patient's safety concerns regarding the study.

Investigators are instructed to follow up on any AEs through to their conclusion (resolution or stabilization) as described in Section 10.3 (Appendix 3).

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

8.2.1. Major Adverse Vascular Events

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

A MAVE is defined as follows:

- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)

- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (nontraumatic; nondiabetic)
- Amputation (nontraumatic; nondiabetic)
- Dermal thrombosis
- Other (specify)

8.2.2. Physical Examination

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

8.2.3. Infusion Site Evaluation

Subcutaneous or IV infusion site evaluations will be performed at the time points specified in the SoA (Section 1.3).

8.2.4. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes, and will include systolic and diastolic blood pressure (BP; mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F).

8.2.5. Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be indicated on the eCRF.

8.2.6. Clinical Safety Laboratory Assessments

Laboratory assessments will be tested at a central laboratory facility. Any clinically significant abnormal results should be followed until resolution or stabilization.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If a suspected event of breakthrough hemolysis occurs, an Unscheduled Visit must take place at which time a sample is collected for analysis of LDH, PK, PD, and ADA by the central laboratory.

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 associated with the underlying disease are not considered AEs unless they are judged by the Investigator to be more severe than expected for the patient's condition.

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 the Sponsor notified.

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

8.2.6.1. Urinalysis and Urine Chemistry

Urine samples will be analyzed for the parameters listed in Section 10.2 (Appendix 2). A microscopic examination of urine samples will be performed if the results of the macroscopic analysis are abnormal.

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

8.2.6.2. Virus Serology

Human immunodeficiency virus testing for HIV-1 and HIV-2 is required of all patients prior to enrollment. Patients who are HIV positive will not be enrolled.

8.2.6.3. Immunogenicity Assessments

Blood samples will be collected to test for presence of ADAs to ravulizumab in serum prior to study drug administration. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ravulizumab. Antibodies to ravulizumab will be evaluated in serum samples collected from all patients according to the SoA (Section 1.3). Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies to ravulizumab will be performed using a validated assay by or under the supervision of the Sponsor.

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

8.3. Adverse Events and Adverse Device Effects

Adverse events and SAEs will be reported to the Investigator or qualified designee by the patient (or when appropriate, by a caregiver, surrogate, or the patient's legally authorized

representative). An adverse device effect (ADE) is an AE deemed related to the use of an investigational medical device. The ADEs and serious ADEs (SADEs) will be determined by the Investigator or qualified designee.

The Investigator or qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, ADE, or SADE and remain responsible for following up events that are serious, considered related to the study drug, investigational medical device, or study procedures; or that caused the patient to discontinue the study drug (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs, SAEs, ADEs, and SADEs are outlined in Section 10.3 (Appendix 3).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All events will be collected from the signing of the ICF until the follow-up contact specified in the SoA (Section 1.3).

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of an SAE (including a death) at any time after a patient has been discharged from the study, regardless of whether or not the event is related to the study drug, the Investigator must promptly notify the Sponsor.

Transfusions are treated as efficacy endpoints (Section 8.1.2). Transfusions administered in the inpatient or outpatient setting should not be captured as AEs or SAEs unless identified as such by the Investigator.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.3.3.1. Regulatory Reporting Requirements for Serious Adverse Events and Serious Adverse Device Effects

Prompt notification by the Investigator to the Sponsor of an SAE (eg, suspected unexpected serious adverse reaction [SUSAR], unanticipated serious adverse device effect [USADE]) is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug or investigational medical device under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug or medical device under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.

The Council for International Organizations of Medical Sciences (CIOMS) or MedWatch reports must be prepared for SUSAR or USADE (Section 10.3 [Appendix 3]) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

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

8.3.4. Pregnancy

Contraception guidance that must be followed for the study is described in Section 10.5 (Appendix 5).

For females of childbearing potential, a serum or urine pregnancy test (ie, beta-human chorionic gonadotropin) will be performed according to the SoA (Section 1.3).

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.5. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of ravulizumab increases the patient's susceptibility to meningococcal infection (*N meningitidis*). To reduce the risk of meningococcal infection, all patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes. Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab).

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

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study patients will be provided a safety card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at each visit as part of the review of the patient safety card

as described in the SoA (Section 1.3). Vaccination(s) for *N meningitidis* will be recorded in the patient's eCRF.

8.3.6. Study Drug Administration Reactions

8.3.6.1. Local and Systemic Reactions

Infusion-site reactions are those localized to the site of SC or IV drug administration and may include those such as erythema, pruritus, and bruising. Infusion-associated reactions (infusion-related reactions) are those systemic in nature which may be immune or nonimmune-mediated generally occurring within hours of drug administration. Immune-mediated reactions may include allergic reactions (eg, anaphylaxis), while non immune-mediated reactions are nonspecific (eg, headache, dizziness, nausea). Monitoring for these reactions will be conducted as part of routine safety assessments for this study.

8.3.6.2. Infusion-associated Reactions

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

8.4. Device Performance Assessments

Device performance will be assessed using the reported outcome of attempted full dose administration (including device failure/malfunction) per the requirements in the IFU.

Investigators and patients must report all device deficiencies observed during the course of the study (Section 10.4, Appendix 4). Device deficiencies will be documented in the eCRF as appropriate.

In the event of a device deficiency, whether or not associated with a missed dose, the ravulizumab OBDS may be sent to a core laboratory for analysis.

8.5. Overdose

For this study, any IV or SC dose of ravulizumab greater than that specified/required in the protocol will be considered an overdose medication error. Overdoses are medication errors which are not considered AEs or ADEs unless there is an untoward medical occurrence resulting from them. The Sponsor does not recommend specific treatment for an overdose unless there are associated laboratory abnormalities or clinical symptoms.

