Official Title:	**A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients With IgA Nephropathy**
NCT Number:	**NCT03841448**
Document Date:	**Protocol Amendment 4, 13 January 2021**

CLINICAL STUDY PROTOCOL
ALN-CC5-005

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy
Short Title:	A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy
Study Drug:	Cemdisiran (ALN-CC5)
EudraCT Number:	2018-002716-27
IND Number:	140087
Protocol Date:	Original protocol 10 September 2018 Amendment 1 [26 November 2018] Amendment 2 [20 September 2019] Amendment 3 [27 April 2020] Amendment 4 [19 January 2021]
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

20 January 2021
Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-CC5-005 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I 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 SYNOPSIS

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Short Title

A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Study Drug

Cemdisiran (ALN-CC5)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 30-40 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in urine protein/creatinine ratio [UPCR] as measured in 24-hour urine at Week 32
Secondary	
• To evaluate the effect of cemdisiran on additional measures of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 • Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the effect of cemdisiran on full clinical remission and measures of albuminuria in adult patients with IgAN	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 36 weeks using all assessments during the period

• To evaluate the pharmacodynamic (PD) effect of cemdisiran ie, C5 level and CAP/CCP • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (UP <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP]and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life (t½), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, t½, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. The standard of care is expected to remain unchanged during this run-in period. Patients will not receive study drug (cemdisiran or placebo) during this time. The second study period is a 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) which will evaluate the efficacy

and safety of subcutaneous (SC) cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 156-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include a Screening period of up to 120 days to determine eligibility of patients and to complete disease-related assessments. The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and new trial participants to comply with the protocol given limitations during the COVID-19 pandemic. Patients will provide written informed consent and visit the study site approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study site 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Study drug administration can be conducted at the study site or by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have tolerated the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, study drug may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms may enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for up to an additional 152 weeks (approximately 3 years). If deemed necessary, the Investigator or Sponsor may shorten the time of the OLE period due to safety or administrative reasons. For patients who do not enter the OLE period, an End of Study (EOS) visit will occur at Week 36 and the patient will then enter the 52-week safety follow-up period.

The first study drug administration of the OLE will be administered at the study site at Week 36. From Week 40 onward in the OLE period (with the exception of the End of Treatment [EOT] and End of Study/Early Termination [EOS/ET] visits), study procedures (including cemdisiran administration) may be performed by a healthcare professional at a location other than the study site, at the discretion of the Investigator, with no more than 6 months between study site visits. If a visit by a healthcare professional at a location other than the study site (eg, at home) is not possible, study drug may be administered by the patient or caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations.

An EOT visit will occur at Week 184 (OLE EOT) and an EOS/ET visit will be completed at Week 188 (OLE EOS/ET). The EOT and EOS/ET visits will be performed at the study site. For patients who complete the treatment period only and who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study site for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 188), unless enrolled in another study with cemdisiran. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 188).

Regular reviews of safety and tolerability data will be performed by a Data Monitoring Committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years and ≤ 65 years of age) with a clinical diagnosis of primary immunoglobulin A (IgA) Nephropathy based on historical biopsy collected within 60 months of Screening, treated for IgA Nephropathy with stable, optimal pharmacological therapy including maximum allowed or tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for at least 3 months prior to the start of the run-in period. Eligible patients must have urine protein levels of ≥1 g/24-hour at Screening from a valid 24-hour urine collection (see Section 6.4.1.1), and mean urine protein levels ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period (Week -2 visit), prior to randomization. In addition, eligible patients must have hematuria defined by ≥10 red blood cells per high powered field (RBC/hpf) by microscopy or a positive urine dipstick (2+ [moderate] and above) measured by a central laboratory at Screening. Eligible patients are required to have been previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal

group B vaccine or be willing to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care (see Section 5.3.2.1 and Section 5.3.2.2 for vaccination time windows). In addition, patients not previously vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) must be willing to receive these vaccinations according to local guidelines.

Patients will be excluded from the study if eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization; treated with systemic steroids for more than 7 days or other immunosuppressant agents in the 6 months prior to randomization; treated with dual RAS blockade in the 3 months prior to entry into the run-in phase; have a diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase; sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period measured in supine position after 10 minutes of rest; have received organ transplant (including hematologic transplant) or have secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease).

Study Drug, Dose, and Mode of Administration

Cemdisiran is a synthetic small interfering RNA (siRNA) targeting complement component 5 (C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (Tri-GalNAc) ligand. Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. Doses of 600 mg of cemdisiran will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and the optional OLE period.

Placebo (normal saline 0.9% for SC administration) will be packaged and administered identically to cemdisiran.

Reference Treatment, Dose, and Mode of Administration

Angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) per physician and manufacturer‘s instructions.

Duration of Treatment and Study

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and patients will receive SC doses of cemdisiran for up to an additional 152 weeks in the optional 156-week OLE. The estimated total time on study, inclusive of Screening (120 days), run-in period (14 weeks), treatment period (36 weeks), extension period (156 weeks) and safety follow-up (52 weeks), for patients is approximately 63 months or 5 years and 4 months.

Statistical Methods

The primary endpoint of the study is the percentage change from baseline in UPCR from a 24-hour urine sample at Week 32. Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study based on the assumption that, in the placebo arm, the estimated geometric mean ratio of UPCR at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction, while the geometric mean ratio is 0.5, or a 50% reduction for the cemdisiran arm. Using these assumptions, sample size of 9 and 18 in the placebo and cemdisiran arms, respectively, will provide a width of 0.80 (± 0.4) for the 90%

confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. The primary analysis will be performed using a restricted maximum likelihood (REML) based Mixed-Effect Model Repeated Measures (MMRM) approach.

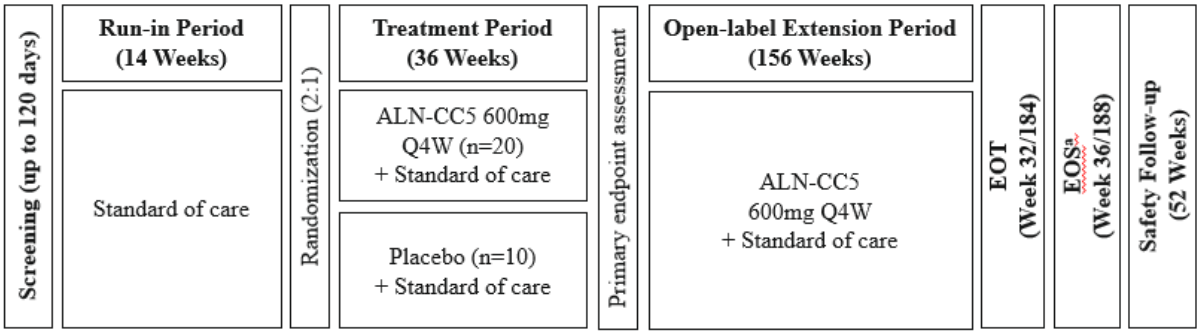
The analysis populations include:

- The modified Intent-to-treat (mITT) population will include all patients who receive any amount of study drug and have at least one post baseline 24-hour proteinuria assessment. Patients will be grouped by assigned treatments (ie, as randomized).
- The Safety Analysis Set will include all patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive a full dose of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive a full dose of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The efficacy endpoints will be analyzed in the mITT population. PK and PD parameters will be analyzed in the PK and PD analysis sets, respectively.

Safety data will be summarized with descriptive statistics using the Safety Analysis Set.

Figure 1: Study Design



Abbreviations: EOS=end of study; EOT=end of treatment; Q4W=once every 4 weeks.
[a] Or at time of withdrawal from the study.

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Discuss Study Information and Collect Informed Consent	6.1 and 6.2	X				(X)									(X)					
Medical History	6.1	X																		
Demographics	6.1		X																	
Inclusion/ Exclusion Criteria	4.1 and 4.2	X					X													
Routine Physical Exam	6.7.3		X				X		X						X	X		X		X
Height, Weight and BMI	6.7.2		X				X		X						X	X		X		X
Vital Signs	6.7.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4		X				X								X	X		X		X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Clinical Laboratory Assessment	6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	6.7.5.2		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Routine Vaccination Status	6.1		X																	
Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccination, if not previously vaccinated and required per local guidance	5.3.2.2 and 6.2		To follow local guidance which can be vaccination during Screening for some countries																	

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		**Screening Period**		**Run-in Period (14 weeks)**			**Treatment Period (36 weeks)**										**Safety Follow-up[a]**			
		Consent	**Screening visit**	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32 (EOT)[b]**	**Week 36 (EOS/ET)[c]**	**Week 49**	**Week 62**	**Week 75**	**Week 88**
	Notes For details, see Section	**D-219 to D-113**	**D-112 to D-99**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1 ±14**	**D28 ±14**	**D56 ±14**	**D84 ±14**	**D112 ±14**	**D140 ±14**	**D168 ±14**	**D196 ±14**	**D224 ±14**	**D252 ±14**	**D343±14**	**D434±14**	**D525±14**	**D616±14**
Start of Meningitis Vaccination (at least 14 days prior to the Day 1 visit)	5.3.2.1 and 6.2				X															
Confirmation of Meningococcal Vaccine Injection Schedule Compliance	As applicable and dependent on which vaccine will be used.						X	X	X	X	X	X	X	X						
Randomization							X													
Study Drug Administration	5.2.2						X	X	X	X	X	X	X	X	X					

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
24-hour Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1					X									X					
24-hour Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1		X								X							X		X
CAP/CCP Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
C5 Levels Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR Calculation	6.4.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1		X				X	X		X			X		X	X	X	X	X	X
Blood Samples for CIC and anti-Gd-IgA1 Antibody Assessment	6.7.5.1		X				X	X		X			X		X					
Exploratory Blood Sample	6.4.4						X		X		X		X		X					

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Blood Sample for Exploratory Genetic Analysis	6.8.						X													
Exploratory Urine Sample	6.4.4.						X		X		X		X		X					
Plasma and Urine PK	See Table 5						X													
Optional Visit at a location other than the study site (eg, at home)	Will be arranged where feasible from Week 4 of the treatment period and during safety follow-up							X									X		X	

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)									Safety Follow-up[a]			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)[b]	Week 36 (EOS/ET)[c]	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
	at Weeks 49 and 75																			
Adverse Events	6.7.6.2						X													
Concomitant Medications	5.3	X	X	X																
Antibiotics Compliance (if applicable)	5.5.3						X													

Abbreviations: BMI=body mass index; C5=complement component 5; CAP=complement alternative pathway; CCP=complement classical pathway; CIC=circulating immune complexes; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOS=end of study; EOT=end of treatment; ET=early termination; Gd-IgA1=galactose-deficient immunoglobulin A1; PK=pharmacokinetics.

Notes:

- If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in Table 1 above, are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization. Sites are encouraged to discuss study information with the patients again at the end of the run-in period and to check key inclusion and exclusion criteria when run-in visits are delayed, as denoted by parentheses in the table above.

- If a patient is unable to complete a site visit due to the COVID-19 pandemic impacting activities at the study site or patient ability or willingness to access the site, study procedures, including cemdisiran administration, may occur at a location other than the study site (eg, at home) at the discretion of the Investigator, based on safety and tolerability.
- In situations where a study visit cannot be completed at the study site or offsite by a healthcare professional at a location other than the study site (eg, at home) or the dose is missed, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events and concomitant medications

[a] The 52-week safety follow-up period will follow the Week 36 EOS/ET visit only for those patients not continuing into the OLE period.

[b] The Week 32 visit is the End of Treatment (EOT) visit for only those patients who do not continue into the OLE period.

[c] The Week 36 visit is the End of Study/Early Termination (EOS/ET) visit for only those patients who do not continue into the OLE period. For patients who continue into the OLE period, the Week 36 visit will be the first administration of cemdisiran in the OLE period (see Table 2).

Table 2: Schedule of Assessments – Open-Label Extension Period (Year 1)

Study Visit (Day/Week)		Open-Label Extension Period													
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88
	Notes For details, see Section	D252 ±14	D280 ±14	D308 ±14	D336 ±14	D364 ±14	D392 ±14	D420 ±14	D448 ±14	D476 ±14	D504 ±14	D532 ±14	D560 ±14	D588 ±14	D616 ±14
Routine Physical Exam	6.7.3						X						X		
Height, Weight and BMI	6.7.2						X						X		
Vital Signs	6.7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4						X						X		
Clinical Laboratory Assessment	6.7.5	X	X	X	X	X	X	X	X		X		X		X
Pregnancy Test	6.7.5.2	X	X	X	X	X	X	X	X		X		X		X
Pneumococcal and *Haemophilus influenzae* type b (Hib) Revaccination, per local guidance	5.3.2.2 and 6.2	To follow local guidance													
Meningitis Revaccination	5.3.2.1 and 6.2	To follow local guidance													
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1													X	

Table 2: Schedule of Assessments – Open-Label Extension Period (Year 1)

Study Visit (Day/Week)		Open-Label Extension Period													
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88
	Notes For details, see Section	D252 ±14	D280 ±14	D308 ±14	D336 ±14	D364 ±14	D392 ±14	D420 ±14	D448 ±14	D476 ±14	D504 ±14	D532 ±14	D560 ±14	D588 ±14	D616 ±14
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1						X				X				
CAP/CCP Blood Sample	6.5	X	X		X		X		X		X		X		X
C5 Levels Blood Sample	6.5	X	X		X		X		X		X		X		X
eGFR Calculation	6.4.3	X	X		X		X		X		X		X		X
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5	X	X		X		X		X		X		X		X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2	X	X		X		X		X		X		X		X
Blood Sample for Antidrug Antibodies	6.7.5.1						X						X		
Exploratory Blood Sample	6.4.4		X		X		X		X		X		X		X
Exploratory Urine Sample	6.4.4		X		X		X		X		X		X		X
Optional visit at a location other than the study site (eg, at home)	Will be arranged for cemdisiran administration from Week 40 through		X												

Table 2: Schedule of Assessments – Open-Label Extension Period (Year 1)

Study Visit (Day/Week)		Open-Label Extension Period													
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88
	Notes For details, see Section	D252 ±14	D280 ±14	D308 ±14	D336 ±14	D364 ±14	D392 ±14	D420 ±14	D448 ±14	D476 ±14	D504 ±14	D532 ±14	D560 ±14	D588 ±14	D616 ±14
	Week 88, unless patients are required to visit the study site as judged necessary by the Investigator. No more than 6 months should elapse between onsite visits.														
Adverse Events	See Section 6.7.6.2	X													
Concomitant Medications	See Section 5.3	X													
Antibiotics Compliance (if applicable)	See Section 5.5.3	X													

Abbreviations: BMI=body mass index; C5=complement component 5; CAP=complement alternative pathway; CCP=complement classical pathway; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate.
Notes:

- From Week 40 onwards, if a patient is unable to complete a site visit, study procedures, including cemdisiran administration, may occur at a location other than the site (eg, at home) at the discretion of the Investigator, based on safety and tolerability. No more than 6 months should elapse between site visits.
- In situations where a study visit cannot be completed at the study site or offsite by a healthcare professional at a location other than the study site (eg, at home) or the dose is missed, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events and concomitant medications.

Table 3: Schedule of Assessments – Open-Label Extension Period (Year 2)

Study Visit (Day/Week)		Open-Label Extension Period												
		Week 92	Week 96	Week 100	Week 104	Week 108	Week 112	Week 116	Week 120	Week 124	Week 128	Week 132	Week 136	Week 140
	Notes For details, see Section	D644±14	D672±14	D700±14	D728±14	D756±14	D784±14	D812±14	D840±14	D868±14	D896±14	D924±14	D952±14	D980±14
Routine Physical Exam	6.7.3		X						X					
Height, Weight and BMI	6.7.2		X						X					
Vital Signs	6.7.1		X						X					
12-Lead ECG	6.7.4		X						X					
Clinical Laboratory Assessment	6.7.5		X			X			X			X		
Pregnancy Test	6.7.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X
Pneumococcal and *Haemophilus influenzae* type b (Hib) revaccination, per local guidance	5.3.2.2 and 6.2	To follow local guidance												
Meningitis Revaccination	5.3.2.1 and 6.2	To follow local guidance												
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1		X						X					
CAP/CCP Blood Sample	6.5		X						X					

Table 3: Schedule of Assessments – Open-Label Extension Period (Year 2)

Study Visit (Day/Week)		Open-Label Extension Period												
		Week 92	Week 96	Week 100	Week 104	Week 108	Week 112	Week 116	Week 120	Week 124	Week 128	Week 132	Week 136	Week 140
	Notes For details, see Section	D644±14	D672±14	D700±14	D728±14	D756±14	D784±14	D812±14	D840±14	D868±14	D896±14	D924±14	D952±14	D980±14
C5 Levels Blood Sample	6.5		X						X					
eGFR Calculation	6.4.3		X			X			X			X		
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5		X			X			X			X		
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2		X			X			X			X		
Blood Sample for Antidrug Antibodies	6.7.5.1		X						X					
Exploratory Blood Sample	6.4.4		X						X					
Exploratory Urine Sample	6.4.4		X						X					
Optional Visit at a location other than the study site (eg, at home)	Will be arranged at Weeks 92, 100, 104, 108, 112, 116, 124, 128, 132, 136, and 140 during the extension period, unless patients are required to visit the study site as judged necessary by the Investigator.	X		X						X				

Table 3: Schedule of Assessments – Open-Label Extension Period (Year 2)

Study Visit (Day/Week)		Open-Label Extension Period												
		Week 92	Week 96	Week 100	Week 104	Week 108	Week 112	Week 116	Week 120	Week 124	Week 128	Week 132	Week 136	Week 140
	Notes For details, see Section	D644±14	D672±14	D700±14	D728±14	D756±14	D784±14	D812±14	D840±14	D868±14	D896±14	D924±14	D952±14	D980±14
Adverse Events	See Section 6.7.6.2	X												
Concomitant Medications	See Section 5.3	X												
Antibiotics Compliance (if applicable)	See Section 5.5.3	X												

Abbreviations: BMI=body mass index; C5=complement component 5; CAP=complement alternative pathway; CCP=complement classical pathway; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate.

