ACCESS-1 STUDY

Study Contacts

Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study.

1. Male or female ≥18 years of age or legal age of majority, whichever is greater, at the time of consent
2. Diagnosis of PNH confirmed by high-sensitivity flow cytometry testing with PNH granulocytes (ie, polymorphonuclear neutrophils [PMNs]) or monocytes ≥5% at the screening visit
3. Active disease, as defined by the presence of 1 or more PNH-related signs or symptoms (eg, fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], history of a MAVE [including thrombosis], dysphagia, or erectile dysfunction) or history of RBC transfusion due to PNH within 3 months of the screening visit
4. LDH level ≥2 × ULN at the screening visit
5. Willing and able to comply with clinic/remote visits and study-related procedures
6. Provide informed consent signed by study patient
7. Able to understand study-related questionnaires

Exclusion Criteria

Note: If a patient screen fails, and if the study is still ongoing, they may be rescreened (up to 2 times) if the investigator determines the patient may be eligible upon rescreening.
A patient who meets any of the following criteria will be excluded from the study:

1. Prior treatment with eculizumab within 3 months prior to screening, ravulizumab within 6 months prior to screening, or other complement inhibitors within 5 half-lives of the respective agent prior to screening.
2. Receipt of an organ transplant, history of bone marrow transplantation or other hematologic transplant.
3. Body weight <40 kilograms at screening visit.
4. Current plans for modification (initiation, discontinuation, or dose / dosing interval change) of the following background concomitant medications, as applicable, during screening and treatment periods: erythropoietin, immunosuppressive drugs, corticosteroids, antithrombotic agents, anticoagulants, iron supplements, and folic acid.
5. Planned use of any complement inhibitor therapy other than study drugs during the treatment period.
6. Any of the following abnormalities at the screening visit (two repeat measurements are allowed per parameter during screening period):
   a. Peripheral blood absolute neutrophil count (ANC) <500/μL (<0.5 × 10^9/L) or
   b. Peripheral blood platelet count <30,000/μL or
   c. Peripheral blood reticulocyte count abnormality defined as <60,000/μL (<0.06 × 10^6/μL, <60 × 10^9/L)

Note: A patient will not be excluded if upon repeat testing the parameter no longer meets the exclusion criterion.
Note: Patients receiving acute treatment (eg, platelet transfusions, granulocyte colony stimulating factors) for these conditions during screening and in the 1-month preceding screening will not be eligible

7. Not meeting meningococcal vaccination requirements for ravulizumab according to the current local prescribing information (where available) and at a minimum documentation of meningococcal vaccination within 5 years prior to screening visit.
   Note: Patients without prior vaccination will be eligible provided they are willing to undergo vaccination prior to initiation of study treatment and vaccination is documented prior to randomization.
8. Any contraindication for receiving *Neisseria meningitidis* vaccination.
9. Unable to take antibiotics for meningococcal prophylaxis (if required by local ravulizumab prescribing information, where available, or national guidelines/local practice, or if necessary when vaccination is less than 2 weeks from study treatment initiation).
10. Any active, ongoing infection or a recent infection requiring ongoing systemic treatment with antibiotics, antivirals, or antifungals within 2 weeks of screening or during the screening period.
11. Documented history of systemic fungal disease or unresolved TB, or evidence of active or latent tuberculosis infection (LTBI) (ie, if not having completed treatment for LTBI) during screening period. Assessment for active TB and LTBI should accord with local practice or guidelines, including those pertaining to risk assessment, and the use of tuberculin skin test or T-cell interferon-gamma release assay.
12. Positive hepatitis B surface antigen or hepatitis C virus RNA during screening.
    Note: Cases with unclear interpretation should be discussed with the medical monitor.
13. Patients with known HIV with history of opportunistic infections in the last 1 year, any history of HIV related malignancy, documented history of CD4 count <500 cells/μL or detectable viral load within the last 6 months (note: CD4 count, and viral load must be available within the last 6 months, and may be conducted by a local laboratory during screening if needed)
    Note: Local testing for HIV may be conducted in patients if required locally or by local regulations.
14. Documented* history of positive RT-PCR, antigen or serology test, or other health authority authorized test for SARS-CoV-2 and:
    a. Have not recovered from COVID-19 (all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient should be resolved to baseline), and
    b. Did not have 2 negative results from a health authority-authorized nucleic acid amplification (RT-PCR) test or other health authority authorized test for COVID-19 taken at least 48 hours apart prior to day 1.