Overdose associated with SC administration of ravulizumab via OBDS is defined as administration of ravulizumab SC greater than the dose contained in 2 full OBDS cartridges. The definition is developed for the practical considerations that a full dose ravulizumab SC administration entails the use of multiple OBDS units, each with a cartridge containing a fixed dose/volume of ravulizumab. The definition is based on the overdose definition for a study drug and the wide dose range of safety tolerance for ravulizumab previously clinically investigated (up to 5400 mg IV, equivalent to ≤ ravulizumab in ten full OBDS cartridges).

8.6. Pharmacokinetic Assessments

The timing for collection of samples for PK is critical to the primary endpoint for this study. The time of the start of the dose administered on Day 1 is the nominal time for all subsequent doses and associated samples. A sample obtained outside of the allotted PK visit windows will be considered a protocol deviation. The timing for the next sample collection will remain relative to the nominal time of the start of dose administration on Day 1.

Blood samples for determination of serum drug concentrations will be collected before administration of study drug at the time points and within the windows indicated in the SoA (Section 1.3). For Day 1 of the SC group and Days 1 and 15 of the IV group, a postdose blood sample will be collected within 30 minutes of the end of the infusion. For Day 57 of the IV group, a blood sample will be collected during the site visit; no dose is administered on Day 57. The date and time (24-hour clock time) of each sample acquisition will be recorded.

In the event of breakthrough hemolysis an additional PK sample will be required. Unused samples may be retained for a period of up to 5 years to perform additional ravulizumab-related assessments as necessary.

The laboratory manual will provide details on sample collection, including blood volume requirements.

Serum ravulizumab concentration over time will be evaluated with primary endpoint (C_{trough} at Day 71) as the main PK parameter of interest. Other PK parameters may be explored.

8.7. Pharmacodynamics

Free C5 concentrations will be evaluated over time. Blood samples will be collected before administration of study drug at the time points and within the windows indicated in the SoA (Section 1.3). For Day 1 of the SC group and Days 1 and 15 of the IV group, a postdose blood sample will be collected within 30 minutes of the end of the infusion. For Day 57 of the IV group, a blood sample will be collected during the site visit; no dose is administered on Day 57. Samples obtained outside of the allotted visit windows will be considered protocol deviations. In the event of breakthrough hemolysis, an additional PD sample will be required. Unused samples may be retained for a period of up to 5 years to perform additional assessments as necessary.

Additional details on sample collection, including blood volume requirements, are provided in the laboratory manual.

8.8. Genetics

Genetics will not be evaluated in this study.

8.9. Biomarkers

Not applicable.

8.10. Medical Resource Utilization and Health Economics

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

9. STATISTICAL METHODS AND PLANNED ANALYSES

9.1. Statistical Hypotheses

The statistical hypothesis is that the Day 71 C_{trough} concentration of patients treated with ravulizumab SC via an OBDS is noninferior to that of patients treated with ravulizumab IV.

9.2. Sample Size Determination

Assuming the ratio of the geometric means of C_{trough} (SC/IV) is 1.03 and the coefficient of variation is 0.4, 62 patients in the ravulizumab SC group and 31 patients in the ravulizumab IV comparison group will achieve 90% power to detect noninferiority using a one-sided test at an alpha level of 0.05 and a PK noninferiority boundary (NIB) of 0.8. The alpha level and NIB are based on recommendations in guidance documents "Standard Approaches to Establishing Bioequivalence" and "Guideline on the Investigation of Bioequivalence", from the US Food and Drug Administration and European Medicines Agency, respectively. This sample size is increased to 105 patients (70 patients in the ravulizumab SC group and 35 patients in the ravulizumab IV group) to account for the possibility that up to 10% of patients may not meet the criteria for inclusion in the PK analysis set. An interim analysis to evaluate futility and perform a sample size re-estimation will be performed. More information on this interim analysis is provided in Section 9.5 and details will be presented in the Statistical Analysis Plan (SAP).This sample size re-estimation may lead to an increase of up to 144 patients (up to 96 patients in the ravulizumab SC group and 48 patients in the ravulizumab IV comparison group).

9.3. Populations for Analyses

The populations for analyses are defined in Table 10 . Dosing windows for inclusion in the PK analysis set are presented in Table 10 .

Table 10: Populations for Analyses

Population	Description
Enrolled	All patients who sign the ICF and who are randomized.
PD analysis set	All patients who receive at least 1 dose of ravulizumab and who have evaluable PD data.
PK analysis set	All patients who have evaluable PK data[a] and for whom: 1. All doses up to Day 64 are compliant with the planned dose and the dosing time windows specified in Table 11 . 2. The predose PK sample on Day 71 has been collected within ± 3 hours from the nominal time of the first dose on Day 1.
Per protocol analysis set	All patients in the PK analysis set who satisfied all key eligibility criteria for the study (inclusion criteria 2, 3, 4, 6, 8 and exclusion criteria 1 through 4; as described in Section 5).
Full analysis set	All patients who receive at least 1 dose of ravulizumab.
Safety analysis set	All patients who receive at least 1 dose of ravulizumab. Patients will be analyzed according to the study drug they actually received.

Abbreviations: ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Evaluable PK data are defined as non-missing results generated from samples that comply with sample integrity requirements during sample collection, storage, shipment, and bioanalysis.

Table 11: Dosing Window Requirements for Inclusion in the Pharmacokinetic Analysis Set

Study Day	15	22	29	36	43	50	57	64
Window for dosing to be compliant for inclusion in the PK analysis set (nominal time in hours from the start of the first dose on Day 1)	± 3	± 6	± 6	± 6	± 6	± 6	± 3	± 3

[a] Refer to Table 2 and Table 3 in Section 1.3 for details on dosing and dosing windows.

The PK analysis set will be used for the primary analysis (Section 9.4.1).

9.4. Statistical Analyses

All data and all outcomes derived from the data will be presented in detailed data listings or summary tabulations. Graphical displays may also be provided when appropriate. All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients.