Notes:

- If a patient is unable to complete a site visit, study procedures, including cemdisiran administration, may occur at a location other than the site (eg, at home) at the discretion of the Investigator, based on safety and tolerability.
- In situations where a study visit cannot be completed at the study site or offsite by a healthcare professional at a location other than the study site (eg, at home) or the dose is missed, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events and concomitant medications.

Table 4: Schedule of Assessments – Open-Label Extension Period (Year 3) and Safety Follow-up

Study Visit (Day/Week)		Open-Label Extension Period												Safety Follow-up			
		Week 144	Week 148	Week 152	Week 156	Week 160	Week 164	Week 168	Week 172	Week 176	Week 180	Week 184 (OLE EOT)	Week 188 (OLE EOS/ET)	Week 201	Week 214	Week 227	Week 240
	Notes For details, see Section	D1008±14	D1036±14	D1064±14	D1092±14	D1120±14	D1148±14	D1176±14	D1204±14	D1232±14	D1260±14	D1288±14	D1316±14	D1407±14	D1498±14	D1589±14	D1680±14
Routine Physical Exam	6.7.3	X						X				X	X		X		X
Height, Weight and BMI	6.7.2	X						X					X		X		X
Vital Signs	6.7.1	X						X				X	X	X	X	X	X
12-Lead ECG	6.7.4	X						X				X	X		X		X
Clinical Laboratory Assessment	6.7.5	X			X			X			X	X	X	X	X	X	X
Pregnancy Test	6.7.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccination, per local guidance	5.3.2.2 and 6.2	To follow local guidance															
Meningitis Revaccination	5.3.2.1 and 6.2	To follow local guidance															
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1												X				

Table 4: Schedule of Assessments – Open-Label Extension Period (Year 3) and Safety Follow-up

Study Visit (Day/Week)		Open-Label Extension Period												Safety Follow-up			
		Week 144	Week 148	Week 152	Week 156	Week 160	Week 164	Week 168	Week 172	Week 176	Week 180	Week 184 (OLE EOT)	Week 188 (OLE EOS/ET)	Week 201	Week 214	Week 227	Week 240
	Notes For details, see Section	D1008±14	D1036±14	D1064±14	D1092±14	D1120±14	D1148±14	D1176±14	D1204±14	D1232±14	D1260±14	D1288±14	D1316±14	D1407±14	D1498±14	D1589±14	D1680±14
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1	X						X							X		X
CAP/CCP Blood Sample	6.5	X						X				X	X		X		X
C5 Levels Blood Sample	6.5	X						X				X	X		X		X
eGFR Calculation	6.4.3	X			X			X			X	X	X	X	X	X	X
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5	X			X			X			X	X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2	X			X			X			X	X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1	X						X					X	X	X	X	X
Exploratory Blood Sample	6.4.4	X						X				X	X				
Exploratory Urine Sample	6.4.4	X						X				X	X				
Optional Visit at a location other than the study site (eg, at home)	Will be arranged at Weeks 148, 152, 156, 160, 164, 172, 176, and 180 during the		X						X					X		X	

Table 4: Schedule of Assessments – Open-Label Extension Period (Year 3) and Safety Follow-up

Study Visit (Day/Week)		Open-Label Extension Period												Safety Follow-up			
		Week 144	Week 148	Week 152	Week 156	Week 160	Week 164	Week 168	Week 172	Week 176	Week 180	Week 184 (OLE EOT)	Week 188 (OLE EOS/ET)	Week 201	Week 214	Week 227	Week 240
	Notes For details, see Section	D1008±14	D1036±14	D1064±14	D1092±14	D1120±14	D1148±14	D1176±14	D1204±14	D1232±14	D1260±14	D1288±14	D1316±14	D1407±14	D1498±14	D1589±14	D1680±14
	extension period, and where feasible, during safety follow up at Weeks 201 and 227, unless patients are required to visit the study site as judged necessary by the Investigator.																
Adverse Events	See Section 6.7.6.2	X															
Concomitant Medications	See Section 5.3	X															
Antibiotics Compliance (if applicable)	See Section 5.5.3	X															

Abbreviations: BMI=body mass index; C5=complement component 5; CAP=complement alternative pathway; CCP=complement classical pathway; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOS=end of study; EOT=end of treatment; ET=early termination.
Notes:

- Except for the EOT and EOS/ET visits, if a patient is unable to complete a site visit, study procedures, including cemdisiran administration, may occur at a location other than the site (eg, at home) at the discretion of the Investigator, based on safety and tolerability.
- In situations where a study visit cannot be completed at the study site or offsite by a healthcare professional at a location other than the study site (eg, at home) or the dose is missed, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events and concomitant medications.

Table 5: Pharmacokinetic Time Points

Phase	Study Day	Protocol Time Relative to Dosing (hh:mm)[a]	PK Blood	Pooled Urine[b]
Treatment phase	Day 1	Predose (within 60 mins)	X	
		00:00 (dose)		X
		01:00 (±5 mins)	X	
		02:00 (±15 mins)	X	
		04:00 (±15 mins)	X	
		06:00 (±15 mins)	X	
		08:00 (±30 mins)	X[c]	X
		12:00 (±30 mins)		
		24:00 (±120 mins)	X[c]	X

Abbreviations: hh=hours; mm=minutes; mins=minutes; PK=pharmacokinetics.

[a] The actual time of blood sample collection must be recorded.
[b] The pooled urine 6-12 hours and 12-24 hours can be collected as outpatient.
[c] Blood samples for PK assessment at these time points postdose may be collected if locally feasible.

TABLE OF CONTENTS

SPONSOR PROTOCOL APPROVAL 2
INVESTIGATOR'S AGREEMENT 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 28
LIST OF TABLES 32
LIST OF FIGURES 32
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 33
1. INTRODUCTION 36
1.1. Disease Overview 36
1.2. Cemdisiran 38
1.3. Study Design Rationale 39
1.4. Dose Rationale 40
1.5. Benefit-Risk Assessment 41
2. OBJECTIVES AND ENDPOINTS 43
3. INVESTIGATIONAL PLAN 45
3.1. Summary of Study Design 45
3.2. Duration of Treatment 46
3.3. Duration of Study 47
3.3.1. Definition of End of Study for an Individual Patient 47
3.4. Number of Planned Patients 47
3.5. Method of Assigning Patients to Treatment Groups 47
3.6. Blinding 47
3.6.1. Emergency Unblinding 48
3.7. Data Monitoring Committee 48
4. SELECTION AND WITHDRAWAL OF PATIENTS 48
4.1. Inclusion Criteria 48
4.2. Exclusion Criteria 49
4.3. Removal from Therapy or Assessment 50
4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments 51
4.3.2. Stopping a Patient's Study Participation 52
4.3.2.1. Patient or Legal Guardian Stops Participation in the Study 52

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data 52
4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study 52
4.3.2.4. Recording Reason for Stopping a Patient's Study Participation 52
4.3.3. Lost to Follow-Up 53
4.3.4. Replacement of Study Patients 53
5. TREATMENTS AND OTHER REQUIREMENTS 53
5.1. Treatments Administered 53
5.2. Study Drug 53
5.2.1. Description 53
5.2.2. Dose and Administration 54
5.2.3. Dose Modifications 54
5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing 55
5.2.4. Preparation, Handling, and Storage 56
5.2.5. Packaging and Labeling 57
5.2.6. Accountability 57
5.3. Concomitant Medications and Procedures 57
5.3.1. Prohibited Concomitant Medications 57
5.3.2. Study-specific Vaccinations 58
5.3.2.1. Meningococcal Vaccinations 58
5.3.2.2. Pneumococcal and Hib Vaccinations 58
5.4. Treatment Compliance 59
5.5. Other Requirements 59
5.5.1. Contraception 59
5.5.2. Alcohol Restrictions 60
5.5.3. Antibiotic Compliance 60
6. STUDY ASSESSMENTS 60
6.1. Screening Assessments 60
6.1.1. Rescreening 61
6.1.2. Retesting 61
6.2. Run-in Period 61
6.3. Baseline Assessments (Treatment Period) 62
6.4. Efficacy Assessments 62
6.4.1. Urine Protein/Creatinine Ratio 62

6.4.1.1. 24-Hour Urine Collection 62
6.4.1.2. Spot Urine Collection 63
6.4.2. Hematuria 63
6.4.3. Changes in Renal Function 63
6.4.4. Markers of Complement Activation, Inflammation and Renal Injury 64
6.5. Pharmacodynamic Assessments 64
6.6. Pharmacokinetic Assessments 64
6.7. Safety Assessments 64
6.7.1. Vital Signs 65
6.7.2. Weight and Height 65
6.7.3. Physical Examination 65
6.7.4. Electrocardiogram 65
6.7.5. Clinical Laboratory Assessments 66
6.7.5.1. Immunogenicity 68
6.7.5.2. Pregnancy Testing 68
6.7.5.3. Additional Liver Function Assessments 68
6.7.6. Adverse Events 69
6.7.6.1. Definitions 69
6.7.6.2. Eliciting and Recording Adverse Events 71
6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee 72
6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee 72
6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities 72
6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee 73
6.7.6.7. Pregnancy Reporting 73
6.7.6.8. Overdose Reporting 73
6.7.7. COVID-19 Data Collection 73
6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository 73
7. STATISTICS 74
7.1. Determination of Sample Size 74
7.2. Statistical Methodology 74
7.2.1. Populations to be Analyzed 75
7.2.2. Examination of Subgroups 75

7.2.3. Handling of Missing Data....75
7.2.4. Baseline Evaluations....75
7.2.5. Efficacy Analyses....76
7.2.5.1. Primary Endpoint....76
7.2.5.2. Secondary Efficacy Endpoints....76
7.2.5.3. Exploratory Endpoints....76
7.2.6. Pharmacodynamic Analysis....76
7.2.7. Pharmacokinetic Analysis....77
7.2.8. Safety Analyses....77
7.2.9. Immunogenicity Analyses....77
7.2.10. Biomarker Analyses....77
7.2.11. Interim Analysis....78
7.2.12. Optional Additional Research....78
8. STUDY ADMINISTRATION....78
8.1. Ethical and Regulatory Considerations....78
8.1.1. Informed Consent....78
8.1.2. Ethical Review....78
8.1.3. Serious Breach of Protocol....79
8.1.4. Study Documentation, Confidentiality, and Records Retention....79
8.1.5. End of Study....80
8.1.6. Termination of the Clinical Study or Site Closure....80
8.2. Data Quality Control and Quality Assurance....80
8.2.1. Data Handling....80
8.2.2. Study Monitoring....80
8.2.3. Audits and Inspections....80
8.3. Publication Policy....81
9. LIST OF REFERENCES....82
10. APPENDICES....85

LIST OF TABLES

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up 10
Table 2: Schedule of Assessments – Open-Label Extension Period (Year 1) 18
Table 3: Schedule of Assessments – Open-Label Extension Period (Year 2) 21
Table 4: Schedule of Assessments – Open-Label Extension Period (Year 3) and Safety Follow-up 24
Table 5: Pharmacokinetic Time Points 27
Table 6: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified 56
Table 7: Clinical Laboratory Assessments 67
Table 8: Hepatic Assessments in Patients Who Experience Elevated Transaminases 69

LIST OF FIGURES

Figure 1: Study Design 9

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECI	Adverse event of clinical interest
ALN-CC5	Cemdisiran
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Aspartate transaminase
AUC	Area under the concentration curve
BMI	Body mass index
C3	Complement component 3
C3a	Activated complement 3
C5	Complement component 5
C5a	Activated complement component 5
CAP	Complement alternative pathway
CCP	Complement classical pathway
CFH	Complement factor H
CI	Confidence interval
CIC	Circulating immune complexes
CL/F	Clearance
C_{max}	Maximum concentration
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice

Abbreviation	Definition
Gd-IgA1	Galactose-deficient Immunoglobulin A 1
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
hpf	High powered field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgAN	IgA Nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function test
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRNA	Messenger RNA
NHP	Nonhuman primates
O-GalNAc	O-linked monosaccharide N-acetylgalactosamine
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
RAS	Renin-angiotensin system
RBC	Red blood cell

Abbreviation	Definition
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
T_{max}	Time to maximum concentration
TMF	Trial Master File
Tri-GalNAc	Triantennary N-acetylgalactosamine
UP	Urine protein
UACR	Urine albumin/creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
V/F	Volume of distribution

1. INTRODUCTION

1.1. Disease Overview

Globally, immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure.[Lai 2016; Wyatt 1998] While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly O-glycosylated IgA1 and the presence of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the galactose-deficient IgA1 molecule (Gd-IgA1), resulting in the formation of pathogenic immune complexes. Some of these circulating complexes may deposit in glomeruli and induce renal injury.[Knoppova 2016] The lack of galactose exposes O-linked monosaccharide N-acetylgalactosamine (O-GalNAc) moieties in the hinge region of IgA1.[Novak 2018] While the binding of autoantibodies to Gd-IgA1 is dependent on the presence of multiple O-GalNAc residues, the IgA1 protein backbone and the spatial arrangement of O-GalNAc moieties are also thought to play a role in the specificity of autoantibodies to Gd-IgA1.[Mestecky 2016; Suzuki 2009]

Both the alternative and lectin complement pathways may be activated, leading to generation of the anaphylatoxins activated complement component 3 (C3a) and activated complement component 5 (C5a) and the membrane attack complex (MAC) C5b-9, with subsequent promotion of inflammatory mediators.[Maillard 2015] Emerging data indicate that mesangial-derived mediators that are released following deposition of IgA1 may lead to podocyte and tubulointerstitial injury.