    *Note: Screening for COVID-19 will not be performed as part of eligibility assessments for this study
15. Known hereditary complement deficiency.
16. Documented history of active, uncontrolled, ongoing systemic autoimmune diseases.
17. Documented history of liver cirrhosis or patients with liver disease with evidence of current impaired liver function or patients with ALT or AST (unrelated to PNH or its complications) >3× ULN at the screening visit (if the AST or ALT returns >3 × ULN, 1 repeat lab of the abnormal parameter(s) is allowed during screening).
18. Patients with an eGFR of <30 mL/min/1.73m^2 (according to Chronic Kidney Disease - Epidemiology Collaboration equation 2009) at screening visit (one repeat assessment allowed during screening).
19. Recent unstable medical conditions, excluding PNH and PNH related complications, within the past 3 months prior to screening visit (eg, myocardial infarction, congestive heart failure with New York Heart Association Class ≥ III, serious uncontrolled cardiac arrhythmia, cerebrovascular accident, active gastrointestinal bleed).
20. Anticipated need for major surgery during the study.
21. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.
22. Participation in another interventional clinical study or use of any experimental therapy within 30 days before screening visit or within 5 half-lives of that investigational product, whichever is greater, except for complement inhibitors.
23. Known hypersensitivity to eculizumab, ravulizumab, pozelimab, cemdisiran or to any components of their respective formulations.
24. Prior discontinuation of eculizumab or ravulizumab due to a safety reason or due to lack of efficacy.

25. Patients with functional or anatomic asplenia.
26. Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, or patients with short life expectancy.
27. Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, eg,
    a. Deemed unable to meet specific protocol requirements, such as scheduled visits.
    b. Deemed unable to administer or tolerate need for chronic injections.
    c. Presence of any other conditions (eg, geographic, social) actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study.
    d. Part of a vulnerable population such as the institutionalized (this may also include patients who are committed to an institution by order issued either by the judicial or the administrative authorities, as applicable).
    e. Patient ineligible for clinical trial participation due to local regulations (eg, under legal protection measures [such as L1121-8 or L1121-8-1 in France], etc).
28. Members of the clinical site study team and/or his/her immediate family unless prior approval granted by the sponsor.
29. Pregnant or breastfeeding women.
30. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 52 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation or tubal occlusion;
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure) and/or
    e. sexual abstinence[†, ‡]

*WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance.
Pregnancy testing and contraception are required for WOCBP. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.
†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
31. Hemoglobin ≤7 g/dL (Note: A patient may receive a blood transfusion during the screening period and is eligible if repeat hemoglobin returns >7 g/dL prior to randomization. More than 2 repeat measurements are allowed.)