Details of the statistical analyses described below will be specified in a separate Statistical Analysis Plan (SAP) before database lock and analysis. Any change to the data analysis methods described in the protocol will require an amendment only if it changes the primary objective 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. Additional exploratory analyses of the data may be conducted as deemed appropriate.

9.4.1. Primary Analysis

The primary analysis to evaluate noninferiority in serum C_{trough} of ravulizumab SC compared with ravulizumab IV will be conducted after all patients have completed all protocol-required assessments in the Randomized Treatment Period.

The primary analysis will be performed on the PK analysis set.

The primary endpoint is the Day 71 serum ravulizumab C_{trough}. The ratio of the geometric mean C_{trough} from the ravulizumab SC group over the geometric mean C_{trough} from ravulizumab IV group with a 2-sided 90% CI will be calculated. If the lower bound of the 90% CI for the ratio of the geometric means (ravulizumab SC/ravulizumab IV) is greater than the NIB of 80%, then the ravulizumab SC treatment will be concluded to be noninferior to the ravulizumab IV treatment.

To obtain the above referenced 90% CI, the C_{trough} data under consideration will be analyzed using analysis of variance. In addition to the formulation (SC or IV), the model for statistical analysis will take into account body weight. The data will be transformed prior to analysis using a logarithmic transformation. The point estimate and CIs will be calculated and constructed for the mean difference of log-transformed parameters. These will then be back-transformed to be presented on the ratio scale.

Sensitivity analyses will be performed by repeating the primary analysis on the Full Analysis Set (FAS) patients with evaluable PK data and the Per Protocol Set (PPS).

9.4.2. Secondary Analyses

Secondary analyses will be performed on the Full Analysis Set (FAS). When applicable, results from the Randomization Treatment Period will be presented in parallel by treatment group, but no formal comparisons will be performed. Summaries of data over time while patients are receiving SC administration of ravulizumab will be based on time since first exposure to ravulizumab SC. At the start of the Extension Period, it will have been 56 days since their first dose of ravulizumab SC for patients randomized to the SC group, while patients initially randomized to the IV group will be getting their first dose of ravulizumab SC. This exposure difference will be taken into account and, as an example, a summary for Day 183 (since first dose of ravulizumab SC) will use study Day 183 data from patients randomized to the SC group and study Day 239 data from patients randomized to the IV group.

9.4.2.1. Pharmacokinetic/Pharmacodynamic

Pharmacokinetic analyses will be performed for all patients from the FAS who have evaluable PK data, as described in PK analysis set in Section 9.3. Since this is a multicenter patient study censoring of PK or PD data may be considered when a sample collection or handling error is inferred.

Graphs of mean serum ravulizumab concentrations versus time will be constructed. Graphs of serum concentrations versus time for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time as appropriate.

Pharmacodynamic analyses will be performed for all patients from the FAS who have evaluable PD data. The PD effects of ravulizumab will be evaluated by assessing the absolute values for free C5 serum concentrations over time. Descriptive statistics will be calculated for the PD data at each sampling time as appropriate. Additional assessments of serum free C5 concentration may be considered as appropriate.

9.4.2.2. Quality of Life and Treatment Administration Satisfaction

Quality of life will be evaluated using FACIT-Fatigue Version 4 Questionnaire as well as the EORTC QLQ-C30 Version 3.0 questionnaire. The data from these questionnaires will be summarized at Baseline and Day 183, as well as each applicable postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from Baseline.

Patient satisfaction with treatment administration will be evaluated using TASQ scores. These data will be summarized at Baseline and Day 183, as well as each applicable postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from Baseline. NOTE: Any safety data generated from this questionnaire will be documented as an AE on the AE eCRF as per the Investigator's medical judgement.

Patient preference as assessed by the PPQ-SC will be summarized. Among patients who receive ravulizumab SC and have evaluable PPQ-SC data, the number and proportion of patients with a preference for ravulizumab SC, eculizumab, or no preference will be presented at the applicable postbaseline time point.

9.4.3. Efficacy Analysis

Lactate dehydrogenase and other disease-related laboratory parameters will be summarized at Baseline and each applicable postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from Baseline.

The number and proportion of patients with breakthrough hemolysis (defined in Section 8.1.3) will be summarized over time by presenting the number and proportion of patients with a breakthrough along with a 2-sided 95% CI for each applicable postbaseline time point. The number and proportion of patients who do not require a transfusion and the number and proportion of patients with stabilized hemoglobin (defined in Section 8.1.4) will be summarized similarly.

9.4.4. Safety Analyses

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

The following definitions will be used for AEs and ADEs:

- Pretreatment AEs: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent AE (TEAE): Any AE that starts during or after the first infusion of study drug.
- All ADEs are by definition occurring during or after the start of the first infusion.

The incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term overall, by severity, and by relationship to treatment. The incidence of SAEs will also be summarized. The incidence of ADEs and SADEs will be summarized similarly by SOC and Preferred Term and by severity. All AEs and ADEs will be coded using Medical Dictionary for Regulatory Activities, version 18 or higher.

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

Observed values and changes from Baseline (last assessment prior to ravulizumab) in ECGs, vital signs, and laboratory assessments will be summarized for all applicable study visits. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all applicable study visits.

Changes from Baseline in ECG intervals (PR, RR, QT, and QTcF) will be summarized for all applicable study visits. The QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

For the immunogenicity data the number and proportion of patients who develop ADAs to ravulizumab and the titer values will be summarized. The proportion of patients with at least 1 positive ADA result over time (ever positive) and the proportion of patients always negative may be explored.

9.4.5. Device Performance Analyses

Device performance will be evaluated by the number and proportion of doses that were completely administered successfully out of all attempted full-dose administration. The reasons for doses not being completely administered will be summarized. For reasons reported as "device-related technical failure" these technical failures will be further summarized by category.

9.4.6. Other Analyses

Additional exploration of PK, PD, ravulizumab OBDS performance data, and patient reported outcomes may be performed as considered necessary.