Given that a biopsy specimen is required to diagnose IgAN, the clinical threshold for performing a biopsy will have a major impact on the prevalence of IgAN. Persistent microscopic hematuria alone and/or mild proteinuria alone are not commonly used as a per cause indication for biopsy in the United States. Thus, the prevalence of IgAN is modest in the United States (10 to 20% of primary glomerulonephritis), higher in some European countries (20 to 30%), and highest in developed countries in Asia (40 to 50%).[Woo 2010] This considerable geographical variability can be explained by several factors, including the variation in access to primary care enabling early diagnosis and the differences in policies for performing renal biopsies as well as for early referrals. For example, in some countries, urine screening tests are conducted in schools or for military service or ahead of employment, explaining the apparent high incidence.[Imai 2007; Wyatt 1998] Ethnic differences can also contribute to the varying prevalence of IgAN. Genome-wide association studies have identified candidate genes as well as risk-associated and protective alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa.[Kiryluk 2014] These genes are involved in antigen presentation, the mucosal defense system, and, notably, the alternative complement pathway (complement factor H [CFH]/CFHR locus).[Kiryluk 2014] Finally, patients may present at any age with IgAN but there is a peak incidence in the second and third decades of life. Most cases of IgAN occur in sporadic (90 to 95%) rather than in familial patterns (5 to 10%).[Lai 2016]

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. The first indication for making a diagnosis comes after careful microscopic examination of a urine sample. The presence of red blood cell (RBC) casts and dysmorphic

RBCs indicates glomerular bleeding. Varying degrees of proteinuria are present in patients with IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio (UPCR) measurement. Hence, IgAN can only be diagnosed definitively upon renal biopsy and study of kidney tissue using immunofluorescence. The pathology of IgAN is characterized by deposition of pathogenic polymeric IgA1 immune complexes and C3 in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix, and variable infiltration of macrophages, monocytes, and T cells. A consensus on the pathologic classification of IgAN has been developed by the International IgA Nephropathy Network in collaboration with the Renal Pathology Society (Oxford classification).[Lai 2016; Working Group of the International Ig 2009a; Working Group of the International Ig 2009b]

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis which is often associated with severe hypertension, but between these extremes, most patients with IgAN pursue a chronic indolent course.[Lai 2016] Some patients present with more severe proteinuria, hypertension, and renal progression over time, typically reaching end-stage renal disease (ESRD) over a span of 20 years. Thus, the severity of proteinuria upon presentation has significant prognostic implications. More importantly, the change in proteinuria over time is being regarded as the current best prognostic indicator: those who had heavy time averaged proteinuria and achieved a partial remission of <1 g/24-hours had a similar course to those who had <1 g/24-hours throughout and fared far better than those who never achieved partial remission.[Reich 2007] These observations support the notion that every effort should be made to reduce proteinuria in IgAN. In addition to the degree of proteinuria, baseline renal function and the degree of histological injury are of prognostic value. For example, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90 to 120 mL/min/1.73 m^2). The rate of glomerular filtration rate (GFR) decline also correlates with glomerulosclerosis and tubular atrophy or interstitial fibrosis on biopsy as outlined by Oxford-MEST-C classification. Spontaneous full recovery in IgAN is rare in adults, especially if associated with significant proteinuria (>0.5 g/24-hour).[Knoop 2017]

Patients with minor urine abnormalities, normal blood pressure, and normal GFR usually do well and require only monitoring. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. Thus, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease that can result in end-stage renal failure. The optimal role of immunosuppressive therapy is uncertain. The available studies are not conclusive since most are relatively small and have limited follow-up.[Lai 2016] STOP-IgAN, a German trial, randomly assigned adults with an eGFR of >30 mL/min/1.73 m^2 and persistent proteinuria of >0.75 g/24-hour despite 6 months of supportive care with RAS inhibitors to receive supportive care alone or supportive care plus immunosuppression (prednisone alone for those with initial GFR >60 mL/min and prednisone combined with cyclophosphamide then azathioprine with initial GFR 30 to 59 mL/min). This strategy did not significantly improve the renal outcome and was associated with increased adverse effects at 36 months.[Rauen 2015] The TESTING trial demonstrated some GFR effect of steroids in Chinese patients, but had to be stopped due to large number of serious adverse events (SAEs) in the steroid arm.[Lv 2017] The 2012 KDIGO guidelines recommend

corticosteroids, albeit at very low level of evidence. Thus, steroids may be tried in some cases as rescue therapy if proteinuria markedly increases or GFR rapidly falls. Further studies to address the role of steroids in IgAN are currently under way. Finally, Rituximab seems to be ineffective in the treatment of patients with progressive IgAN.[Lafayette 2016]

1.2. Cemdisiran

Alnylam Pharmaceuticals, Inc. is developing cemdisiran (ALN-CC5), a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of IgAN. Cemdisiran comprises a small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (Tri-GalNAc) ligand.

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19 to 25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA.[Elbashir 2001] Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [Soutschek 2004], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo in animal models (including in rodents and nonhuman primates [NHP]) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations.[Soutschek 2004; Zimmermann 2006] Another approach for liver-specific gene silencing is subcutaneously (SC) administered siRNA conjugated to an N-acetylgalactosamine (GalNAc) carbohydrate ligand.[Ashwell and Morell 1974] Conjugation of a Tri-GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

Cemdisiran (containing siRNA drug substance, ALN-62643, targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via SC injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the cemdisiran siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of MAC formation and C5a release. This in turn would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN resulting in renal function improvement.[Maillard 2015] Both lectin and alternative pathways of complement have been implicated in IgAN pathology. Cemdisiran-mediated silencing of C5 will inhibit MAC formation and C5a release regardless of the activating pathway and may be a superior approach in IgAN where the contribution of different pathways may be heterogenous between patients.[Medjeral-Thomas 2018]

The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities, other than an increased susceptibility

to Neisserial infections, in subjects with known genetic C5 deficiencies.[Ross and Densen 1984] Subjects with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. These infections include invasive meningococcal disease, disseminated gonococcal infections as well as diseases caused by typically commensal Neisseria species.[Crew 2019a; Crew 2019b; McQuillen and Ram 2019; Ram 2010] In addition, safety data on the treatment of healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH) with cemdisiran in Study ALN-CC5-001 indicate that cemdisiran is generally well-tolerated; the maximum tolerated dose was 900 mg. There were no SAEs or discontinuations due to adverse events (AEs) during this study, and most AEs were mild or moderate in severity. In Study ALN-CC5-001, the frequency of anti-drug antibodies (ADA) was low. Two of 48 healthy volunteers (1 cemdisiran-treated and 1 placebo-treated) were ADA positive during the study. The cemdisiran-treated volunteer had transient ADA positivity, with a negative result later in the study and no impact on pharmacokinetics (PK) or pharmacodynamics (PD). The placebo-treated volunteer was ADA positive at baseline (predose) and remained positive through Day 70.

A detailed description of the chemistry, pharmacology, nonclinical PK and toxicology, as well as preliminary efficacy and safety of cemdisiran is provided in the current edition of the Investigator's Brochure (IB).

1.3. Study Design Rationale

In contrast to the RBC lysis which characterizes the pathophysiology of PNH, which requires extremely high level of C5 inhibition for protection, mesangial cells are the cellular targets of dysregulated complement in IgAN. These cells are nucleated cells which possess complement regulatory proteins as well as the ability to shed membrane associated MAC to defend against MAC-mediated damage, a key step in renal damage in IgAN. It is therefore hypothesized that a lesser degree of cemdisiran-mediated C5 knockdown will be required for disease control in patients with IgAN than in patients with PNH.[Morgan 1989; Rosse 1973] This hypothesis is supported by the observation that atypical hemolytic uremic syndrome patients who achieve C5 inhibition maintain good disease control despite complement activity levels consistent with higher free C5 levels.[Cugno 2014] Therefore, cemdisiran monotherapy may be a viable treatment option in patients with IgAN at levels of C5 silencing achieved in Study ALN-CC5-001.

This therapeutic hypothesis will be tested in a multicenter, multinational, double-blind, placebo-controlled study to evaluate the effect of multiple doses of cemdisiran given by SC injection in patients with IgAN with persistent proteinuria (≥1 g/24-hours) despite the standard of care (angiotensin converting enzyme inhibitors [ACE] or angiotensin II receptor blockers [ARB]) and additional medications if necessary for blood pressure control followed by a treatment extension to evaluate long-term safety and clinical activity. The study population has been selected based on two major factors: 1) the severity of proteinuria upon presentation has significant prognostic implications.[Coppo and D'Amico 2005] IgAN patients with heavy proteinuria ≥1 g/24-hours have a significantly worse renal outcome than those who have proteinuria <1 g/24-hours.[Reich 2007] 2) For patients with persistent proteinuria, despite the nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, no disease-specific therapies are currently available, and an unmet need persists for novel

interventions. Since proteinuria can result both from active inflammation as well as irreversible scarring of renal tissue and in lieu of a protocol biopsy, the study will enrich our patients for presence of potentially reversible disease activity by requiring presence of hematuria and relatively preserved renal function with eGFR >30 mL/min. To ensure the selection of patients who are truly at risk of progression of kidney disease despite standard of care, the first period of the study consists of a run-in period during which patients will not receive study drug (cemdisiran or placebo). The run-in period will be an observational period during which patients' treatment with standard of care, blood pressure, kidney function, degree of hematuria, and proteinuria will be documented. The standard of care is expected to remain unchanged during this run-in period. Only patients whose

- proteinuria level remains ≥1 g/24-hours within 2 weeks before the end of the run-in period,
- continue to meet blood pressure and eGFR criteria

will be eligible to enroll in the 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) portion of the study.

Randomization to cemdisiran or placebo will be performed in a 2:1 ratio so that more patients will receive cemdisiran. This will allow a more precise estimation of the effect of cemdisiran with only marginal loss of power. Inclusion of a placebo arm will allow better assessment of safety and interpretation of the efficacy of cemdisiran.

The primary endpoint for the study is percent change from baseline in 24-hour UPCR at Week 32. This is justified for a Phase 2 study given the slow progression of renal disease and the established role of proteinuria as a marker of disease progression.

1.4. Dose Rationale

In the Phase 1/2 Study (ALN-CC5-001), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week, or monthly), and 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). Treatment with cemdisiran was generally well-tolerated in both healthy volunteers and patients with PNH. There were no SAEs and no discontinuations due to AEs during this study, including at the highest doses administered. Most AEs observed were mild or moderate in severity.

Dose selection for the current study is based on the expected level of C5 and complement activity inhibition necessary for efficacy in patients with IgAN and the extent to which different doses of cemdisiran can inhibit production of C5. C5 silencing is a novel approach for the treatment of IgAN and little clinical precedent exists for inhibiting the terminal complement pathway in this disease. Since complement regulation is not impaired in IgAN like it is in PNH, and the kidney glomerular cells are nucleated cells, it is expected that the level of silencing needed for efficacy in IgAN is lower than that needed for PNH (see IB Section 2.4). For this proof-of-concept study, a dose was selected that is expected to produce rapid and robust C5 suppression and complement activity inhibition across the patient population, allowing an

unambiguous evaluation of whether C5 silencing results in proteinuria improvement in IgAN. In Study ALN-CC5-001, a single dose of 600 mg cemdisiran achieved a C5 level of 12.3±1.47 µg/mL by Day 14 and 2.3±0.76 µg/mL by Day 56, corresponding to 60.9% reduction in complement alternative pathway (CAP) activity and a 69.3% reduction in complement classical pathway (CCP) activity by Day 14 and 90.2% and 91.4% reduction in CAP and CCP activities, respectively, by Day 56. Single and multiple biweekly doses of 600 mg were well-tolerated with an acceptable safety profile in healthy volunteers in Study ALN-CC5-001A. In this initial study, the cemdisiran dose of 600 mg that was safe and well-tolerated was chosen for evaluation. This dose will yield robust C5 silencing and will have maximal opportunity to produce a meaningful clinical effect in patients with IgAN. Since the relationship between C5 levels and complement activity is non-linear, with small C5 fluctuations resulting in a larger increase in complement activity, a monthly dose regimen was selected to maintain a constant level of C5 silencing. Additionally, a more consistent effect of cemdisiran on C5 protein and CCP level is predicted after monthly dosing when compared to quarterly dosing based on a modeling approach.

During the open-label extension (OLE) period, patients treated with both cemdisiran and placebo will have the option to receive a 600 mg dose of cemdisiran every four weeks for up to an additional 152 weeks.

IgAN can result in progressive renal impairment; however, patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2) who may have sustained irreversible damage to the kidney are not eligible for participation in this trial. As the kidney is not the major elimination pathway for cemdisiran and based on available nonclinical and clinical data obtained with cemdisiran (with 10.6 to 31.6% of the cemdisiran dose recovered in a 24-hour urine collection in the ALN-CC5-001 study), it is expected that moderate renal impairment (eGFR<60 mL/min/1.73 m^2) will not affect the PK of cemdisiran to the extent that a dose adjustment would be required. Therefore, patients with moderate renal impairment are eligible for study enrollment. More information on urine PK can be found in the IB.

1.5. Benefit-Risk Assessment

To date, no medications have been approved specifically for the treatment of IgAN. Therefore, there is a large unmet need for novel interventions, particularly in patients who are at risk of progressive renal disease such as those with persistent proteinuria despite treatment with RAS inhibitors. Available data from studies on the role of immunosuppressive therapy in IgAN are not conclusive as most are relatively small and have limited follow-up.[Lai 2016] Use of immunosuppressive drugs and high-dose steroids are also associated with increased AEs which is particularly common in patients with lower GFR.[Sarcina 2016]

Given the biological target of cemdisiran, the available nonclinical and clinical data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities, and injection site reactions (ISRs). C5 inhibition is associated with increased susceptibility for Neisserial infections (including disseminated gonococcal infections) and the potential risk of other infections, particularly those due to encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), as well as *Aspergillus* in immunocompromised and neutropenic patients. Therefore, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B

vaccine are required. Patients will be instructed to contact the study site if any early signs of meningococcal infections are experienced. In addition, patients with functional or anatomic asplenia will be excluded and only patients previously vaccinated or who agree to receive vaccination for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines at screening will be enrolled. Investigators in Study ALN-CC5-005 should educate patients on the risk of disseminated gonococcal infection and encourage safe sex practices. All national/local screening recommendations for gonorrhea in the general population should also be followed. Finally, given the reported evidence of a higher risk of disseminated gonococcal infections with treatment with eculizumab, Investigators are encouraged to evaluate any patient who has a *Neisseria gonorrhoeae* infection for the signs and symptoms of disseminated infection.[Crew 2019a; McQuillen and Ram 2019] No cases of Neisserial infection or other infections due to encapsulated bacteria were observed in healthy volunteers or in patients with PNH (Study ALN-CC5-001).

As cemdisiran is targeted for delivery to the liver, patients will be closely monitored for changes in LFTs and patients with a medical history or evidence of chronic liver disease or cirrhosis will be excluded. Criteria for dose withholding and stopping of cemdisiran are provided in Section 5.2.3.1. Patients will also be monitored for the development of ISRs and rotation of injection site is recommended during the study.

Considering anti-glycan autoantibodies recognizing Gd-IgA1 are implicated in the pathogenesis of IgA nephropathy, exposure to the GalNAc moiety of cemdisiran may pose a theoretical risk of stimulating the production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy. This could presumably occur when ADAs to cemdisiran's Tri-GalNAc cross-react with Gd-IgA1. The risk of developing these cross-reactive antibodies is likely low. This is based on the low incidence of ADA to cemdisiran in study ALN-CC5-001 (see Section 1.2) and the distinct difference in structure of the O-GalNAc moieties on a Gd-IgA1 glycoprotein and the Tri-GalNAc moiety in cemdisiran. This low risk is further mitigated by excluding patients with confirmed pre-existing IgG/IgM/IgA ADAs to total drug and real time monitoring for development of de novo IgG/IgM/IgA ADAs after dosing with cemdisiran. Patients with confirmed de novo ADAs will be discontinued from study drug but will continue to be monitored until the End of Study (EOS) visit and subsequent safety follow-up. Patients who develop positive ADAs will be followed until ADA titers return to baseline. Additional ADA samples will also be collected if any clinical evidence of progression of IgAN disease and/or relevant safety findings.

Detailed information about the known and expected benefits and risks of cemdisiran and additional information on the clinical and nonclinical data may be found in the current version of the IB.

Cumulatively, clinical data regarding the role of complement pathways in IgAN progression, robust nonclinical and clinical data with cemdisiran (see IB for more information), and prior and ongoing clinical experience with other RNAi therapeutics in humans suggest cemdisiran will have a favorable risk profile in the intended population and supports the initial clinical development of cemdisiran in IgAN. In addition, cemdisiran may address the unmet medical need for the first efficacious and disease-specific treatment for patients with IgAN.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in UPCR as measured in 24-hour urine at Week 32
Secondary	
• To evaluate the effect of cemdisiran on additional measures of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 • Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 • Frequency of AEs
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the effect of cemdisiran on full clinical remission and measures of albuminuria in adult patients with IgAN • To evaluate the pharmacodynamic (PD) effect of cemdisiran ie, C5 level and CAP/CCP • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 36 weeks using all assessments during the period • The slope of eGFR computed for the entire study period, including the open label extension, using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (UP <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32

• To assess the incidence of antidrug antibodies (ADA)	• Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life ($t_{½}$), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, $t_{½}$, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. Patients will not receive study drug (cemdisiran or placebo) during this time. The standard of care is expected to remain unchanged during this run-in period. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of SC cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 156-week optional OLE period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include a Screening period of up to 120 days to determine eligibility of patients and to complete disease-related assessments. The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and new trial participants to comply with the protocol given limitations during the COVID-19 pandemic. Patients will provide written informed consent and visit the study site approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and eGFR criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at screening.

During the run-in period, patients will visit the study site 14, 8, and 2 weeks prior to randomization (Weeks 0, 6, and 12 of the run-in period). If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a patient cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Study drug administration can be conducted at the study site or by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have tolerated the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, study drug

may be administered by the patient or caregiver under the oversight of the Investigator, and in consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on study drug administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms may enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for up to an additional 152 weeks (approximately 3 years). If deemed necessary, the Investigator or Sponsor may shorten the time of the OLE period due to safety or administrative reasons. For patients who do not enter the OLE period, an End of Study (EOS) visit will occur at Week 36 and the patient will then enter the 52-week safety follow-up period (Table 1).