Schedule of Events for the Open-Label Treatment Period

		Screening		Open-Label Treatment Period (OLTP)[1]									
Study Procedure (Visit)[2]													**EOS**
		V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Week		Up to -6	-4 to -2	0	2	4	8	10	12	16	18	20	24	26
Day		Up to -42	-28 to -14	1	15	29	57	71	85	113	127	141	169	183
Window (day)					±2	±3	±3	±3	±3	±7	±3	±3	±7	±3
Screening/Baseline:														
eCOA device dispensation			X											
Inclusion/Exclusion		X	X	X										
Informed consent		X												
FBR informed consent (optional)		X												
Genomics informed consent (optional)		X												
Medical history[3]		X												
Prior medications[4]		X												
Demographics		X												
Height		X												
Hepatitis B and C testing		X												
Vaccination / revaccination for *Neisseria meningitidis*[5]			X											
Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (if needed)[6]			X											
Tuberculosis history and assessment[7]		X												
Risk assessment for *Neisseria gonorrhea*[8]		X												
Randomization				X										
Treatment:														
IVRS/IWRS		X		X	X	X	X	X	X	X	X	X	X	X
Ravulizumab arm	Ravulizumab IV Q8W[10]			X	X			X			X			X[30]
Pozelimab and cemdisiran treatment arm[11]	Pozelimab 30 mg/kg IV loading dose			X[12]										
	Pozelimab 400 mg SC Q4W[12]			X[12]		X	X		X	X		X	X[31]	
	Cemdisiran 200 mg SC Q4W[12]			X		X	X		X	X		X	X[31]	
Injection training/patient instructions[12]						X	X		X	X		X	X	
Patient diary[13]						X	X	X	X	X	X	X	X	X
Concomitant meds and procedures		X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening		Open-Label Treatment Period (OLTP)[1]										
Study Procedure (Visit)[2]													**EOS**
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Week	Up to -6	-4 to -2	0	2	4	8	10	12	16	18	20	24	26
Day	Up to -42	-28 to -14	1	15	29	57	71	85	113	127	141	169	183
Window (day)				±2	±3	±3	±3	±3	±7	±3	±3	±7	±3
Transfusion record update	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibiotics prophylaxis (recommended)[14]								X					
Clinical outcome assessments (COAs):													
FACIT-Fatigue			X	X	X	X		X	X		X	X	X
EORTC-QLQ-C30			X	X	X	X		X	X		X	X	X
EQ-5D-5L			X										X
TSQM			X		X	X		X	X		X	X	X
PNH symptom-specific questionnaire (daily)[15]								X					
PGIS (PNH Symptoms/Impacts/ Fatigue)			X	X	X	X		X	X		X	X	X
PGIC (PNH Symptoms/Impacts/ Fatigue)					X			X				X	X
Safety and Anthropometric:													
For ravulizumab arm only: Provide patient safety brochure for ravulizumab			X										
Patient safety card for *Neisseria meningitidis*[9]			X	X	X	X	X	X	X	X	X	X	X
Body weight	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs[16]	X		X	X	X	X	X	X	X	X	X	X	X
Physical examination[17]	X				X	X		X					X
Electrocardiogram	X							X					X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis assessment[18]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[19]:													
Titers to measure *N. meningitidis* (only if required per local practice/regulations)	X												
Hematology[20]	X		X	X	X	X		X	X	X	X	X	X
Coagulation parameters	X		X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (long panel) including LDH[21]	X		X	X	X	X	X	X	X	X	X	X	X
D-dimer			X					X				X	X
Immunoglobulin G			X		X			X					
Pregnancy test (applicable patients): serum (S) or urine (U)	S		U		U	U		U	U		U	U	U
Urinalysis	X		X	X	X	X		X	X		X	X	X
Direct antiglobulin test (DAT or Coombs test)			X			X							X

		Screening		Open-Label Treatment Period (OLTP)[1]										
Study Procedure (Visit)[2]														**EOS**
		V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
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Day		Up to -42	-28 to -14	1	15	29	57	71	85	113	127	141	169	183
Window (day)					±2	±3	±3	±3	±3	±7	±3	±3	±7	±3
Pharmacokinetics, ADA, and Total C5 Sampling:														
Pozelimab and cemdisiran arm	Pozelimab PK sample[22]			X	X	X	X		X	X		X	X	
	Cemdisiran and its metabolites PK sample[23]			X					X			X		
	ADA sample for pozelimab[25]			X					X				X	
	ADA sample for cemdisiran[25]			X					X				X	
	Total C5 (plasma)[27]			X	X	X	X		X	X		X	X	X
Ravulizumab arm	Ravulizumab PK[24]			X	X	X		X	X	X	X		X	X
	ADA sample for pozelimab[25]													X[26]
	ADA sample for cemdisiran[25]													X[26]
	Total C5 (plasma)[27]			X	X	X	X		X	X		X	X	X
Biomarkers:														
Free hemoglobin[27]		X		X[28]		X	X		X			X	X	X
Haptoglobin[27]				X[28]		X	X		X			X	X	X
Complement hemolytic assay (serum CH50 and AH50)[27]				X[28]	X	X	X		X	X	X	X	X	X
sC5b-9 (plasma)[27]				X[28]	X	X	X		X	X	X	X	X	X
PNH erythrocyte cells[27]		X							X					X
PNH granulocytes and monocytes[27]		X							X					X
Exploratory research serum sample[27]				X[28]			X					X	X	X
Exploratory research plasma sample[27]				X[28]			X					X	X	X
Optional pharmacogenomics (RNA & DNA)														
Whole blood sample for DNA isolation (optional)[29]				X										
Whole blood sample for RNA isolation (optional)				X					X					X