9.5. Interim Analysis for Futility and Sample Size Re-estimation

An interim analysis will be performed when 50% of the planned patients (n = 105) have been assessed for the primary endpoint (ie, 34 patients in the ravulizumab SC group and 17 patients in the ravulizumab IV comparison group). This is expected to yield at least 45 patients who meet the criteria for inclusion in the PK analysis set.

The initial part of the analysis will be to assess futility in order to allow the Sponsor to stop the study early if it is unlikely to lead to a significant final result. This will conserve resources and not expose additional patients to the study drug in the event that noninferiority appears very unlikely.

Following the futility assessment, but using the same set of patients and data, an interim sample size re-estimation analysis to reassess the required size of the study based on estimation of the primary endpoint will also be performed.

Enrollment of patients will proceed without interruption while the analysis is ongoing.

There are no plans to stop the study for demonstration of noninferiority at the interim analysis.

Futility Analysis

A nonbinding futility boundary based on conditional power for noninferiority (CPni) of 20% will be used so that if the Sponsor decides to continue the study, even if the futility boundary is crossed, there will be no impact to the primary analysis Type I error rate.

Sample Size Re-estimation

The sample size re-estimation (SSR) analysis will also be based on the CPni calculated using the results obtained at this interim analysis. The CPni will be calculated assuming the 'observed effect' values; ie, the population mean C_{trough} equals the sample mean C_{trough} at the time of the sample size re-estimation. The maximum total number of patients will be 144. The sample size will never be reduced from the planned sample size of 105 patients. If the CPni is at least 90% for the planned total sample size of 105 patients, then no increase in sample size will be made.

The decision to be made based on this sample size re-estimation analysis will follow the following rule (Table 12):

If CPmin $\leq$ CPni $<$ 0.9, increase the sample size by just the right amount such that CPni is increased to 90%, subject to a cap of 144 patients. The range CPmin $\leq$ CPni $<$ 0.9 is called the promising zone for noninferiority. Specifically, if CPni is in its promising zone, this decision rule

increases the sample size, to the smaller of 144 patients or the number needed to boost CPni to 90%.

Table 12: Criteria for Futility Analysis and Sample Size Re-estimation

	Decision
CPni ≤ 20%	Consider stopping for futility
20% < CPni < CPmin%	Continue to N = 105
CPmin% ≤ CPni < 90%	Increase to smaller of N = 144 or N needed for CPni = 90%
90% ≤ CPni	Continue to N = 105

Abbreviations: CPmin = CPni = conditional power for noninferiority; N = number [of patients].

The lower bound of the promising zone, CPmin, will be determined following the approach explained in Mehta and Pocock (Mehta, 2011) and is not explicitly stated here to avoid potential study bias following any decision made based on this sample size re-estimation analysis. Further details will be provided in the SAP.

9.6. Other Statistical Issues

9.6.1. Missing or Invalid Data

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

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH-GCP and ISO guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IBs, and other relevant documents must be submitted to an IRB/IEC by the Investigator and/or by the Sponsor based on applicable local regulations. These documents must be reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC 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, ICH guidelines, the IRB/IEC, European regulation 536/2014, ISO 14155 for clinical studies (if applicable), and all other applicable local regulations
- The clinical investigation cannot begin until the required approval/favorable opinion from the IRB/IEC or regulatory authority has been obtained, if appropriate, as well as any additional requirements imposed by the IRB/IEC or regulatory authority to be followed.

10.1.2. Informed Consent Process

The Investigator or designee will explain the nature of the study to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act requirements, ISO 14155 for clinical studies, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be reconsented to the most current version of the ICF(s) during their participation in the study, if applicable.

The Investigator must retain the original version of the signed ICF(s). A copy of the signed ICF(s) must be provided to the patient.

A patient who is rescreened is not required to sign another ICF unless an updated ICF is available.

10.1.3. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or other information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities.

10.1.4. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient. Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on the US National Institutes of Health website www.clinicaltrials.gov or EU website www.clinicaltrialsregister.eu/ or other publicly accessible websites as appropriate and in accordance with local regulations.

10.1.6. Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing risk-based monitoring to include source data review and 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 patients 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. Study monitors will communicate with investigative sites on a regular basis regarding the study and all protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at their sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected 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 the Sponsor 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, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further ravulizumab development

10.1.8. Publication Policy

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

10.1.9. Remote Visit Options in Times of Emergency

To ensure patient safety and treatment continuity in times of emergency (eg, COVID-19 pandemic), the following will apply where patients are not able to reach the study sites, and until patients are able to resume study visits at the site.

Alternative visit options, such as remote visits, may be at the Investigator's discretion and oversight, in accordance with the local regulations. Remote visit options may include visits conducted at the patient's home, an alternative qualified healthcare facility, or virtually through phone or video conference. All assessments that can be conducted remotely for the study visit day should be conducted according to the Schedule of Activities (Section 1.3) at the discretion of the Investigator by trained qualified staff and in accordance with all national, state, and local laws or regulations. Information about AEs and concomitant medications may be collected from the patient by telephone or other means of communication on the day of the remote visit. In case of any signs or symptoms indicating an SAE, the patient will need to be evaluated at the study site.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 13 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or as required by local regulations.

Table 13: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Distribution width Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Blood urea nitrogen (BUN) C-reactive protein Creatinine	Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Chloride Potassium Bicarbonate Sodium	Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)	Total protein
	Glucose (nonfasting)	Alkaline phosphatase, Gamma glutamyltransferase, Lactate dehydrogenase	Albumin Uric acid
Coagulation	D-dimer, international normalized ratio, partial thromboplastin time, prothrombin time		
Routine urinalysis	- Appearance, color, specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, creatinine and protein:creatinine ratio - Microscopic examination (if blood or protein is abnormal)		
Other Screening tests	- Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) - Follicle stimulating hormone testing - Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies The results of each test must be entered into the eCRF.		
Complement activity	Free C5, PNH clone size		

Abbreviations: C5 = complement component 5; eCRF = electronic case report form; PNH = paroxysmal nocturnal hemoglobinuria.