The first study drug administration of the OLE will be administered at the study site at Week 36. From Week 40 onward in the OLE period (with the exception of the End of Treatment [EOT] and End of Study/Early Termination [EOS/ET] visits), study procedures (including cemdisiran administration) may be performed by a healthcare provider at a location other than the study site, at the discretion of the Investigator, with no more than 6 months between study site visits (Table 2, Table 3, and Table 4). Patients may be required to visit the study site more frequently, as judged necessary by the Investigator or if visits at a location other than the study site (eg, at home) cannot be arranged. If a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible, study drug may be administered by the patient or caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations.

An EOT visit will occur at Week 184 (OLE EOT) and an EOS or Early Termination (ET) visit will be completed at Week 188 (OLE EOS/ET). The EOT and EOS/ET visits will be performed at the study site. For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study site for safety follow-up visits approximately 13, 26, 39, and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 188), unless enrolled in another study with cemdisiran. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 188).

Regular reviews of safety and tolerability data will be performed by an independent data monitoring committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

3.2. Duration of Treatment

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and patients will receive 600 mg SC doses of cemdisiran for up to 152 additional weeks in the optional 156-week OLE.

3.3. Duration of Study

The maximum estimated total time on study, inclusive of screening (maximum of 120 days), run-in period (14 weeks), treatment period (36 weeks), optional OLE period (156 weeks) and safety follow-up (52 weeks), is approximately 63 months or 5 years and 4 months.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the EOS visit (Week 36 for those patients who do not consent to continue to participate in the study in the OLE period and Week 188 for patients who enter the OLE period). Upon study completion (regardless if EOS visit is at Week 36 or Week 188) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.

For patients withdrawing from the study after receiving one dose of cemdisiran at a minimum (ET), all efforts should be made to conduct the EOS/ET assessments. Patients should then be encouraged to enter the safety follow-up period.

3.4. Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the cemdisiran or placebo arms. Randomization will be stratified by baseline urine proteinuria levels (≥1 g/24h and <2 g/24h versus ≥2 g/24h).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at Screening and prior to randomization.

3.6. Blinding

All site personnel including sponsor delegated clinical research associates, data management Contract Research Organization, and patients will be blinded to study drug treatment during the efficacy period (up to Week 36). Sponsor personnel will not be blinded to study treatment. Cemdisiran and placebo will be packaged identically. The study drug will be administered under the supervision of the Investigator or at a location other than the study site (eg, at home) by a healthcare professional (see Section 5.2.2). If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible, study drug may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on study drug administration prior to dosing. Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by the healthcare professional. Syringe masking is not required if study drug is being administered at home by the patient or caregiver, as it is not considered a significant risk to unblinding. See the Pharmacy

Manual for additional details. Further details on blinding and unblinding arrangements will be documented in a Randomization and Blinding Plan document.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study site personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the Trial Master File (TMF).

Further details on blinding and unblinding arrangements will be documented in a Randomization and Blinding Plan document.

3.7. Data Monitoring Committee

An independent DMC will perform regular reviews of safety, tolerability, and immunogenicity data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a Charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of unblinded data (safety, tolerability, PD, ADA, circulating immune complexes [CIC] and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Male or female ≥18 years and ≤65 years of age at the time of informed consent

Patient and Disease Characteristics

2. Clinical diagnosis of primary IgAN as demonstrated by historical biopsy collected within 60 months of screening
3. Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB for at least 3 months prior to start of run-in period.
4. Urine protein ≥1 g/24-hour at Screening from a valid 24-hour urine collection (see Section 6.4.1.1), and mean urine UP ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization
5. Hematuria as defined by ≥10 RBCs per high powered field (RBC/hpf) by microscopy or a positive urine dipstick (2+ [moderate] and above) measured by a central laboratory at screening

6. Females of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception 14 days before first dose, throughout study participation, and for 90 days after last dose administration
7. Previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or willingness to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care
8. Previously vaccinated or willingness to receive vaccinations for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines for vaccination use

Informed Consent

9. Patient is willing and able to provide written informed consent and to comply with the study requirements

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Concomitant significant renal disease other than IgAN
2. A diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase
3. Secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease)
4. Diagnosis of Henoch-Schonlein Purpura (IgA Vasculitis)
5. eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization (local results may be used for assessment of eligibility)

Laboratory Assessments

6. Has any of the following laboratory parameter assessments:
    a. Alanine transaminase (ALT) >1.5×upper limit of normal (ULN), International Normalized Ratio (INR) >2 (or >3.5 if on anticoagulants), or total bilirubin >1.5×ULN (unless bilirubin elevation is due to Gilbert's syndrome)
7. Confirmed positive IgG/IgM/IgA ADAs to cemdisiran at screening
8. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
9. Positive hepatitis B virus (HBV) surface antigen, HBV core antibody, hepatitis C virus (HCV) antibody (unless HCV viral load demonstrated negative)

Prior/Concomitant Therapy

10. Treatment with systemic steroids for more than 7 days or other immunosuppressant agents in the 6 months prior to randomization
11. Treatment with dual RAS blockade in the 3 months prior to entry into the run-in phase

12. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment

Medical Conditions

13. Known human immunodeficiency virus (HIV) infection, HCV infection, or HBV infection
14. Malignancy (except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate cancer) within the last 5 years
15. Active psychiatric disorder, including, but not limited to schizophrenia, bipolar disorder, or severe depression despite current pharmacological intervention
16. Known medical history or evidence of chronic liver disease or cirrhosis
17. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
18. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc
19. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
20. Known contraindication to meningococcal vaccines (group ACWY conjugate and group B vaccines) required for this study. Refer to the most recent local product information for each vaccine for the current list of contraindications
21. Unable to take antibiotics for meningococcal prophylaxis, if required by local standard of care
22. Sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period, measured in supine position after 10 minutes of rest
23. Receipt of an organ transplant (including hematologic transplant)
24. History of meningococcal infection within 12 months before Screening
25. Patients with systemic bacterial or fungal infections that require systemic treatment with antibiotics or antifungals
26. Patients with functional or anatomic asplenia

Alcohol Use

27. Patients who consume more than 14 units of alcohol a week (unit 1 glass of wine [125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is

considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE), including confirmed positive test for ADA to cemdisiran
- Or, study is terminated by the Sponsor

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.7.5.2 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the Week 36/EOS or Week 188/OLE EOS visit and safety follow-up so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 2, Table 3, and Table 4), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.7.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 36-week treatment period will be encouraged to remain on the study and complete assessments through Week 36; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 1).

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete the OLE EOS/ET assessments; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 4).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient/legal guardian considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Week 36 visit and the 52-week safety follow-up. If a patient/legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 36-week treatment period, every effort should be made to conduct the assessments scheduled to be performed at the Week 36 EOS/ET visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the

observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.7.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study site. The following actions must be taken if a patient misses a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study during the 36-week treatment period or the OLE will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of cemdisiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection

(WFI) for SC administration. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to cemdisiran.

5.2.2. Dose and Administration

Patients will be administered cemdisiran (600 mg) or placebo (at the same volume as the active drug) as an SC injection once every 4 weeks in combination with standard of care in the 32-week period of the 36-week treatment period. During the OLE period, patients will be administered cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care.

Study drug injections will be administered under the supervision of the Investigator or a healthcare professional. For patients that have tolerated the study drug at the study site, study drug administration may be conducted by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period (with the exceptions of the EOT and EOS/ET visits, which must be performed at the study site). If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, study drug may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on study drug administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing.

From Week 40 onward in the OLE, except for the EOT and EOS/ET visits, study procedures, including cemdisiran administration, may occur at a location other than the study site (eg, at home) at the discretion of the Investigator, based on safety and tolerability, with no more than 6 months between study site visits. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible, study drug may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on study drug administration prior to dosing.

The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy Manual. In addition, instructions and procedures related to administration of study drug by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

5.2.3. Dose Modifications

Dose modifications are not permitted.

The visit window for the treatment and OLE periods is ±14 days, but the interval between 2 doses may not be shorter than 14 days. If a dose is not administered within 14 days of the date determined by the Schedule of Assessments (see Table 1, Table 2, Table 3, and Table 4), then the dose is considered missed and should not be given.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted. In situations where study drug is administered at a location other than the study site (eg, at home), or the dose is missed, the Investigator (or delegate) will verbally contact the patient to assess any AEs and concomitant medications.

5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing

1. LFT results (Table 7) from the previous collection should be reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 6.
    a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. Perform assessments per Table 6 and Table 8.
    c. If an alternative cause is found, provide appropriate care.
3. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
4. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 6.

Table 6: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 8 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 7
	• Monitor at least every two weeks: LFT and coagulation per Table 7
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold cemdisiran dosing until recovery to ≤1.5×ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 8 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 7
	• Monitor at least weekly: LFT and coagulation per Table 7 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study site or the healthcare professional performing administration at a location other than the study site (eg, at home) will be responsible for preparation of study drug doses, according to procedures detailed in the Pharmacy Manual. In cases where study drug is administered at a location other than the study site (eg, at home) by a patient/caregiver, dosing may be prepared and administered by the patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual and Patient/Caregiver Storage and Administration Instructions.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

Cemdisiran (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of 0.5 mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study site according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

The standard of care treatment should be held stable throughout the run-in and treatment periods. Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1, Table 2, Table 3, and Table 4). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

For other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug, for 7 days after the last dose of study drug.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements (if started prior to Screening, then may continue during the study at the same dose)
- Hydroxychloroquine
- Creatine supplements

5.3.2. Study-specific Vaccinations

5.3.2.1. Meningococcal Vaccinations

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, at least 14 days prior to randomization to cemdisiran or placebo, as per the Schedule of Assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions and according to the Advisory Committee on Immunization Practices (ACIP) or other locally applicable recommendations for patients with complement deficiencies. On days of vaccination, urinary samples should be collected prior to administration of vaccines. Revaccination should be assessed in accordance with local guidelines throughout the OLE period.

Patients will be immunized against *Neisseria meningitidis* according to the following specifications:

- Patients who have previously completed the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) at least 14 days but no more than 3 years from randomization can start study assessments after confirming eligibility. Documented vaccine history must be available to, and verified by, study site staff at the time of Screening.
- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines per the Schedule of Assessments.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the Schedule of Assessments.
- If required locally, patients will receive prophylactic antibiotics according to the local standard of care after randomization to cemdisiran or placebo.

5.3.2.2. Pneumococcal and Hib Vaccinations

Patients will receive vaccinations for Hib and *Streptococcus pneumoniae*, if not previously vaccinated, according to current national/local vaccination guidelines for vaccination use. Hib and pneumococcal vaccinations, if required at Screening per national/local guidelines, should be

administered at least 14 days prior to randomization. At Screening, patient vaccination records will be checked for compliance with local recommendations for the use of these vaccines. Revaccination should be assessed in accordance with local guidelines throughout the OLE period.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained healthcare professionals at a location other than the study site (eg, at home).

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration or until study completion.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of child-bearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries e.g. France, in order to comply with local requirements as described in the corresponding patient consent forms.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.7.5.2).

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. Antibiotic Compliance

Patients who require prophylactic antibiotics after randomization to cemdisiran or placebo (see Section 5.3.2.1) per local standard of care will undergo antibiotic compliance checks. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments. Antibiotic dose adjustments will be permitted in the case of renal impairment. All dose adjustments must comply with the manufacturer's instructions.

6. STUDY ASSESSMENTS

The Schedule of Assessments are provided in Table 1, Table 2, Table 3, and Table 4 . If a patient is unable to complete a site visit, routine physical examination/body system assessment, height, weight, body mass index (BMI), vital signs and collection of blood and urine samples for efficacy, safety, PD, PK, and exploratory assessments may be conducted at a location other than the study site (eg, at home) by a trained healthcare professional as locally feasible (refer to instructions for home nurses in the Laboratory Manual).

6.1. Screening Assessments

An ICF approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF.

The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and any new trial participant to comply with the protocol given limitations during the COVID-19 pandemic.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor; see Section 6.1.1.

Patient demographic data and medical history/disease history will be obtained. In particular, the MEST-C score and degree of IgG, IgA, IgM, C3, C1q, C4d and C5b-9 stains will be obtained from pathology reports, if available, and documented. Any changes to medical history occurring between the Screening assessment and Day 1 will be updated prior to study drug administration.

Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and BMI, 12-lead electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, urinalysis, spot urine assessments, ADA, and CIC assessments. Vaccination records will also be checked for compliance with national/local guidelines for pneumococcal and Hib vaccinations.

6.1.1. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). A patient who is unable to complete screening and run-in visits due to COVID-19 associated delays may be rescreened with approval of the Sponsor. A patient will be re-consented if rescreening occurs outside of the 120-day screening window. In this case, all screening procedures must be repeated.

6.1.2. Retesting

If in the Investigator's judgement, the laboratory abnormalities at screening or in the run-in period are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale is to be documented. Laboratory values can be retested once during screening or the run-in period as long as the patient can be evaluated for eligibility and randomized within the allowed Screening or run-in period. Two retests will be permitted for hematuria during Screening, if the first test is negative.

6.2. Run-in Period

During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): Hib and pneumococcal vaccinations (if required at Screening per national/local guidelines; vaccination should occur at least 14 days prior to randomization), vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine assessments, and eGFR. Clinical laboratory tests will be performed centrally; however, eGFR may also be assessed locally at the end of the run-in period (Week -2) to facilitate assessment of patient eligibility and administer meningococcal vaccination on the same day. Meningococcal vaccines should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a patient cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Sites are encouraged to discuss study information with the patients again at the end of the run-in period and to check key inclusion and exclusion criteria when run-in visits are delayed.

6.3. Baseline Assessments (Treatment Period)

Prior to dosing on Day 1, patients will be reassessed for eligibility, and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK, ADA, CIC, and anti-Gd-IgA1 antibodies.

In addition, prior to administration of study drug, the following assessments will be performed: full physical examination, body weight and height, vital signs, ECG, urine pregnancy test, eGFR assessment, spot urine, and urinalysis.

Collection of blood and urine samples for PK analysis on Day 1 will be performed as outlined in Table 5.

6.4. Efficacy Assessments

6.4.1. Urine Protein/Creatinine Ratio

Primary efficacy will be assessed by determining the percent change from baseline in UPCR from a 24-hour urine sample after 32 weeks of treatment. 24-hour urine samples for determination of UPCR will be collected throughout the study as outlined in the Schedules of Assessments and will be analyzed by a central laboratory.

6.4.1.1. 24-Hour Urine Collection

Patients will be required to provide two separate valid 24-hour urine collections 2 weeks prior to randomization (to assess eligibility after the run-in period), at Week 32 (to assess the primary endpoint), and at the EOS/ET visit. Patients will also be asked to provide a single valid 24-hour urine sample for other 24-hour urinary assessments outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Both UPCR as well as UACR will be calculated in an aliquot of each 24-hour urine collection. Rigorous exercise and significant change in diet (in particular salt intake) should be avoided within 48 hours before collection of 24-hour urine samples, whenever possible. The two valid 24-hour urine samples may be collected within 2 weeks before assessment is due while the one valid 24-hour urine sample may be collected within one week before the assessment takes place. If any of the collections do not meet validity criteria outlined below, then repeat collections must be scheduled within the time frames outlined above to assure the minimum number of valid collections required for each of the study time points. The duration of collection and volume of urine in the collection will be recorded in the eCRF. In addition to protein, albumin, sodium and creatinine will also be quantified in each of the 24-hour urine samples.

A 24-hour urine collection will only be considered valid if the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.

Primary efficacy will be evaluated by comparing the percent change from baseline in 24-hour UPCR at Week 32 in patients treated with cemdisiran versus those treated with placebo.

Secondary and exploratory efficacy assessments include comparisons of the proportion of patients with partial or complete clinical remission, respectively, as measured by the amount of total protein in a 24-hour urine sample. Partial clinical remission is defined as having UP <1 g/24-hours and complete clinical remission is defined as UP <0.3 g/24-hours. Each will be assessed at Week 32.

Additionally, using 24-hour samples, the percent change from baseline in total protein will be evaluated as a secondary endpoint and the change from baseline in urine UACR at Week 32 as an exploratory endpoint.

6.4.1.2. Spot Urine Collection

Urinary protein, albumin and creatinine levels from spot urine collections prior to dosing will also be measured to assess the effect of cemdisiran on UPCR and UACR as outlined in the Schedule of Assessments.

The change from baseline in UPCR at Week 32 will be evaluated in spot urine samples as a secondary efficacy assessment. Spot urine samples will be collected at the time points outlined in the Schedule of Assessments (Table 1).

6.4.2. Hematuria

Hematuria from spot urine collections will also be evaluated to assess the effect of cemdisiran on disease course in patients with IgAN. The degree of hematuria will be assessed by microscopic examination of the spun urine sediment (RBC/hpf) and by urine dipstick. Single void collections for random urine sample for hematuria evaluation should be collected. If the investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated.

Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to study drug administration, if applicable.