1. Study procedure visits on days 15, 71, 113, 127, 141, and 169 may be at the clinical site, or another preferred location such as patient's home. The location will be dependent on availability (and if approved by the sponsor) of home healthcare visiting professional, and preferences of the investigator and patient. Visits may also be conducted at another preferred location depending on extenuating circumstances such as due to SARS-CoV-2 infection provided the assessments can be performed by the visiting healthcare professional.
2. When multiple procedures are performed on the same day, the sequence of procedures is as follows: COA assessments; ECG/vital signs/physical examination; blood collection (first coagulation draw then chemistry draw followed by all other labs); and study drug administration. It is particularly important that the scheduled blood draws are obtained prior to the administration of ravulizumab or pozelimab and cemdisiran, especially efficacy parameters such as LDH (ie, measurements reflect a time point at the end of the dosing interval). During blood sample collection, handling, and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, consideration should be given to repeating the lab sample if clinically warranted and, in all cases, where an LDH is ≥2 × ULN in association with potassium ≥6 mmol/L. Specific instructions for avoiding hemolysis is provided in the relevant section of the protocol.

3. Medical history including, transfusions, breakthrough hemolysis history, and laboratory parameters for measurement of hemolysis (such as LDH, bilirubin, haptoglobin, reticulocyte count, and hemoglobin) should be obtained for the past 52 weeks, if possible. Prior history of thrombosis and infections of the ***Neisseria spp***. will be collected. Patients with a known C5 mutation (ie, C5 variants R885H/C) are not eligible, however, if a C5 mutation is later suspected and confirmed while the study is ongoing, the information should be included as part of the patient's medical history. Patients who are poor responders to ravulizumab treatment during the study may be asked for a mutation analysis to be conducted locally as part of the study, if the patient consents to such testing.
4. Including detailed medication history for PNH treatment and *Neisseria meningitidis* vaccination history and other vaccinations as applicable.
5. Patients will require administration with meningococcal vaccination unless documentation is provided of prior immunization in the past 5 years or less than 5 years if required according to current national vaccination guidelines for vaccination use with complement inhibitors/local ravulizumab prescribing information. For patients who require administration with meningococcal vaccination(s) during the screening/period, administration should occur preferably at least 2 weeks prior to day 1, or at another time point according to local ravulizumab prescribing information/national guidelines.
6. Vaccination for *Streptococcus pneumoniae and Haemophilus influenzae* Type B should be per current national/local vaccination guidelines.
7. Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator.
8. A risk factor assessment for *Neisseria gonorrhea* will be performed in accordance with local practice/national guidelines and regular testing and counseling is advised for at-risk patients.
9. Patient safety card for *Neisseria meningitidis* infection will be provided to the patient on day 1 or any other visit when needed. Site should review the instructions on the safety card with the patient at each visit.
10. Patients who are randomized to ravulizumab will receive ravulizumab according to the labeled posology with the first dose of ravulizumab administered on day 1 (or up to 2 days after the day 1 visit) according to the patient's weight (≥40 kg to <60 kg, 2400 mg IV; ≥60 kg to <100 kg, 2700 mg IV; ≥100 kg, 3000 mg IV). The first maintenance dose should be administered 2 weeks after the loading dose as follows: (≥40 kg to <60 kg, 3000 mg IV; ≥60 kg to <100 kg, 3300 mg IV; ≥100 kg, 3600 mg IV). Thereafter, the maintenance dose is to be administered IV Q8W (±7 days). As the first maintenance dose is to be administered exactly 2 weeks after the loading dose, the week 2 visit should proceed within the visit window, the day of or preceding the ravulizumab administration. If ravulizumab administration does not coincide with the day of clinic visit, as applicable, assuming that both the treatment and visit windows are respected, then the clinic visit should always precede the infusion of ravulizumab dosing. A body weight should be performed prior to administration of ravulizumab to allow for weight-based dosing. Patients who opt not to enroll into the follow on OLE study or who will not screen for the R3918-PNH-2022 will have the last dose of ravulizumab at week 18 (day 127).
11. Patients who are randomized to pozelimab and cemdisiran combination arm will receive pozelimab 30 mg/kg IV along with pozelimab 400 mg SC and cemdisiran 200 mg SC on day 1. Patients should be monitored for at least 30 minutes after completion of pozelimab 30 mg/kg IV and should be monitored for at least another 30 minutes after the completion of the first pozelimab and cemdisiran SC dosing. Subsequent SC doses of the combination will be administered Q4W and may either be performed by the site personnel or another healthcare professional at patient's home (if available), or administration by patient or designated person at the patient's preferred location. The final dosing of the SC combination in the OLTP is at week 24. The dose of pozelimab and cemdisiran should be given Q4W (every 28 days) and on the day of the corresponding study visit whenever possible. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed. If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 7 days before or up to 7 days after the planned dosing date as long as the dosing takes place after the corresponding study visit has been completed. For example, the week 8 (D57) visit can take place from D54 to D60 given the visit window. The dose of pozelimab and cemdisiran therefore can be given from D54 to D64 but only on or after the week 8 visit assessments have been performed. Similarly, the week 16 (D113) visit can take place from D106 to D 120 given the visit window. The dose of pozelimab and cemdisiran can be given from D106 to D120 but only on or after the week 16 visit assessments have been performed. Pozelimab and cemdisiran should be administered on the same day whenever possible.
12. If the sponsor has endorsed self-injection, injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient syringe preparation and self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided (or reviewed as needed).
13. Patient diary: If needed, for self-administration or administration by a designated person with pozelimab and cemdisiran combination treatment only, a patient diary may be provided to collect information on study treatment administration. Patient diary may be provided at week 4 visit or a subsequent visit. If patient diary is provided to the patient then it should be reviewed at each clinic visit and data collected into the case report forms (CRFs). On the final visit, the diary should be collected by the site.

14. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until up to 52 weeks after discontinuation of pozelimab and cemdisiran. For post-treatment prophylaxis for ravulizumab, consult the local prescribing information/ national guidelines/local practice. If vaccination for *Neisseria meningitidis* occurs less than 2 weeks prior to day 1, then antibiotic prophylaxis must be administered for at least 2 weeks from the day of vaccination.
15. Patient will complete PNH Symptom-Specific Questionnaire daily for 14 days prior to day 1 visit and continuing through the OLTP.
16. Vital signs include temperature, sitting blood pressure and pulse. Vital signs will be obtained pre-dose after the patient has been sitting quietly for at least approximately 5 minutes, where applicable.
17. Physical examination will include an evaluation of the head and neck, lungs, heart, abdomen, extremities, and skin. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.
18. If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50, drug concentrations of pozelimab/ravulizumab/cemdisiran, ADA (against pozelimab) and exploratory research serum and plasma will be collected unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur to evaluate the patient and to collect CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50 drug concentrations of ravulizumab/pozelimab/cemdisiran, and ADA (against pozelimab). In addition, an exploratory research serum and plasma sample should be collected.
19. Clinical lab samples will be collected first before study drug administration. The coagulation blood sample must always be collected first, followed immediately by the blood chemistry sample. The same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing.
20. Hemoglobin will be assessed as part of the hematology analysis. Hematology sample should be collected before study treatment administration.
21. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration.
22. Blood samples for pozelimab PK will be obtained on the specified days prior to the pozelimab dosing. On study visit day 1, obtain blood samples prior to IV administration of pozelimab and also within 15 minutes after the end of the pozelimab IV infusion.
23. Cemdisiran and its metabolite PK samples will be collected on the specified days before and 1 to 4 hours post cemdisiran administration. The post dose sample may be collected at the clinic or by a visiting health care professional (if available).
24. Blood samples for ravulizumab PK will be obtained prior to IV administration of ravulizumab and also within 15 minutes after the end of ravulizumab IV infusion.
25. Blood samples for ADA will be collected on the specified days before the study drug administration. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional blood samples may be collected at or near the onset of the event for PK, ADA and other analyses.
26. For patients randomized to combination arm as well as patients in ravulizumab arm who will be continuing in the transition period, blood samples are collected pre-dose to assess ADA of pozelimab and cemdisiran.
27. Blood samples for total C5, free hemoglobin, haptoglobin, CH50, AH50, sC5b-9, and PNH erythrocytes, granulocytes, monocytes, and exploratory research serum and plasma will be obtained on the specified days prior to ravulizumab or the combination administration.
28. All biomarkers collected specifically on V3/day 1 must be collected pre-dose.
29. Whole blood samples for DNA extraction (optional) should be collected on day 1 (pre-dose) but can be collected at a later study visit.
30. A ravulizumab dose will be given at week 26 only if the patient intends to continue into OLE or R3918-PNH-2022. Patients who do not continue into a subsequent study with the pozelimab/cemdisiran combination will not receive a ravulizumab dose at EOS.
31. For patients planning to enroll in the OLE, day 1 of the R3918-PNH-2050 study must be scheduled 4 weeks after the week 24 dose of the combination treatment (ie, 2 weeks after the week 26 EOS visit in the R3918-PNH-2021) to ensure no interruption in treatment administration.