10.3. Appendix 3: Adverse Events and Adverse Device Effects: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Adverse Event

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

Events Meeting the Adverse Event 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 drug 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. • "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 fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the Adverse Event 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. • Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to investigational product are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Serious Adverse Event

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). Transfusions administered in the inpatient or outpatient setting should not be captured as AEs or SAEs unless identified as such by the Investigator.

A serious adverse event 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 patient 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 were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient 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 based upon appropriate medical judgment may jeopardize the patient 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.

Suspected Unexpected Serious Adverse Reactions

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

Adverse Device Effect

Adverse Device Effect Definition
• An AE related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. • An ADE includes any event that is a result of use error or intentional misuse. Use error refers to an act or omission of an act which results in a different device response than intended by the manufacturer or the user. An unexpected physiological response of the subject does not in itself constitute a use error. • Missing dose (no dose) and partial dose (under dose) medication errors occurring with the use of the device are considered ADEs. Each ADE must be associated with 1 study device (ie, 1 OBDS kit in the current study). • Ravulizumab SC overdose involving multiple OBDS kits is a medication error pertaining to the SC drug administration route therefore will not be considered an ADE. Overdose medication errors from both IV and SC ravulizumab administration defined under Section 8.5. ADEs may arise from the following occasions (Note: These examples are strictly hypothetical and have no implications to the ravulizumab OBDS or any other devices): • **Normal use example:** injection site reactions not associated with any apparent device deficiency, use error or abnormal use of the device • **Device deficiency example**: A bent needle leading to injection site laceration • **Use error example**: With all the intentions to follow the IFU to complete the required dosing, a subject forgot to properly prepare the device application site skin by trimming the hairs leading to the device falling off in the middle of the dosing that led to a partial dosing • **Misuse (abnormal use) example**: A subject, against the device indications specified in the ravulizumab OBDS IB, used the device to administer a substance other than the investigational drug, resulting in toxicity stemming from the substance For this study, one ADE is associated with one investigational device (ie, one OBDS kit). The kit number associated with each ADE must be recorded in the CRF under the ADE.
Medication Error Adverse Device Effects
Two OBDS kits will be used to deliver the full 490 mg dose of ravulizumab SC. Missed dose (no dose) and partial dose (under dose) medication errors associated with study devices or the use of study devices are considered ADEs. • MISSING DOSE: Any missing dose or no dose delivered associated with ravulizumab SC administration using OBDS is to be considered an ADE. The kit number associated with the no dose ADE should be recorded together with the ADE. • PARTIAL DOSE: Following a partial dose there may be an ADE associated with one device. Therefore, one partial dose ADE is associated with one OBDS unit and one kit number is required in the recording of the partial dose ADE.

Serious Adverse Device Effect

Serious Adverse Device Effect Definition
A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

Unanticipated Serious Adverse Device Effect

Unanticipated Serious Adverse Device Effect Definition
An unanticipated serious adverse device effect (USADE) is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the ravulizumab OBDS IB as an expected event (21CFR803.3).

Device Deficiency

Device Deficiency Definition
A device deficiency is an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may be due to malfunction, misuse, user error, inadequate labeling or insufficient information provided by the manufacturer. If a medication error is associated with a device deficiency/malfunction, it is considered an ADE.

Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE or 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 or SAE information in the eCRF.

It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion or designee in lieu of completion of the AE/SAE report. If applicable, additional information such as relevant medical records should be submitted with a signed SAE/SADE cover page to Alexion Global Drug Safety (GDS) via email: PPD or facsimile: PPD In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before sending to GDS.

- 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 Event Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03, published 14 Jun 2010. Each CTCAE term is a Lowest Level Term (LLT) per the MedDRA. Each LLT will be coded to a MedDRA Preferred Term:

- Grade 1: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
- Grade 2: Moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)
- Grade 3: Severe (severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL)
- Grade 4: Life-threatening (urgent intervention indicated)
- Grade 5: Fatal (death related to AE)

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

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for an SAE as described above.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and occurrence of each AE/SAE and between study device and occurrence of each ADE/SADE. An Investigator causality assessment must be provided for all AEs and ADEs (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 (unrelated): There is no evidence to suggest that there was a reasonable possibility that the drug caused the adverse event.
  - Related: There is evidence to suggest that there was a reasonable possibility that the drug caused the adverse event.
- The Investigator will use clinical judgment to determine the relationship to the study drug or the investigational medical device.

Adverse Event and Serious Adverse Event Recording
• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated. • This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document. The Investigator will also consult the IB in his/her assessment. • There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion or designee. 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 GDS.** • 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 Adverse Events and Serious Adverse Events
• 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 or designee 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 patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any post-mortem findings including histopathology if available. • The site will enter new or updated SAE data into the electronic system as soon as it becomes available, but no later than 24 hours. The Investigator will submit any updated SAE data to the GDS within 24 hours of awareness of the information.

Reporting of Serious Adverse Events and Serious Adverse Device Effects

SAE and SADE Reporting to Alexion or Designee via the RAVE Safety Gateway
All SAEs and SADEs must be reported to Alexion GDS within 24 hours of the Investigator or site staff awareness. These timelines for reporting SAE and SADE information to the Sponsor need to be followed for the initial SAE report and for all follow-up SAE information. The Investigator or designee must record the SAE data in the eCRF and verify the accuracy of the information with corresponding source documents. The SAE report should be submitted electronically via the RAVE Safety Gateway. In the event that either the electronic data capture (EDC) or the RAVE Safety Gateway is unavailable at the site(s), the SAE must be reported on the paper SAE contingency form. Facsimile transmission or email may be used in the event of electronic submission failure. For all SAEs, the Investigator must provide the following: • Appropriate and requested follow-up information in the time frame detailed below • Causality of the SAE(s) • Treatment of/intervention for the SAE(s) • Outcome of the SAE(s) • Supporting medical records and laboratory/diagnostic information

SAE and SADE Reporting to Alexion or Designee via the RAVE Safety Gateway

- The primary mechanism for reporting an SAE to Alexion or designee will be the RAVE Safety Gateway
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE/SADE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure.