6.4.3. Changes in Renal Function

Changes in renal function will be monitored using measurements of serum creatinine and eGFR (mL/min/1.73m^2) as outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). The calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for all patients. For assessment of eligibility at the last visit of run-in period, 2 weeks prior to randomization, local lab can be utilized. This will allow evaluation for eligibility on the same day. A sample will also be sent to central lab.

Renal function will also be estimated as creatinine clearance based on the 24-hour urine collection. The creatinine clearance is a widely used test to estimate the GFR using the following formula:

GFR = [UCr x V] / SCr

SCr is the serum creatinine concentration and the value assessed closest to collection of 24-hour urine collection will be utilized for purpose of above calculation. UCr is the urine creatinine concentration and V is the urine flow rate or volume.

Blood and urine samples for renal function assessments will be collected prior to administration of study drug on dosing days, if applicable.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed for the treatment period and the entire study period (including the OLE).

6.4.4. Markers of Complement Activation, Inflammation and Renal Injury

Samples for measurement of markers of complement activation, inflammation and renal injury will be collected at the time points outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and analyzed by central laboratories. On dosing days, blood samples will be collected predose.

6.5. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at the time points outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Samples will be collected prior to administration of cemdisiran or placebo on dosing days.

Analysis of PD will include the impact of cemdisiran administration on plasma C5 protein levels (assessed by a mass spectrometry-based method) and serum complement activity (assessed by CAP enzyme linked immunosorbent assay [ELISA] and CCP ELISA). Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

6.6. Pharmacokinetic Assessments

Blood samples and urine samples will be collected for assessment of cemdisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples and urine samples for PK analysis is in Table 5.

The concentration of cemdisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests, including assessment of IgG/IgM/IgA ADA, CIC, and anti-Gd-IgA1 antibodies. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.7.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for at least 10 minutes. On Day 1, vital signs will be collected predose (no more than 4 hours prior to dosing) and 4 hours (±30 minutes) postdose. On all other dosing days, vital signs will be collected predose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral or tympanic method. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.7.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4; height at screening only and dosing weight during the clinical study site visits) and will be recorded in the eCRF.

6.7.3. Physical Examination

Routine physical examinations will be conducted according to the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

At screening and Day 1 predose, a full physical examination will be performed. At all other time points, including Day 1 at 4 hours (±30 minutes) postdose, a directed physical examination will be performed.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Directed physical examinations will include examination of the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.7.4. Electrocardiogram

Twelve-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained, as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Patients should be supine for at least 5 minutes before each ECG is obtained. A single 12-lead ECG will be performed at Screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings

1 minute apart. 12-lead ECGs will be performed predose (on the same day as dosing); 60 minutes (±15 minutes) postdose; and 4 hours (±30 minutes) postdose in relation to the Day 1 and Week 32 cemdisiran or placebo doses.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.7.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, eGFR will also be assessed locally. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 7 and include: hematology, serum chemistry and urinalysis parameters. Parameters will be assessed as specified in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 7 which are measured locally should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions. If central laboratory tests are not feasible due to COVID-19 restrictions, local laboratory tests for safety monitoring can be performed with approval from the Sponsor.

Clinical laboratory assessments may be collected at the clinical study site or at a location other than the study site (eg, at home) by a trained healthcare professional. On dosing days blood samples will be collected predose.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 7: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the CKD-EPI formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH	Nitrite
Specific gravity	Blood
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.7.5.1)	
Antidrug antibodies	
Hepatic Tests (Screening Only)	
Hepatitis C, including: HCV RNA PCR – qualitative and quantitative assays	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Pregnancy Testing (Females of Child-bearing Potential Only) (see Section 6.7.5.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus

core; HCV=hepatitis C virus; IgG= IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RNA=ribonucleic acid.

6.7.5.1. Immunogenicity

Blood samples will be collected to evaluate ADA and CIC. IgG/IgM/IgA ADAs to total drug will be assessed at screening and during the study. ADA samples will be tested in real time. Clinical study decision will be based on confirmed positive ADA results from the IgG/IgM/IgA assay. Confirmed positive ADA samples will be further characterized for cemdisiran domain specificity against the Tri-GalNAc component if a reliable method is established. Blood samples for ADA and CIC testing must be collected before study drug administration as specified in the Schedule of Assessments. Blood samples to evaluate ADAs will be collected at screening to assess study eligibility and at the ET visit, if applicable. ADA and CIC will be routinely monitored during the treatment period and throughout the OLE period and safety follow-up (ADA only), as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). Finally, ADA and CIC samples will also be collected and analyses will be performed and prioritized if any clinical evidence of progression of IgAN disease and/or relevant safety findings. Patients who are confirmed positive for IgG/IgM/IgA ADAs at baseline will be excluded from study treatment. In addition, patients who develop de novo ADAs will be discontinued from study drug but will be followed until EOS visit and during safety follow-up. These patients will also be monitored until ADA levels return to baseline.

Exploratory analysis of anti-Gd-IgA1 antibody levels will be conducted; serum samples for these analyses will be drawn when CIC samples are collected.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.7.6.7 for follow-up instructions).

6.7.5.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 8 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 7, and other assessments or evaluations per Investigator discretion, as appropriate.

Table 8: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
Herpes Zoster Virus IgM, IgG	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.7.6. Adverse Events

6.7.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at a location other than the study site (eg, at home), blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

Based on the biological target and the available nonclinical and clinical data, AEs of Clinical Interest (AECI) for this study are:

- Severe infections as judged by the Investigator
- ALT or AST >3×ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of cemdisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR.

For information on recording and reporting of AECIs, see Section 6.7.6.2 and Section 6.7.6.3 , respectively.

Adverse Event Severity

AEs are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.7.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording all SAEs and only AEs related to study procedures that are observed or reported by the patient during the run-in period (before the administration of the first dose of study drug) regardless of their relationship to study drug through the end of study. All AEs, including non-serious AEs, occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study site and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.7.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AECIs (Section 6.7.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.7.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study site staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Investigator Site File.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's Site File.

6.7.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.7.6.4.

6.7.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The Investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.7.7. COVID-19 Data Collection

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected, where permitted by local regulations.

6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with IgAN, as well as their responses to treatment.

To permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the

safety, mechanism of action, and/or efficacy of cemdisiran, a set of biological specimens will be collected at the intervals indicated in the Schedule of Assessments.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, the samples will be collected as part of this study. Examples of potential exploratory investigations would include DNA, RNA, protein, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

The sample size of the study was determined based on the precision of the estimate of the treatment effect for the primary endpoint – the percent change from baseline in UPCR from a 24-hour urine sample at Week 32. It should be noted that geometric mean ratio of UPCR at Week 32 to baseline is statistically equivalent to mean of the change from baseline in logarithm of UPCR. Therefore, the effect size of the study is defined as the difference of change from baseline between cemdisiran and placebo in the logarithm of UPCR.

Based on the [Fellstrom 2017] study, we assume that in the placebo arm the geometric mean ratio of UPCR at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction, while the geometric mean ratio is 0.5, or a 50% reduction for the cemdisiran arm. Using these assumptions, sample size of 9 and 18 in the placebo and cemdisiran arms will provide a width of 0.80 (± 0.4) for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the

methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

Descriptive statistics including the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum values will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

Additional data summaries to help understand any impact of COVID-19 on PK/PD, efficacy and safety assessments will be outlined in the SAP.

7.2.1. Populations to be Analyzed

The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive a full dose of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive a full dose of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The primary population used to evaluate efficacy will be the mITT Population. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the mITT and Safety Analysis Set.

Baseline value for 24-hour UPCR will be calculated as the average of two valid 24-hour urine assessments before randomization (at the Week -2 visit).

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint of the study is the percentage change from baseline in 24-hour UPCR at Week 32. The 24-hour UPCR will be log transformed for analyses. The primary analysis will be performed using a restricted maximum likelihood (REML) based Mixed-Effect Model Repeated Measures (MMRM) approach. The outcome variable is change from baseline in 24-hour UPCR in log-scale at the Week 16 and Week 32 visits. Analysis will include fixed effects of treatment (cemdisiran vs. placebo), scheduled visits (Week 16 and Week 32), interaction term of treatment and scheduled visits, baseline 24-hour UPCR in log-scale (continuous), and patient as a random effect. The least square mean difference and its 90% confidence interval will be estimated . In addition, placebo-adjusted geometric mean percent change at the Week 32 visit and its 90% CI will be presented.

A sensitivity analysis for the impact of missing data and the normality assumptions on the log-transformed UPCR data will be performed. Details will be provided in the SAP.

7.2.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include percent change from baseline in 24-hour proteinuria (g/24 hours) at Week 32, percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in UP in 24-hour urine assessments and UPCR by spot urine at Week 32 will be analyzed similarly to the analysis of the primary variable as appropriate. The descriptive statistics for change from baseline in hematuria (urine dipstick) at Week 32 will be provided.

7.2.5.3. Exploratory Endpoints

Change from baseline in exploratory efficacy variables will be summarized. Percent of patients in full clinical remission and incidence of ADA will be tabulated by treatments.

The slope of eGFR for the double-blind period will be estimated for each treatment and the slope of eGFR for the entire study period including the OLE will be analyzed. Other inferential statistics for exploratory efficacy variables may be presented as needed. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Assessment of the PD effect of the treatment will be performed descriptively, including plotting graphically levels of serum C5 protein and CAP/CCP over time and relative to baseline levels. Inferential statistics may be generated as deemed necessary.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. Pharmacokinetic parameters include, but will not be limited to: AUC, C_{max}, T_{max}, t½, CL/F, V/F, cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe) in the urine of cemdisiran (25-mer) and 23-mer.

Other parameters may be calculated, if deemed necessary. Summary statistics and figures will be presented. Inferential statistics may be generated when deemed necessary.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized by treatment arm and overall.

AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary. All SAEs occurring before the first dose of study drug and AEs related to study procedures will be listed. The number and percentage of patients experiencing AEs after the first dose of the study drug or events that worsened in severity after dosing will be summarized. AEs will be presented by maximum severity and relationship to study medication. SAEs and AEs leading to discontinuation of treatment will also be tabulated.

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation.

Frequency of AEs of clinical interest will also be summarized and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

All safety analyses will be conducted using the Safety Analysis Set.

Additional data summaries to help understand any impact of COVID-19 on safety assessments will be outlined in the SAP.

7.2.9. Immunogenicity Analyses

Antidrug antibody, CIC and anti-Gd-IgA1 antibody results will be summarized descriptively.

7.2.10. Biomarker Analyses

Urine and serum complement activation products, inflammation and renal injury markers will be summarized descriptively.

7.2.11. Interim Analysis

No formal interim analysis is planned.

7.2.12. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the ICF and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.7.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study site periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data

verification. The Investigator should contact the Sponsor and designee, immediately if contacted by a regulatory agency or an IRB/IEC about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 18 months after completion of the study at all sites. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Ashwell G,Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Adv Enzymol Relat Areas Mol Biol. 1974;41(0):99-128.

Coppo R,D'Amico G. Factors predicting progression of IgA nephropathies. J Nephrol. 2005 Sep-Oct;18(5):503-12.

Crew PE, Abara WE, McCulley L, Waldron PE, Kirkcaldy RD, Weston EJ, et al. Disseminated Gonococcal Infections in Patients Receiving Eculizumab: A Case Series. Clin Infect Dis. 2019a Aug 1;69(4):596-600.

Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC,Bersoff-Matcha SJ. Unusual Neisseria species as a cause of infection in patients taking eculizumab. J Infect. 2019b Feb;78(2):113-8.

Cugno M, Gualtierotti R, Possenti I, Testa S, Tel F, Griffini S, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. J Thromb Haemost. 2014 Sep;12(9):1440-8.

Elbashir SM, Lendeckel W,Tuschl T. RNA interference is mediated by 21- and 22-nucleotide RNAs. Genes Dev. 2001 Jan 15;15(2):188-200.

Fellstrom BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017 May 27;389(10084):2117-27.

Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clinical journal of the American Society of Nephrology. 2007;2(6):1360-6.

Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014 Nov;46(11):1187-96.

Knoop T, Vikse BE, Mwakimonga A, Leh S,Bjorneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrol Dial Transplant. 2017 Nov 1;32(11):1841-50.

Knoppova B, Reily C, Maillard N, Rizk DV, Moldoveanu Z, Mestecky J, et al. The Origin and Activities of IgA1-Containing Immune Complexes in IgA Nephropathy. Front Immunol. 2016;7:117.

Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. Journal of the American Society of Nephrology. 2016:ASN. 2016060640.

Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nat Rev Dis Primers. 2016 Feb 11;2:16001.

Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2017 Aug 1;318(5):432-42.

Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current Understanding of the Role of Complement in IgA Nephropathy. J Am Soc Nephrol. 2015 Jul;26(7):1503-12.

McQuillen DP,Ram S. No Good Deed Goes Unpunished: Eculizumab and Invasive Neisserial Infections. Clin Infect Dis. 2019 Aug 1;69(4):601-3.

Medjeral-Thomas NR, Troldborg A, Constantinou N, Lomax-Browne HJ, Hansen AG, Willicombe M, et al. Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin–Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H–Related Protein-5 (FHR5) Deposition. Kidney Intl Rep. 2018;3(2):426-38.

Mestecky J, Novak J, Moldoveanu Z,Raska M. IgA nephropathy enigma. Clinical Immunology. 2016;172:72-7.

Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochem J. 1989 Nov 15;264(1):1-14.

Novak J, Barratt J, Julian BA,Renfrow MB, editors. Aberrant Glycosylation of the IgA1 Molecule in IgA Nephropathy. Seminars in nephrology; 2018: Elsevier.

Ram S, Lewis SA,Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010;23(4):740-80.

Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med. 2015 Dec 3;373(23):2225-36.

Reich HN, Troyanov S, Scholey JW,Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. Journal of the American Society of Nephrology. 2007;18(12):3177-83.

Ross SC,Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984 Sep;63(5):243-73.

Rosse WF. Variations in the red cells in paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1973 Mar;24(3):327-42.

Sarcina C, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, et al. Changes in Proteinuria and Side Effects of Corticosteroids Alone or in Combination with Azathioprine at Different Stages of IgA Nephropathy. Clin J Am Soc Nephrol. 2016 Jun 6;11(6):973-81.

Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004 Nov 11;432(7014):173-8.

Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest. 2009 Jun;**119**(6):1668-77.

Woo KT, Chan CM, Chin YM, Choong HL, Tan HK, Foo M, et al. Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades. Nephron Clin Pract. 2010;116(4):c337-46.

Working Group of the International Ig ANN, the Renal Pathology S, Cattran DC, Coppo R, Cook HT, Feehally J, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009a Sep;76(5):534-45.

Working Group of the International Ig ANN, the Renal Pathology S, Roberts IS, Cook HT, Troyanov S, Alpers CE, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009b Sep;76(5):546-56.

Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. J Am Soc Nephrol. 1998 May;9(5):853-8.

Zimmermann TS, Lee AC, Akinc A, Bramlage B, Bumcrot D, Fedoruk MN, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006 May 04;441(7089):111-4.

10. APPENDICES

None.

ALN-CC5-005 PROTOCOL AMENDMENT 4
SUMMARY OF CHANGES DATED 19 JANUARY 2021
COMPARED TO PROTOCOL AMENDMENT 3 DATED 27 APRIL 2020

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose for this protocol amendment is to extend the open-label extension (OLE) period by an additional 2 years. This will allow patients who are nearing the end of the current 1-year OLE period to continue to receive cemdisiran on-study and will allow for collection of additional data on long-term treatment with cemdisiran.

Several additional changes are being implemented as outlined below.

- Clarification that off-site visit flexibility applies from Week 40 of the OLE period, as described in Protocol Administrative Letter 3
- Clarification that masking of the study drug syringe is not required during home administration by a patient/caregiver as it is not considered a significant risk to unblinding
- Addition of creatine supplementation to list of prohibited concomitant medications, as these supplements may increase plasma and urine creatinine and may, therefore, confound study assessments
- Clarification that electrocardiogram (ECG) readings are to be recorded one minute apart
- Specification that only patients who receive a full dose of study drug and have 1 relevant postdose sample will be analyzed in the pharmacokinetic (PK) and pharmacodynamic (PD) analysis sets.

A detailed summary of changes is provided in Section 2. The following changes are not detailed: administrative changes, changes associated with administrative letters (between protocol amendments 3 and 4), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. PROTOCOL AMENDMENT 4 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 4 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: To extend the open-label extension period from 1 year (52 weeks) to 3 years (156 weeks)

The primary change occurs in Table 2 (Schedule of Assessments – Open Label Extension Period and Safety Follow-up)

Revised text: Assessment timing during Year 1 of the OLE period was updated and **Table 3 (Schedule of Assessments – Year 2) and Table 4 (Schedule of Assessments- Year 3 and Safety Follow-up)** were added. The End of Treatment visit will be at **Week 184** and the End of Study/Early Termination visit will be at **Week 188**.