  Email: PPD
  Facsimile: PPD
- When further information becomes available, the eCRF should be updated with the new information and an updated SAE report should be submitted to Alexion GDS via the RAVE Safety Gateway.
- After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE contingency form to Alexion GDS.

SAE or SADE Reporting to Alexion or Designee via Paper Contingency CRF

- If applicable, additional information such as relevant medical records should be submitted to Alexion GDS via the email address or fax number noted above.
- All paper forms and follow-up information submitted to the Sponsor outside of the RAVE Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file.

10.4. Appendix 4: Investigational Medical Product or Device Complaints

If the use of an investigational medical product or device led to an AE or ADE as defined in Section 10.3 (Appendix 3), the event will be evaluated by Alexion's GDS and the recording and reporting procedures will be followed as described.

Complaints are written, electronic, or oral communications that allege deficiencies about an investigational medical device's identity, quality, durability, reliability, safety, or performance, Upon identification of a product complaint, on either ravulizumab IV dosing solution or ravulizumab OBDS, the site or patient must contact Medical Vigilance Solutions using the local phone number in the IFU document. The site must complete the Product Quality Complaints Form (See the Pharmacy Manual for details).

The following includes potential issues that may warrant lodging a complaint:

- Medical device failure: the ravulizumab OBDS drug-device combination product is used in compliance with the IFU, but does not perform as described (eg, incomplete dose or no dose delivered)
- Labeling irregularity (eg, missing or illegible information on any part of the packaging or IFU)
- Change in appearance of the study drug (eg, color change or presence of particulate matter in the cartridge)
- Evidence of tampering or compromised packaging of the ravulizumab OBDS kit
- Indicator light turns red during the infusion, and device beeps repeatedly
- User error: The ravulizumab OBDS drug-device combination product is not used in compliance with the IFU.

Additional details will be provided in the IFU.

The Investigator is responsible for ensuring that all product complaints that occur after signing of the ICF through 30 days after the last dose of study drug or at the end of the study, whichever is later, are reported.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

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

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

Highly effective contraceptive methods include:

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

Acceptable contraceptive methods include:

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

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

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

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

Pregnancy Testing

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

Additional pregnancy testing should be performed per the time points specified in the SoA (Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection and Reporting of Pregnancy Data

- Pregnancy data will be collected during this study for all patients and a female spouse/partner of male patients. Exposure during pregnancy (also referred to as exposure *in utero*) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
- If a female patient or a male patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GDS via facsimile or email (Section 10.3 [Appendix 3]). 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 an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile (see Section 10.3 [Appendix 3]).
- Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs (Section 8.2).
- Any female patient who becomes pregnant while participating in the study will be discontinued from study drug.

10.6. Appendix 6: Quality of Life Questionnaires

10.6.1. Functional Assessment of Chronic Illness Therapy--Fatigue Subscale Version 4

FACIT-Fatigue will be administered and recorded on paper.

FACIT Fatigue Scale (Version 4)

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

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

10.6.2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

EORTC QLQ-C30 will be administered and recorded on paper.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your first initial: |____|
Your birth date (Day, Month, Year): |__|__||__|__||__|__|__|__|
Today's date (Day, Month, Year): |__|__||__|__||__|__|__|__|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you:

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.6.3. Treatment Administration Satisfaction Questionnaires

The Treatment Administration Satisfaction Questionnaires (TASQ-IV and TASQ-SC) will be administered and recorded on paper.

Used with permission from the developer, Genentech/Roche.

10.6.3.1. Treatment Administration Satisfaction Questionnaire – Intravenous

Instructions: Please complete the following questions based on your Soliris treatment. Your Soliris was given through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion. Please answer the questions **based on your most recent Soliris IV infusion**.

1. Thinking about the IV infusion, how satisfied or dissatisfied are you with the IV infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the IV infusion, how do you rate the pain, swelling, or redness you experienced at the site of the drug injection?

None	Mild	Moderate	Severe	Very Severe

3. Thinking about the IV infusion, how do you rate the pain you experience with the IV infusion process?

None	Mild	Moderate	Severe	Very Severe

4. Thinking about the IV infusion, are the side effects of the IV infusion as you expected?

Much better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

5. Before you receive the IV infusion do you feel anxious about having the infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. When you receive the IV infusion do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much

7. When you receive the IV infusion do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

8. Thinking about IV infusion, how confident are you that the IV infusion is treating your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

9. When you receive the IV treatment do you feel restricted by the IV infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

10. Thinking about the IV infusion, how convenient is it for you to get your IV infusion?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

11. Thinking about the IV infusion, how do you feel about the amount of time it takes to get your IV infusion?

	Too short	Just right	Too long

12. Thinking about the IV infusion, do you feel that the length of time to get your IV infusion was as you expected?

Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

13. Thinking about the IV infusion, how bothered are you by the amount of time it takes to get the infusion?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

14. How much does the IV infusion:

a. Interfere with your usual or daily activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much

b. Limit your daily activities?

Never	Rarely	Sometimes	Most of the time	Always

15. Because of the length of time to apply the IV infusion do you feel that you have lost or gained time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

16. When you receive the IV infusion treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

17. Does the IV infusion impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

18. Thinking about the IV infusion, if given the option, which would you prefer (both options treat your disease in the same way)? Please check one.

- ☐ Prefer intravenous (IV) injection given through a port or a thin plastic tube and a needle into your vein (IV drip). This treatment option usually takes 30 minutes to 2 hours.
- ☐ Prefer subcutaneous (SC) injection, applied with a device on the thigh or abdomen (or belly). This treatment option usually takes 10 – 30 minutes.
- ☐ No preference for treatment option.

19. Thinking about the IV infusion, would you recommend the way you received the treatment (IV infusion) to another patient?

Definitely yes Probably yes I don’t know Probably not Definitely not

10.6.3.2. Treatment Administration Satisfaction Questionnaire – Subcutaneous

Instructions: Please complete the following questions based on your ravulizumab treatment. Your ravulizumab was given through 2 devices placed onto your thigh or abdomen (or belly) area, called a subcutaneous or SC infusion. Please answer the questions **based on your most recent ravulizumab SC infusion**.

1. Thinking about the SC infusion, how satisfied or dissatisfied are you with the SC infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. Thinking about the SC infusion, how do you rate the pain, swelling, or redness you experienced at the site of the drug infusion?

None	Mild	Moderate	Severe	Very Severe

3. Thinking about the SC infusion, how do you rate the pain you experience with the SC infusion process?

None	Mild	Moderate	Severe	Very Severe

4. Thinking about the SC infusion, are the side effects of the SC infusion as you expected?

Much better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

5. Before you receive the SC infusion do you feel anxious about having the infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. When you receive the SC infusion do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much

7. When you receive the SC infusion do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

8. Thinking about SC infusion, how confident are you that the SC infusion is treating your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much

9. When you receive the SC treatment do you feel restricted by the SC infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much

10. Thinking about the SC infusion, how convenient is it for you to get your SC infusion?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

11. Thinking about the SC infusion, how do you feel about the amount of time it takes to get your SC infusion?

Too short	Just right	Too long	

12. Thinking about the SC infusion, do you feel that the length of time to get your SC infusion was as you expected?

Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected

13. Thinking about the SC infusion, how bothered are you by the amount of time it takes to get the infusion?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

14. How much does the SC infusion:

a. Interfere with your usual or daily activities?

Not at all	A little bit	Somewhat	Quite a bit	Very much

b. Limit your daily activities?

Never	Rarely	Sometimes	Most of the time	Always

15. Because of the length of time to apply the SC infusion do you feel that you have lost or gained time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

16. When you receive the SC infusion treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

☐ Yes, I had more than enough time to talk to my nurse and/or doctor.

☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.

☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.

☐ No, I did not have enough time to talk to my nurse and/or doctor.

☐ No, I did not talk to my nurse and/or doctor at all.

17. Does the SC infusion impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

18. Thinking about the SC treatment, if given the option, which would you prefer (both options treat your disease in the same way)? Please check one.

☐ Prefer intravenous (IV) injection given through a port or a thin plastic tube and a needle into your vein (IV drip). This treatment option usually takes 35 minutes to 2 hours.

☐ Prefer subcutaneous (SC) injection, applied with a device on the thigh or abdomen (or belly). This treatment option is usually takes 10 to 20 minutes.

☐ No preference for treatment option.

19. Thinking about the SC treatment, would you recommend the way you received the treatment (SC infusion) to another patient?

Definitely yes Probably yes I don’t know Probably not Definitely not

10.6.4. Patient Preference Questionnaire

The PPQ will be administered and recorded on paper.

Allocation number: _____ Date Completed (dd/mon/yyyy):_____

Paroxysmal Nocturnal Hemoglobinuria Patient Preference Questionnaire—Subcutaneous (PNH-PPQ-SC)

As a patient in clinical trial ALXN1210-PNH-303, you received infusions of Soliris® (eculizumab) (prior to the trial) and subcutaneous injections of Ultomiris® SC (ravulizumab). **Based on your experience with these two medications, please answer the following questions.**

1. Overall, which of the two medications do you prefer? **Mark one box.**
   - ☐ Soliris (eculizumab) via infusion
   - ☐ Ultomiris SC (ravulizumab) via subcutaneous injection
   - ☐ I do not have a preference

2. Which of the two medications do you prefer in terms of each of the following factors? **Mark one box on each line. If you think something does not apply to you, check "I do not have a preference".**

Which medication do you prefer based on…	Strongly Prefer **Soliris (eculizumab)**	Somewhat Prefer **Soliris (eculizumab)**	**I do not have a Preference**	Somewhat Prefer **Ultomiris SC (ravulizumab)**	Strongly Prefer **Ultomiris SC (ravulizumab)**
A) Frequency of treatment	☐	☐	☐	☐	☐
B) Time required to receive treatment	☐	☐	☐	☐	☐
C) Controlling symptoms of PNH	☐	☐	☐	☐	☐
D) Side effects of treatment	☐	☐	☐	☐	☐
E) Discomfort caused by treatment	☐	☐	☐	☐	☐
F) Mode of administration (infusion vs subcutaneous injection)	☐	☐	☐	☐	☐
G) Environment (clinic/home) where you receive treatment	☐	☐	☐	☐	☐
H) Being able to plan activities	☐	☐	☐	☐	☐
I) Having control of your life	☐	☐	☐	☐	☐
J) Convenience of travel	☐	☐	☐	☐	☐
K) Convenience of treatment	☐	☐	☐	☐	☐
L) Anxiety related to treatment	☐	☐	☐	☐	☐
M) Your overall quality of life	☐	☐	☐	☐	☐
N) Other:	☐	☐	☐	☐	☐

PNH-PPQ-SC
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Allocation number: _____ Date Completed (dd/mon/yyyy):_____

3. Which of the factors in Question 2 was the **most important to you** when deciding which medication you prefer? **Please circle only one letter below.**