Section(s) also reflecting this change:

- Synopsis
- Figure 1, Study Design
- Section 1.4, Dose Rationale
- Section 3.1, Summary of Study Design
- Section 3.2, Duration of Treatment
- Section 3.3, Duration of Study
- Section 4.3.1, Discontinuation of Study Drug or Declining Procedural Assessments
- Section 5.2.2, Dose and Administration
- Section 5.3.2, Study-specific Vaccinations
- Section 6.4, Efficacy Assessments
- Section 6.5, Pharmacodynamic Assessments
- Section 6.7, Safety Assessments

Purpose: To clarify that study drug syringe masking is not required when study drug is administered at home by the patient/caregiver.

The primary change occurs in Section 3.6, Blinding

Revised text: Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by ~~a site pharmacist prior to administration by a~~ the healthcare professional ~~or a patient/caregiver~~. **Syringe masking is not required if study drug is being administered at home by the patient or caregiver as it is not considered a significant risk to unblinding.**

Section(s) also reflecting this change: None.

Purpose: To state that creatine supplements should be avoided during the study.

The primary change occurs in Section 5.3.1, Prohibited Concomitant Medications

Added text: The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements (if started prior to Screening, then may continue during the study at the same dose)
- Hydroxychloroquine
- **Creatine supplements**

Section(s) also reflecting this change: None.

Purpose: To clarify that ECG readings are to be recorded 1 minute apart.

The primary change occurs in Section 6.7.4, Electrocardiogram

Revised text: A single 12-lead ECG will be performed at screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings ~~approximately~~ 1 minute apart.

Section(s) also reflecting this change: None.

Purpose: To specify that only patients who receive a full dose of study drug and have at least 1 relevant postdose sample will be analyzed in the PK and PD analysis sets.

The primary change occurs in Section 7.2.1, Populations to be Analyzed

Revised text: The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive ~~any amount~~ **a full dose** of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive ~~any amount~~ **a full dose** of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

Section(s) also reflecting this change: Synopsis.

Purpose: Administrative changes, changes associated with administrative letters (between protocol amendments 3 and 4), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

CLINICAL STUDY PROTOCOL

ALN-CC5-005

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy
Short Title:	A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy
Study Drug:	Cemdisiran (ALN-CC5)
EudraCT Number:	2018-002716-27
IND Number:	140087
Protocol Date:	Original protocol 10 September 2018 Amendment 1 [26 November 2018] Amendment 2 [20 September 2019] Amendment 3 [27 April 2020]
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

27 April 2020

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-CC5-005 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I 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 SYNOPSIS

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Short Title

A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Study Drug

Cemdisiran (ALN-CC5)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 30-40 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in urine protein/creatinine ratio [UPCR] as measured in 24-hour urine at Week 32
Secondary	
• To evaluate the effect of cemdisiran on additional measures of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 • Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the effect of cemdisiran on full clinical remission and measures of albuminuria in adult patients with IgAN	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 36 weeks using all assessments during the period

• To evaluate the pharmacodynamic (PD) effect of cemdisiran ie, C5 level and CAP/CCP • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (UP <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP]and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life (t½), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, t½, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods Figure 1. The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. The standard of care is expected to remain unchanged during this run-in period. Patients will not receive study drug (cemdisiran or placebo) during this time. The second study period is a 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) which will evaluate the efficacy and safety of subcutaneous (SC) cemdisiran compared to SC placebo in

combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 120 days to determine eligibility of patients and to complete disease-related assessments. The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and new trial participants to comply with the protocol given limitations during the COVID-19 pandemic. Patients will provide written informed consent and visit the study site approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study site 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Study drug administration may be conducted by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have demonstrated the ability to tolerate the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, cemdisiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study site at Week 40 and every 8 weeks thereafter during the OLE. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged for cemdisiran

administration in between 8-weekly study site visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study site as judged necessary by the Investigator, or if visits at a location other than the study site (eg, at home) cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only and who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study site for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by a Data Monitoring Committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years and ≤ 65 years of age) with a clinical diagnosis of primary immunoglobulin A (IgA) Nephropathy based on historical biopsy collected within 60 months of Screening, treated for IgA Nephropathy with stable, optimal pharmacological therapy including maximum allowed or tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for at least 3 months prior to the start of the run-in period. Eligible patients must have urine protein levels of ≥1 g/24-hour at Screening from a valid 24-hour urine collection (see Section 6.4.1.1), and mean urine protein levels ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period (Week -2 visit), prior to randomization. In addition, eligible patients must have hematuria defined by ≥10 red blood cells per high powered field (RBC/hpf) by microscopy or a positive urine dipstick (2+ [moderate] and above) measured by a central laboratory at Screening. Eligible patients are required to have been previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or be willing to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care (see Section 5.3.2.1 and Section 5.3.2.2 for vaccination time windows). In addition, patients not previously vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) must be willing to receive these vaccinations according to local guidelines.

Patients will be excluded from the study if eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization; treated with systemic steroids for more than 7 days or other immunosuppressant agents in the 6 months prior to randomization; treated with dual RAS blockade in the 3 months prior to entry into the run-in phase; have a diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase; sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period measured in supine position after 10 minutes of rest; have received organ transplant (including hematologic transplant) or have secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease).

Study Drug, Dose, and Mode of Administration

Cemdisiran is a synthetic small interfering RNA (siRNA) targeting complement component 5 (C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (Tri-GalNAc) ligand. Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. Doses of 600 mg of cemdisiran will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and the optional OLE period.

Placebo (normal saline 0.9% for SC administration) will be packaged and administered identically to cemdisiran.

Reference Treatment, Dose, and Mode of Administration

Angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) per physician and manufacturer‘s instructions.

Duration of Treatment and Study

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and patients will receive SC doses of cemdisiran for a further 52 weeks in the optional OLE. The estimated total time on study, inclusive of Screening (120 days), run-in period (14 weeks), treatment period (36 weeks), extension period (52 weeks) and safety follow-up (52 weeks), for patients is approximately 43 months or 3 years and 7 months.

Statistical Methods

The primary endpoint of the study is the percentage change from baseline in UPCR from a 24-hour urine sample at Week 32. Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study based on the assumption that, in the placebo arm, the estimated geometric mean ratio of UPCR at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction, while the geometric mean ratio is 0.5, or a 50% reduction for the cemdisiran arm. Using these assumptions, sample size of 9 and 18 in the placebo and cemdisiran arms, respectively, will provide a width of 0.80 (± 0.4) for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. The primary analysis will be performed using a restricted maximum likelihood (REML) based Mixed-Effect Model Repeated Measures (MMRM) approach.

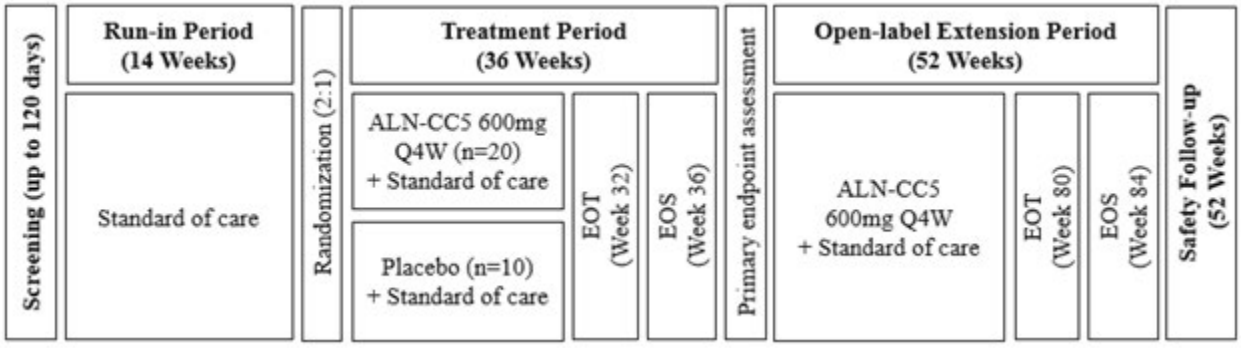
The analysis populations include:

- The modified Intent-to-treat (mITT) population will include all patients who receive any amount of study drug and have at least one post baseline 24-hour proteinuria assessment. Patients will be grouped by assigned treatments (ie, as randomized).
- The Safety Analysis Set will include all patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The efficacy endpoints will be analyzed in the mITT population. PK and PD parameters will be analyzed in the PK and PD analysis sets, respectively.

Safety data will be summarized with descriptive statistics using the Safety Analysis Set.

Figure 1: Study Design



Abbreviations: Q4W=once every 4 weeks; EOS=end of study; EOT=end of treatment

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Discuss Study Information and Collect Informed Consent	6.1 and 6.2	X				(X)									(X)					
Medical History	6.1	X																		
Demographics	6.1		X																	
Inclusion/Exclusion Criteria	4.1 and 4.2	X					X													
Routine Physical Exam	6.7.3		X				X		X						X	X		X		X
Height, Weight and BMI	6.7.2		X				X		X						X	X		X		X
Vital Signs	6.7.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4		X				X								X	X		X		X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Clinical Laboratory Assessment	6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	6.7.5.2		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Routine Vaccination Status	6.1		X																	
Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccination, if not previously vaccinated and required per local guidance	5.3.2.2 and 6.2		To follow local guidance which can be vaccination during Screening for some countries																	
Start of Meningitis Vaccination (at	5.3.2.1 and 6.2				X															

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
least 14 days prior to the Day 1 visit)																				
Confirmation of Meningococcal Vaccine Injection Schedule Compliance	As applicable and dependent on which vaccine will be used.						X	X	X	X	X	X	X	X						
Randomization							X													
Study Drug Administration	5.2.2						X	X	X	X	X	X	X	X	X					
24-hour Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1					X									X					

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
24-hour Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1		X								X							X		X
CAP/CCP Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
C5 Levels Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR Calculation	6.4.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Blood Sample for Antidrug Antibodies	6.7.5.1		X				X	X		X			X		X	X	X	X	X	X
Blood Samples for CIC and anti-Gd-IgA1 Antibody Assessment	6.7.5.1		X				X	X		X			X		X					
Exploratory Blood Sample	6.4.4						X		X		X		X		X					
Blood Sample for Exploratory Genetic Analysis	6.8.						X													
Exploratory Urine Sample	6.4.4.						X		X		X		X		X					
Plasma and Urine PK	See Table 3						X													

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Optional Visit at a location other than the study site (eg, at home)	Will be arranged where feasible from Week 4 of the treatment period and during safety follow-up at Weeks 49 and 75							X									X		X	
Adverse Events	6.7.6.2						X													
Concomitant Medications	5.3	X	X	X																

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up

Study Visit (Day/Week)		Screening Period		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow-up			
		Consent	Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-219 to D-113	D-112 to D-99	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±14	D28 ±14	D56 ±14	D84 ±14	D112 ±14	D140 ±14	D168 ±14	D196 ±14	D224 ±14	D252 ±14	D343±14	D434±14	D525±14	D616±14
Antibiotics Compliance (if applicable)	5.5.3						X													

Notes:

- If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in Table 1 above, are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.
- If a patient is unable to complete a site visit due to the COVID-19 pandemic impacting activities at the study site or patient ability or willingness to access the site, study procedures, including cemdisiran administration, may occur at a location other than the study site (eg, at home) at the discretion of the Investigator, based on safety and tolerability.
- In situations where a study visit cannot be completed at the study site or offsite by a healthcare professional at a location other than the study site (eg, at home) or the dose is missed, the study Investigator (or delegate) may verbally contact the patient within the study visit window to assess for any adverse events and concomitant medications.

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow-up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow-up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Routine Physical Exam	6.7.3						X				X		X	X		X		X
Height, Weight and BMI	6.7.2						X				X			X		X		X
Vital Signs	6.7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4						X						X	X		X		X
Clinical Laboratory Assessment	6.7.5	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Pregnancy Test	6.7.5.2	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1													X				
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1						X				X					X		X
CAP/CCP Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
C5 Levels Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
eGFR Calculation	6.4.3	X	X		X		X		X		X		X	X	X	X	X	X

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow-up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow-up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5	X	X		X		X		X		X		X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2	X	X		X		X		X		X		X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1				X						X			X	X	X	X	X
Exploratory Blood Sample	6.4.4		X		X		X		X		X		X	X				
Exploratory Urine Sample	6.4.4		X		X		X		X		X		X	X				
Optional Visit at a location other than the study site (eg, at home)	Will be arranged for cemdisiran administration in between 8-weekly study site visits at Weeks 44, 52, 60, 68 and 76 during the extension period, and where feasible, during safety follow up at Weeks 97 and 123, unless patients are required to visit			X		X		X		X		X			X		X	

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow-up

Study Visit (Day/Week)		**Open-Label Extension Period (52 weeks)**													**Safety Follow-up**			
		Week 36	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80** (OLE EOT)	**Week 84** (OLE EOS/ET)	**Week 97**	**Week 110**	**Week 123**	**Week 136**
	Notes For details, see Section	**D252 ±7**	**D280 ±7**	**D308 ±7**	**D336 ±7**	**D364 ±7**	**D392 ±7**	**D420 ±7**	**D448 ±7**	**D476 ±7**	**D504 ±7**	**D532 ±7**	**D560 ±7**	**D588 ±7**	**D679 ±14**	**D770 ±14**	**D861±14**	**D952 ±14**
	the study site as judged necessary by the Investigator.																	
Adverse Events	See Section 6.7.6.2	X																
Concomitant Medications	See Section 5.3	X																
Antibiotics Compliance (if applicable)	See Section 5.5.3	X																

Table 3: Pharmacokinetic Time Points

Phase	Study Day	Protocol Time Relative to Dosing (hh:mm)[a]	PK Blood	Pooled Urine[b]
Treatment phase	Day 1	Predose (within 60 mins)	X	
		00:00 (dose)		X
		01:00 (±5 mins)	X	
		02:00 (±15 mins)	X	
		04:00 (±15 mins)	X	
		06:00 (±15 mins)	X	
		08:00 (±30 mins)	X[c]	X
		12:00 (±30 mins)		
		24:00 (±120 mins)	X[c]	X

Abbreviations: hh=hours; mm=minutes; mins=minutes; PK=pharmacokinetics.

[a] The actual time of blood sample collection must be recorded.
[b] The pooled urine 6-12 hours and 12-24 hours can be collected as outpatient.
[c] Blood samples for PK assessment at these time points postdose may be collected if locally feasible.

TABLE OF CONTENTS

SPONSOR PROTOCOL APPROVAL 2
INVESTIGATOR'S AGREEMENT 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 21
LIST OF TABLES 25
LIST OF FIGURES 25
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 26
1. INTRODUCTION 29
1.1. Disease Overview 29
1.2. Cemdisiran 31
1.3. Study Design Rationale 32
1.4. Dose Rationale 33
1.5. Benefit-Risk Assessment 34
2. OBJECTIVES AND ENDPOINTS 36
3. INVESTIGATIONAL PLAN 38
3.1. Summary of Study Design 38
3.2. Duration of Treatment 39
3.3. Duration of Study 39
3.3.1. Definition of End of Study for an Individual Patient 39
3.4. Number of Planned Patients 40
3.5. Method of Assigning Patients to Treatment Groups 40
3.6. Blinding 40
3.6.1. Emergency Unblinding 40
3.7. Data Monitoring Committee 41
4. SELECTION AND WITHDRAWAL OF PATIENTS 41
4.1. Inclusion Criteria 41
4.2. Exclusion Criteria 42
4.3. Removal from Therapy or Assessment 43
4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments 44
4.3.2. Stopping a Patient's Study Participation 45
4.3.2.1. Patient or Legal Guardian Stops Participation in the Study 45

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data 45
4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study....45
4.3.2.4. Recording Reason for Stopping a Patient's Study Participation 45
4.3.3. Lost to Follow-Up....46
4.3.4. Replacement of Study Patients 46
5. TREATMENTS AND OTHER REQUIREMENTS 46
5.1. Treatments Administered....46
5.2. Study Drug....46
5.2.1. Description....46
5.2.2. Dose and Administration 47
5.2.3. Dose Modifications....47
5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing....48
5.2.4. Preparation, Handling, and Storage 49
5.2.5. Packaging and Labeling....50
5.2.6. Accountability....50
5.3. Concomitant Medications and Procedures 50
5.3.1. Prohibited Concomitant Medications 50
5.3.2. Study-specific Vaccinations 51
5.3.2.1. Meningococcal Vaccinations....51
5.3.2.2. Pneumococcal and Hib Vaccinations 51
5.4. Treatment Compliance....52
5.5. Other Requirements 52
5.5.1. Contraception....52
5.5.2. Alcohol Restrictions 53
5.5.3. Antibiotic Compliance....53
6. STUDY ASSESSMENTS 53
6.1. Screening Assessments 53
6.1.1. Rescreening....54
6.1.2. Retesting 54
6.2. Run-in Period....54
6.3. Baseline Assessments (Treatment Period)....55
6.4. Efficacy Assessments 55

6.4.1. Urine Protein/Creatinine Ratio 55
6.4.1.1. 24-Hour Urine Collection 55
6.4.1.2. Spot Urine Collection 56
6.4.2. Hematuria 56
6.4.3. Changes in Renal Function 56
6.4.4. Markers of Complement Activation, Inflammation and Renal Injury 57
6.5. Pharmacodynamic Assessments 57
6.6. Pharmacokinetic Assessments 57
6.7. Safety Assessments 57
6.7.1. Vital Signs 57
6.7.2. Weight and Height 58
6.7.3. Physical Examination 58
6.7.4. Electrocardiogram 58
6.7.5. Clinical Laboratory Assessments 59
6.7.5.1. Immunogenicity 60
6.7.5.2. Pregnancy Testing 61
6.7.5.3. Additional Liver Function Assessments 61
6.7.6. Adverse Events 62
6.7.6.1. Definitions 62
6.7.6.2. Eliciting and Recording Adverse Events 64
6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee 65
6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee 65
6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities 66
6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee 66
6.7.6.7. Pregnancy Reporting 66
6.7.6.8. Overdose Reporting 66
6.7.7. COVID-19 Data Collection 67
6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository 67
7. STATISTICS 67
7.1. Determination of Sample Size 67
7.2. Statistical Methodology 68
7.2.1. Populations to be Analyzed 68

7.2.2. Examination of Subgroups 68
7.2.3. Handling of Missing Data....69
7.2.4. Baseline Evaluations....69
7.2.5. Efficacy Analyses 69
7.2.5.1. Primary Endpoint....69
7.2.5.2. Secondary Efficacy Endpoints....69
7.2.5.3. Exploratory Endpoints 69
7.2.6. Pharmacodynamic Analysis....70
7.2.7. Pharmacokinetic Analysis 70
7.2.8. Safety Analyses 70
7.2.9. Immunogenicity Analyses 71
7.2.10. Biomarker Analyses....71
7.2.11. Interim Analysis....71
7.2.12. Optional Additional Research....71
8. STUDY ADMINISTRATION 71
8.1. Ethical and Regulatory Considerations 71
8.1.1. Informed Consent 71
8.1.2. Ethical Review....72
8.1.3. Serious Breach of Protocol 72
8.1.4. Study Documentation, Confidentiality, and Records Retention....72
8.1.5. End of Study 73
8.1.6. Termination of the Clinical Study or Site Closure 73
8.2. Data Quality Control and Quality Assurance 73
8.2.1. Data Handling....73
8.2.2. Study Monitoring....73
8.2.3. Audits and Inspections....74
8.3. Publication Policy....74
9. LIST OF REFERENCES....75
10. APPENDICES 78

LIST OF TABLES

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow-up 10

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow-up....17

Table 3: Pharmacokinetic Time Points 20

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified 49

Table 5: Clinical Laboratory Assessments 59

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases 62

LIST OF FIGURES

Figure 1: Study Design....9

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECI	Adverse event of clinical interest
aHUS	Atypical hemolytic uremic syndrome
ALN-CC5	Cemdisiran
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Aspartate transaminase
AUC	Area under the concentration curve
BMI	Body mass index
C3	Complement component 3
C3a	Activated complement 3
C5	Complement component 5
C5a	Activated complement component 5
CAP	Complement alternative pathway
CCP	Complement classical pathway
CFH	Complement factor H
CI	Confidence interval
CIC	Circulating immune complexes
CL/F	Clearance
C_{max}	Maximum concentration
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine

Abbreviation	Definition
GCP	Good Clinical Practice
Gd-IgA1	Galactose-deficient Immunoglobulin A 1
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
hpf	High powered field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgAN	IgA Nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function test
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRNA	Messenger RNA
NHP	Nonhuman primates
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
RAS	Renin-angiotensin system
RBC	Red blood cell

Abbreviation	Definition
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
T_{max}	Time to maximum concentration
TMF	Trial Master File
Tri-GalNAc	Triantennary N-acetylgalactosamine
UP	Urine protein
UACR	Urine albumin/creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
V/F	Volume of distribution

1. INTRODUCTION

1.1. Disease Overview

Globally, immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure.[Lai 2016; Wyatt 1998] While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly O-glycosylated IgA1 (Gd-IgA1) and the presence of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule, resulting in the formation of pathogenic immune complexes. Some of these circulating complexes may deposit in glomeruli and induce renal injury.[Knoppova 2016] The lack of galactose exposes O-linked monosaccharide N-acetylgalactosamine (O-GalNAc) moeities in the hinge region of IgA1.[Novak 2018] While the binding of autoantibodies to Gd-IgA1 is dependent on the presence of multiple O-GalNAc residues, the IgA1 protein backbone and the spatial arrangement of O-GalNAc moieties are also thought to play a role in the specificity of autoantibodies to Gd-IgA1.[Mestecky 2016; Suzuki 2009]

Both the alternative and lectin complement pathways may be activated, leading to generation of the anaphylatoxins activated complement component 3 (C3a) and activated complement component 5 (C5a) and the membrane attack complex (MAC) C5b-9, with subsequent promotion of inflammatory mediators.[Maillard 2015] Emerging data indicate that mesangial-derived mediators that are released following deposition of IgA1 may lead to podocyte and tubulointerstitial injury.

Given that a biopsy specimen is required to diagnose IgAN, the clinical threshold for performing a biopsy will have a major impact on the prevalence of IgAN. Persistent microscopic hematuria alone and/or mild proteinuria alone are not commonly used as a per cause indication for biopsy in the United States. Thus, the prevalence of IgAN is modest in the United States (10 to 20% of primary glomerulonephritis), higher in some European countries (20 to 30%), and highest in developed countries in Asia (40 to 50%).[Woo 2010] This considerable geographical variability can be explained by several factors including the variation in access to primary care enabling early diagnosis and the differences in policies for performing renal biopsies as well as for early referrals. For example, in some countries, urine screening tests are conducted in schools or for military service or ahead of employment, explaining the apparent high incidence.[Imai 2007; Wyatt 1998] Ethnic differences can also contribute to the varying prevalence of IgAN. Genome-wide association studies have identified candidate genes as well as risk-associated and protective alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa.[Kiryluk 2014] These genes are involved in antigen presentation, mucosal defense system and notably the alternative complement pathway (complement factor H [CFH]/CFHR locus).[Kiryluk 2014] Finally, patients may present at any age with IgAN but there is a peak incidence in the second and third decades of life. Most cases of IgAN occur in sporadic (90 to 95%) rather than in familial patterns (5 to 10%).[Lai 2016]

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. The first indication for making a diagnosis comes after careful microscopic examination of a urine sample. The presence of red blood cell (RBC) casts and dysmorphic RBCs indicates glomerular bleeding. Varying degrees of proteinuria are present in patients with

IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio (UPCR) measurement. Hence, IgAN can only be diagnosed definitely upon renal biopsy and study of kidney tissue using immunofluorescence. The pathology of IgAN is characterized by deposition of pathogenic polymeric IgA1 immune complexes and C3 in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. A consensus on the pathologic classification of IgAN has been developed by the International IgA Nephropathy Network in collaboration with the Renal Pathology Society (Oxford classification).[Cattran 2009; Lai 2016; Roberts 2009]

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis which is often associated with severe hypertension, but between these extremes, most patients with IgAN pursue a chronic indolent course.[Lai 2016] Some patients present with more severe proteinuria, hypertension and renal progression over time, typically reaching end-stage renal disease (ESRD) over a span of 20 years. Thus, the severity of proteinuria upon presentation has significant prognostic implications. More importantly, the change in proteinuria over time is being regarded as the current best prognostic indicator: those who had heavy time averaged proteinuria and achieved a partial remission of <1 g/24-hours had a similar course to those who had <1 g/24-hours throughout and fared far better than those who never achieved partial remission.[Reich 2007] These observations support the notion that every effort should be made to reduce proteinuria in IgAN. In addition to the degree of proteinuria, baseline renal function and the degree of histological injury are of prognostic value. For example, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90 to 120 mL/min/1.73 m^2). The rate of glomerular filtration rate (GFR) decline also correlates with glomerulosclerosis and tubular atrophy or interstitial fibrosis on biopsy as outlined by Oxford-MEST-C classification. Spontaneous full recovery in IgAN is rare in adults, especially if associated with significant proteinuria (>0.5 g/24-hour).[Knoop 2017]

Patients with minor urine abnormalities, normal blood pressure, and normal GFR usually do well and require only monitoring. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. Thus, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease that can result in end-stage renal failure. The optimal role of immunosuppressive therapy is uncertain. The available studies are not conclusive since most are relatively small and have limited follow-up.[Lai 2016] STOP-IgAN, a German trial, randomly assigned adults with an eGFR of >30 mL/min/1.73 m^2 and persistent proteinuria of >0.75 g/24-hour despite 6 months of supportive care with RAS inhibitors to receive supportive care alone or supportive care plus immunosuppression (prednisone alone for those with initial GFR >60 mL/min and prednisone combined with cyclophosphamide then azathioprine with initial GFR 30-59 mL/min). This strategy did not significantly improve the renal outcome and was associated with increased adverse effects at 36 months.[Rauen 2015] The TESTING trial demonstrated some GFR effect of steroids in Chinese patients, but had to be stopped due to large number of serious adverse events (SAEs) in the steroid arm.[Lv 2017] The 2012 KDIGO guidelines recommend corticosteroids, albeit at very low level of evidence. Thus, steroids may be tried in some cases as

rescue therapy if proteinuria markedly increases or GFR rapidly falls. Further studies to address the role of steroids in IgAN are currently under way. Finally, Rituximab seems to be ineffective in the treatment of patients with progressive IgAN.[Lafayette 2016]

1.2. Cemdisiran

Alnylam Pharmaceuticals, Inc. is developing cemdisiran (ALN-CC5), a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of atypical hemolytic uremic syndrome (aHUS) and IgAN. Cemdisiran comprises a small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (Tri-GalNAc) ligand.

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19-25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA.[Elbashir 2001] Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [Soutschek 2004], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo in animal models (including in rodents and nonhuman primates [NHP]) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations.[Soutschek 2004; Zimmermann 2006] Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a GalNAc carbohydrate ligand.[Ashwell and Morell 2006] Conjugation of a Tri-GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

Cemdisiran (containing siRNA drug substance, ALN-62643, targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via subcutaneous (SC) injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the cemdisiran siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of MAC formation and C5a release. This in turn would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN resulting in renal function improvement.[Maillard 2015] Both lectin and alternative pathways of complement have been implicated in IgAN pathology. Cemdisiran-mediated silencing of C5 will inhibit MAC formation and C5a release regardless of the activating pathway and may be a superior approach in IgAN where the contribution of different pathways may be heterogenous between patients.[Medjeral-Thomas 2018]

The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities, other than an increased susceptibility to Neisserial infections, in subjects with known genetic C5 deficiencies.[Ross and Densen 1984]

Subjects with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. These infections include invasive meningococcal disease, disseminated gonococcal infections as well as diseases caused by typically commensal Neisseria species.[Crew 2018a; Crew 2018b; McQuillen and Ram 2018; Ram 2010] In addition, safety data on the treatment of healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH) with cemdisiran in Study ALN-CC5-001 indicate that cemdisiran is generally well-tolerated; the maximum tolerated dose was 900 mg. There were no SAEs or discontinuations due to adverse events (AEs) during this study, and most AEs were mild or moderate in severity. In Study ALN-CC5-001, the frequency of ADA was low. Two of 48 healthy volunteers (1 cemdisiran-treated and 1 placebo-treated) were ADA positive during the study. The cemdisiran-treated volunteer had transient ADA positivity, with a negative result later in the study and no impact on PK or PD. The placebo-treated volunteer was ADA positive at baseline (predose) and remained positive through Day 70.

A detailed description of the chemistry, pharmacology, nonclinical pharmacokinetics (PK) and toxicology, as well as preliminary efficacy, and safety of cemdisiran is provided in the current edition of the Investigator's Brochure (IB).

1.3. Study Design Rationale

In contrast to the RBC lysis which characterises the pathophysiology of PNH, which requires extremely high level of C5 inhibition for protection, endothelial cells and mesangial cells are the cellular targets of dysregulated complement in aHUS and IgAN, respectively. These cells are nucleated cells which possess complement regulatory proteins as well as the ability to shed membrane associated MAC to defend against MAC-mediated damage, a key step in thrombotic microangiopathy progression in aHUS and renal damage in IgAN. It is therefore hypothesized that a lesser degree of cemdisiran mediated C5 knockdown will be required for disease control in patients with IgAN and aHUS than in patients with PNH.[Morgan 1989; Rosse 1973] This hypothesis is supported by the observation that aHUS patients who achieve C5 inhibition maintain good disease control despite complement activity levels consistent with higher free C5 levels.[Cugno 2014] Therefore, cemdisiran monotherapy may be a viable treatment option in patients with IgAN at levels of C5 silencing achieved in Study ALN-CC5-001.

This therapeutic hypothesis will be tested in a multicenter, multinational, double-blind, placebo-controlled study to evaluate the effect of multiple doses of cemdisiran given by SC injection in patients with IgAN with persistent proteinuria (≥1 g/24-hours) despite the standard of care (angiotensin converting enzyme inhibitors [ACE] or angiotensin II receptor blockers [ARB]) and additional medications if necessary for blood pressure control followed by a treatment extension to evaluate long-term safety and clinical activity. The study population has been selected based on two major factors: 1) the severity of proteinuria upon presentation has significant prognostic implications.[Coppo and D'amico 2005] IgAN patients with heavy proteinuria ≥1 g/24-hours have a significantly worse renal outcome than those who have proteinuria <1 g/24-hours.[Reich 2007] 2) For patients with persistent proteinuria, despite the nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, no disease-specific therapies are currently available, and an unmet need persists for novel interventions. Since proteinuria can result both from active inflammation as well as irreversible scarring of renal tissue and in lieu of a protocol biopsy, we enrich our patients for presence of

potentially reversible disease activity by requiring presence of hematuria and relatively preserved renal function with eGFR >30 mL/min. To ensure the selection of patients who are truly at risk of progression of kidney disease despite standard of care, the first period of the study consists of a run-in period during which patients will not receive study drug (cemdisiran or placebo). The run-in period will be an observational period during which patients' treatment with standard of care, blood pressure, kidney function, degree of hematuria, and proteinuria will be documented. The standard of care is expected to remain unchanged during this run-in period. Only patients whose

- proteinuria level remains ≥1 g/24-hours within 2 weeks before the end of the run-in period,
- continue to meet blood pressure and eGFR criteria

will be eligible to enroll in the 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) portion of the study.

Randomization to cemdisiran or placebo will be performed in a 2:1 ratio so that more patients will receive cemdisiran. This will allow a more precise estimation of the effect of cemdisiran with only marginal loss of power. Inclusion of a placebo arm will allow better assessment of safety and interpretation of the efficacy of cemdisiran.

The primary endpoint for the study is percent change from baseline in 24-hour urine protein/creatinine ratio (UPCR) at Week 32. This is justified for a phase 2 study given the slow progression of renal disease and the established role of proteinuria as a marker of disease progression.

1.4. Dose Rationale

In the Phase 1/2 Study (ALN-CC5-001), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). Treatment with cemdisiran was generally well tolerated in both healthy volunteers and patients with PNH. There were no SAEs and no discontinuations due to AEs during this study, including at the highest doses administered. Most AEs observed were mild or moderate in severity.

Dose selection for the current study is based on the expected level of C5 and complement activity inhibition necessary for efficacy in patients with IgAN and the extent to which different doses of cemdisiran can inhibit production of C5. C5 silencing is a novel approach for the treatment of IgAN and little clinical precedent exists for inhibiting the terminal complement pathway in this disease. Since complement regulation is not impaired in IgAN like it is in PNH, and the kidney glomerular cells are nucleated cells, it is expected that the level of silencing needed for efficacy in IgAN is lower than that needed for PNH (see IB Section 2.4). For this proof-of-concept study, a dose was selected that is expected to produce rapid and robust C5 suppression and complement activity inhibition across the patient population, allowing an unambiguous evaluation of whether C5 silencing results in proteinuria improvement in IgAN. In

Study ALN-CC5-001, a single dose of 600 mg cemdisiran achieved a C5 level of 12.3±1.47 µg/mL by Day 14 and 2.3±0.76 µg/mL by Day 56, corresponding to 60.9% reduction in complement alternative pathway (CAP) activity and a 69.3% reduction in complement classical pathway (CCP) activity by Day 14 and 90.2% and 91.4% reduction in CAP and CCP activities, respectively, by Day 56. Single and multiple biweekly doses of 600 mg were well-tolerated with an acceptable safety profile in healthy volunteers in Study ALN-CC5-001A. In this initial study, the cemdisiran dose of 600 mg that was safe and well-tolerated was chosen for evaluation. This dose will yield robust C5 silencing and will have maximal opportunity to produce a meaningful clinical effect in patients with IgAN. Since the relationship between C5 levels and complement activity is non-linear, with small C5 fluctuations resulting in a larger increase in complement activity, a monthly dose regimen was selected to maintain a constant level of C5 silencing. Additionally, a more consistent effect of cemdisiran on C5 protein and CCP level is predicted after monthly dosing when compared to quarterly dosing based on a modeling approach.