A	B	C	D	E	F	G	H	I	J	K	L	M	N

The following is a list of statements about treatment for PNH with **Soliris (eculizumab)**. **For each statement, please circle or mark one number per line to indicate your response.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
4.	**Soliris (eculizumab)** was effective in treating symptoms of PNH…	0	1	2	3	4
5.	I felt confident receiving **Soliris (eculizumab)** at clinic……..…	0	1	2	3	4
6.	Treatment with **Soliris (eculizumab)** disrupted my life……	0	1	2	3	4
7.	While I was receiving treatments with **Soliris (eculizumab)**, I was able to enjoy life……..……..	0	1	2	3	4
8.	Treatment with **Soliris (eculizumab)** was simple……	0	1	2	3	4

The following is a list of statements about treatment for PNH with **Ultomiris SC (ravulizumab)**. **For each statement, please circle or mark one number per line to indicate your response.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
9.	**Ultomiris SC (ravulizumab)** was effective in treating symptoms of PNH……..……..	0	1	2	3	4
10.	I felt confident receiving **Ultomiris SC (ravulizumab)** at home……..……..	0	1	2	3	4
11.	Treatment with **Ultomiris SC (ravulizumab)** disrupted my life…….....	0	1	2	3	4
12.	While I was receiving treatments with **Ultomiris SC (ravulizumab)** I was able to enjoy life……..……	0	1	2	3	4
13.	Treatment with **Ultomiris SC (ravulizumab)** was simple…….....	0	1	2	3	4

10.7. Appendix 7: Management of Potential Infusion-associated Adverse Events During Study Drug Administration

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

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug. All AEs that may indicate an infusion-related response will be graded according to the CTCAE v4.03 or higher.

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

Clinical Criteria for Diagnosing Anaphylaxis:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that patient's baseline

Source: (Sampson, 2006)

10.8. Appendix 8: COVID-19 Risk Assessment

PNH can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. 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 partaking in the study. Given that treatment for PNH 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. Apart from the predictable risk of infection with *Neisseria meningitidis*, which is an important identified risk and directly related to the mechanism of action of ravulizumab (terminal C5 inhibitor [targeted immunosuppressant]), the mechanism that might lead to other serious infections, including viral infections in participants treated with ravulizumab, remains unclear. 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 14.

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

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless 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.

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or participant study discontinuations due to COVID-19).

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

10.9. Appendix 9: Abbreviations

Abbreviation	Definition
ADA	antidrug antibody
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
BP	blood pressure
C5	complement component 5
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
e-diary	electronic diary
EORTC	European Organisation for Research and Treatment of Cancer
ET	early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale
FAS	Full Analysis Set
GCP	good clinical practice
GDS	Global Drug Safety
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
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
IFU	instructions for use
IRB	Institutional Review Board
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLT	lowest level term
mAb	monoclonal antibody
MAVE	major adverse vascular event
NIB	noninferiority boundary
NO	nitric oxide
OBDS	on-body delivery system
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPQ-SC	Patient Preference Questionnaire - Subcutaneous

Abbreviation	Definition
qw	every week
q8w	once every 8 weeks
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire - Core 30 scale
RBC	red blood cell
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SoA	schedule of activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TASQ	Treatment Administration Satisfaction Questionnaire
TEAE	treatment-emergent adverse event
TSA	telescopic screw assembly
USADE	unanticipated serious adverse device effect
ULN	upper limit of normal

10.10. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 4	Global	19 Nov 2019	• To increase the Extension Period to up to 3.5 years. All patients will enter an Extension Period and receive ravulizumab subcutaneous (SC) via the on-body delivery system (OBDS) for up to 3.5 years, or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first. • To update the definition for the pharmacokinetic (PK) analysis set based on an assessment of compliance with the dosing and PK sampling windows specified in the Schedule of Activities (SoA; Section 1.3) and on PK simulations conducted to confirm permitted dosing and sampling windows.
Amendment 3	Global	17 May 2019	• To reduce the patient burden by eliminating three in-clinic study visits for patients in the ravulizumab SC treatment group during the Randomized Treatment Period and replacing with self-administration of ravulizumab SC by the patient in the home setting • To provide additional information required by ISO guidelines for investigational devices
Amendment 2	Global	20 Sep 2018	• Modification of the criteria of the assessment of causality of adverse events by the Investigator • To capture medication errors occurring with the use of ravulizumab OBDS as adverse device effects (ADEs) • Administrative changes including introduction of the possibility of recording quality of life assessments data optionally on paper
Amendment 1	France	01 Aug 2018	To remove free hemoglobin testing, add restriction on ova donation for female subjects, and address minor inconsistencies.
Original protocol	Not applicable	25 Jun 2018	Not applicable

11. REFERENCES

Borowitz MJ, Craig FE, Digiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry B Clin Cytom. 2010;78(4):211-230.

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2811.

Brodsky RA. Complement in hemolytic anemia. Blood. 2015;126(22):2459-2465.

Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med. 2002;346(7):469-475.

Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-4996.

Hill A, Sapsford RJ, Scally A, et al. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. Br J Haematol. 2012;158(3):409-414.

Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2010;85(8):553-559.

Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008;31(3):213-224.

Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001;98(12):3241-3248.

Mehta C, Pocock S. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Medicine. 2011;30:3267-3284.

Sahelijo L, Mujeebuddin A, Mitchell D, et al. First in human single-ascending dose study: safety, biomarker, pharmacokinetics and exposure-response relationships of ALXN1210, a humanized monoclonal antibody to C5, with marked half-life extension and potential for significantly longer dosing intervals [abstract]. Blood. 2015;126(23):4777.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Sheridan D, Yu ZX, Zhang Y, et al. Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action. PLoS One. 2018;13(4):e0195909.

Theodore-Oklota C, Humphrey L, Wiesner C, Snchnetzler G, Hudgens S, Campbell A. Validation of a treatment satisfaction questionnaire in non-Hodgkin lymphoma: assessing the change from intravenous to subcutaneous administration of rituximab. Patient Prefer Adherence. 2016;10:1767-1776.