During the extension treatment period, patients treated with both cemdisiran and placebo will have the option to receive a 600 mg dose of cemdisiran every four weeks for an additional 52 weeks.

IgAN can result in progressive renal impairment; however, patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2) who may have sustained irreversible damage to the kidney are not eligible for participation in this trial. As the kidney is not the major elimination pathway for cemdisiran and based on available nonclinical and clinical data obtained with cemdisiran (with 10.6 to 31.6% of the cemdisiran dose recovered in a 24-hour urine collection in the ALN-CC5-001 study), it is expected that moderate renal impairment (eGFR<60 mL/min/1.73 m^2) will not affect the PK of cemdisiran to the extent that a dose adjustment would be required. Therefore, patients with moderate renal impairment are eligible for study enrollment. More information on urine PK can be found in the IB.

1.5. Benefit-Risk Assessment

To date, no medications have been approved specifically for the treatment of IgAN. Therefore, there is a large unmet need for novel interventions, particularly in patients who are at risk of progressive renal disease such as those with persistent proteinuria despite treatment with RAS inhibitors. Available data from studies on the role of immunosuppressive therapy in IgAN are not conclusive as most are relatively small and have limited follow-up.[Lai 2016] Use of immunosuppressive drugs and high-dose steroids are also associated with increased AEs which is particularly common in patients with lower GFR.[Sarcina 2016]

Given the biological target of cemdisiran, the available nonclinical and clinical data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities and injection site reactions (ISRs). C5 inhibition is associated with increased susceptibility for Neisserial infections (including disseminated gonococcal infections) and the potential risk of other infections, particularly those due to encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), as well as *Aspergillus* in immunocompromised and neutropenic patients. Therefore, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine are required. Patients will be instructed to contact study site if any early signs of

meningococcal infections are experienced. In addition, patients with functional or anatomic asplenia will be excluded and only patients previously vaccinated or who agree to receive vaccination for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines, at Screening, will be enrolled. Investigators in Study ALN-CC5-005 should educate patients on the risk of disseminated gonococcal infection and encourage safe sex practices. All national/local screening recommendations for gonorrhea in the general population should also be followed. Finally, given the reported evidence of a higher risk of disseminated gonococcal infections with treatment with eculizumab, Investigators are encouraged to evaluate any patient who has a *Neisseria gonorrhoeae* infection for the signs and symptoms of disseminated infection.[Crew 2018a; McQuillen and Ram 2018] No cases of Neisserial infection or other infections due to encapsulated bacteria were observed in healthy volunteers or in patients with PNH (Study ALN-CC5-001).

As cemdisiran is targeted for delivery to the liver, patients will be closely monitored for changes in LFTs and patients with a medical history or evidence of chronic liver disease or cirrhosis have been excluded. Criteria for dose withholding, and stopping of cemdisiran are provided in Section 5.2.3.1. Patients will also be monitored for the development of ISRs and rotation of injection site are recommended during the study.

Considering anti-glycan autoantibodies recognizing Gd-IgA1 are implicated in the pathogenesis of IgA nephropathy, exposure to the GalNAc moiety of cemdisiran may pose a theoretical risk of stimulating the production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy. This could presumably occur when antidrug antibodies (ADAs) to cemdisiran's Tri-GalNAc cross-react with Gd-IgA1. The risk of developing these cross-reactive antibodies is likely low. This is based on the low incidence of ADA to cemdisiran in study ALN-CC5-001 (see Section 1.2) and the distinct difference in structure of the O-GalNAc moieties on a Gd-IgA1 glycoprotein and the Tri-GalNAc moiety in cemdisran. This low risk is further mitigated by excluding patients with confirmed pre-existing IgG/IgM/IgA ADAs to total drug and real time monitoring for development of de novo IgG/IgM/IgA ADAs after dosing with cemdisiran. Patients with confirmed de novo ADAs will be discontinued from study drug but will continue to be monitored until EOS visit and subsequent safety follow-up. Patients who develop positive ADA will be followed until ADA titers return to baseline. Additional ADA samples will also be collected if any clinical evidence of progression of IgAN disease and/or relevant safety findings.

Detailed information about the known and expected benefits and risks of cemdisiran and additional information on the clinical and nonclinical data may be found in the current version of the IB.

Cumulatively, clinical data regarding the role of complement pathways in IgAN progression, robust nonclinical and clinical data with cemdisiran (see IB for more information), and prior and ongoing clinical experience with other RNAi therapeutics in humans suggest cemdisiran will have a favorable risk profile in the intended population and supports the initial clinical development of cemdisiran in IgAN. In addition, cemdisiran may address the unmet medical need for the first efficacious and disease-specific treatment for patients with IgAN.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in UPCR as measured in 24-hour urine at Week 32
Secondary	
• To evaluate the effect of cemdisiran on additional measures of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 • Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 • Frequency of AEs
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the effect of cemdisiran on full clinical remission and measures of albuminuria in adult patients with IgAN • To evaluate the pharmacodynamic (PD) effect of cemdisiran ie, C5 level and CAP/CCP • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 36 weeks using all assessments during the period • The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (UP <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32

• To assess the incidence of antidrug antibodies (ADA)	• Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life (t½), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, t½, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. Patients will not receive study drug (cemdisiran or placebo) during this time. The standard of care is expected to remain unchanged during this run-in period. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of SC cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 120 days to determine eligibility of patients and to complete disease-related assessments. The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and new trial participants to comply with the protocol given limitations during the COVID-19 pandemic. Patients will provide written informed consent and visit the study site approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and eGFR criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study site 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Study drug administration may be conducted by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have demonstrated the ability to tolerate the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than

the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, cemdisiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study site at Week 40 and every 8 weeks thereafter during the OLE. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study site visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study site as judged necessary by the Investigator, or if visits at a location other than the study site (eg, at home) cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study site for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Visits at a location other than the study site (eg, at home), where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by an independent data monitoring committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

3.2. Duration of Treatment

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the 36-week treatment period and patients will receive 600 mg SC doses of cemdisiran for 52 weeks in the optional OLE.

3.3. Duration of Study

The maximum estimated total time on study, inclusive of Screening (maximum of 120 days), run-in period (14 weeks), treatment period (36 weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is approximately 43 months or 3 years and 7 months.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the EOS visit (Week 36 for those patients who do not consent to continue to participate in the study in the

OLE period and Week 84 for patients who enter the OLE period). Upon study completion (regardless if EOS visit is at Week 36 or Week 84) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.

For patients withdrawing from the study after receiving one dose of cemdisiran at a minimum (ET), all efforts should be made to conduct the EOS/ET assessments. Patients should then be encouraged to enter the safety follow-up period.

3.4. Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the cemdisiran or placebo arms. Randomization will be stratified by baseline urine proteinuria levels (≥1 g/24h and <2 g/24h versus ≥2 g/24h).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at Screening and prior to randomization.

3.6. Blinding

All site personnel including sponsor delegated clinical research associates, data management CRO and patients will be blinded to study drug treatment during the efficacy period (up to Week 36). Sponsor personnel will not be blinded to study treatment. Cemdisiran and placebo will be packaged identically. The study drug will be administered under the supervision of the Investigator or at a location other than the study site (eg, at home) by a healthcare professional (see Section 5.2.2). If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, cemdisiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by a site pharmacist prior to administration by a healthcare professional or a patient/caregiver. See the Pharmacy Manual for additional details. Further details on blinding and unblinding arrangements will be documented in a Randomization and Blinding Plan document.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If

time permits, clinical study site personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the Trial Master File (TMF).

Further details on blinding and unblinding arrangements will be documented in a Randomization and Blinding Plan document.

3.7. Data Monitoring Committee

An independent DMC will perform regular reviews of safety, tolerability, and immunogenicity data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a Charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of unblinded data (safety, tolerability, pharmacodynamics (PD), ADA, circulating immune complexes (CIC) and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Male or female ≥18 years and ≤65 years of age at the time of informed consent

Patient and Disease Characteristics

2. Clinical diagnosis of primary IgAN as demonstrated by historical biopsy collected within 60 months of Screening
3. Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB for at least 3 months prior to start of run-in period
4. Urine protein ≥1 g/24-hour at Screening from a valid 24-hour urine collection (see Section 6.4.1.1), and mean urine protein ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization
5. Hematuria as defined by ≥10 RBCs per high powered field (RBC/hpf) by microscopy or a positive urine dipstick (2+ [moderate] and above) measured by a central laboratory at Screening
6. Females of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception 14 days before first dose, throughout study participation, and for 90 days after last dose administration

7. Previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or willingness to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care
8. Previously vaccinated or willingness to receive vaccinations for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines for vaccination use

Informed Consent

9. Patient is willing and able to provide written informed consent and to comply with the study requirements

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Concomitant significant renal disease other than IgAN
2. A diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase
3. Secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease)
4. Diagnosis of Henoch-Schonlein Purpura (IgA Vasculitis)
5. eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization (local results may be used for assessment of eligibility)

Laboratory Assessments

6. Has any of the following laboratory parameter assessments:
    a. Alanine transaminase (ALT) >1.5×upper limit of normal (ULN), International Normalized Ratio (INR) >2 (or >3.5 if on anticoagulants), or total bilirubin >1.5×ULN (unless bilirubin elevation is due to Gilbert's syndrome)
7. Confirmed positive IgG/IgM/IgA ADAs to cemdisiran at Screening
8. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
9. Positive hepatitis B virus (HBV) surface antigen, HBV core antibody, hepatitis C virus (HCV) antibody (unless HCV viral load demonstrated negative)

Prior/Concomitant Therapy

10. Treatment with systemic steroids for more than 7 days or other immunosuppressant agents in the 6 months prior to randomization
11. Treatment with dual RAS blockade in the 3 months prior to entry into the run-in phase
12. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment

Medical Conditions

13. Known human immunodeficiency virus (HIV) infection, HCV infection or HBV infection
14. Malignancy (except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate cancer) within the last 5 years
15. Active psychiatric disorder, including, but not limited to schizophrenia, bipolar disorder, or severe depression despite current pharmacological intervention
16. Known medical history or evidence of chronic liver disease or cirrhosis
17. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
18. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc
19. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
20. Known contraindication to meningococcal vaccines (group ACWY conjugate and group B vaccines) required for this study. Refer to the most recent local product information for each vaccine for the current list of contraindications
21. Unable to take antibiotics for meningococcal prophylaxis, if required by local standard of care
22. Sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period, measured in supine position after 10 minutes of rest
23. Receipt of an organ transplant (including hematologic transplant)
24. History of meningococcal infection within 12 months before Screening
25. Patients with systemic bacterial or fungal infections that require systemic treatment with antibiotics or antifungals
26. Patients with functional or anatomic asplenia

Alcohol Use

27. Patients who consume more than 14 units of alcohol a week (unit 1 glass of wine [125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE), including confirmed positive test for ADA to cemdisiran
- Or, study is terminated by the Sponsor

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.7.5.2 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the Week 36/EOS or Week 84/OLE EOS visit and safety follow-up so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 2), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.7.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 36-week treatment period will be encouraged to remain on the study and complete assessments through Week 36; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 1).

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete the OLE EOS/ET assessments; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 2).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient/legal guardian considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Week 36 visit, including entering the 52-week safety follow-up. If a patient/legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 36-week treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the Week 36 EOS/ET visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.7.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study site. The following actions must be taken if a patient misses a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study during the 36-week treatment period or the OLE will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of cemdisiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to cemdisiran.

5.2.2. Dose and Administration

Patients will be administered cemdisiran (600 mg) or placebo (at the same volume as the active drug) as an SC injection once every 4 weeks in combination with standard of care in the 32-week period of the 36-week treatment period. During the 52-week OLE phase, patients will be administered cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. Study drug administration may be conducted by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have demonstrated the ability to tolerate the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, cemdisiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy Manual. In addition, instructions and procedures related to administration of study drug by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

To maintain the blind during the treatment period, the syringes are to be masked prior to study drug withdrawal. A full description of the blinding procedure is included in the Pharmacy Manual.

5.2.3. Dose Modifications

Dose modifications are not permitted.

The visit window for the treatment period is ±14 days, but the interval between two doses may not be shorter than 14 days. If a dose is not administered within 14 days of the date determined by the Schedule of Assessments (see Table 1), then the dose is considered missed and should not be given.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted. In situations where study drug is administered at a location other than the study site (eg, at home), or the dose is missed, the

study physician (or delegate) will verbally contact the patient to assess any AEs and concomitant medications.

5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing

1. LFT results (Table 5) from the previous visit should be reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 4.
    a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. Perform assessments per Table 4 and Table 6.
    c. If an alternative cause is found, provide appropriate care.
3. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
4. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 4.

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least every two weeks: LFT and coagulation per Table 5
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold cemdisiran dosing until recovery to ≤1.5×ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least weekly: LFT and coagulation per Table 5 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study site or the healthcare professional performing administration at a location other than the study site (eg, at home) will be responsible for preparation of cemdisiran doses, according to procedures detailed in the Pharmacy Manual. In cases where study drug is administered at a location other than the study site (eg, at home) by a patient/caregiver, dosing may be prepared and administered by the patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual and Patient/Caregiver Storage and Administration Instructions.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

Cemdisiran (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of a 0.5-mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study site according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

The standard of care treatment should be held stable throughout the run-in and treatment periods. Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 and Table 2). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

For other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug/placebo, for 7 days after the last dose of either study drug or placebo.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements (if started prior to Screening, then may continue during the study at the same dose)
- Hydroxychloroquine

5.3.2. Study-specific Vaccinations

5.3.2.1. Meningococcal Vaccinations

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, at least 14 days prior to randomization to cemdisiran or placebo, as per the Schedule of Assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions and according to the Advisory Committee on Immunization Practices (ACIP) or other locally applicable recommendations for patients with complement deficiencies. On days of vaccination, urinary samples should be collected prior to administration of vaccines.

Patients will be immunized against *Neisseria meningitidis* according to the following specifications:

- Patients who have previously completed the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) at least 14 days but no more than 3 years from randomization can start study assessments after confirming eligibility. Documented vaccine history must be available to, and verified by, study site staff at the time of Screening.
- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines per the Schedule of Assessments.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the Schedule of Assessments.
- If required locally, patients will receive prophylactic antibiotics according to the local standard of care after randomization to cemdisiran or placebo.

5.3.2.2. Pneumococcal and Hib Vaccinations

Patients will receive vaccinations for Hib and *Streptococcus pneumoniae*, if not previously vaccinated, according to current national/local vaccination guidelines for vaccination use. Hib and pneumococcal vaccinations, if required at Screening per national/local guidelines, should be administered at least 14 days prior to randomization. At Screening, patient vaccination records will be checked for compliance with local recommendations for the use of these vaccines.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained healthcare professionals at a location other than the study site (eg, at home).

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration or until study completion.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries e.g. France, in order to comply with local requirements as described in the corresponding patient consent forms

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.7.5.2).

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. Antibiotic Compliance

Patients who require prophylactic antibiotics after randomization to cemdisiran or placebo (see Section 5.3.2.1) per local standard of care will undergo antibiotic compliance checks. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments. Antibiotic dose adjustments will be permitted in the case of renal impairment. All dose adjustments must comply with the manufacturer's instructions.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 and Table 2. If a patient is unable to complete a site visit due to the COVID-19 pandemic impacting activities at the study site or patient ability or willingness to access the site, routine physical examination/body system assessment, height, weight, body mass index (BMI), vital signs and collection of blood and urine samples for efficacy, safety, PD, PK, and exploratory assessments may be conducted at a location other than the study site (eg, at home) by a trained healthcare professional as locally feasible (refer to instructions for home nurses in the Laboratory Manual).

6.1. Screening Assessments

An ICF approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF.

The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and any new trial participant to comply with the protocol given limitations during the COVID-19 pandemic.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor; see Section 6.1.1.

Patient demographic data and medical history/disease history will be obtained. In particular, the MEST-C score and degree of IgG, IgA, IgM, C3, C1q, C4d and C5b-9 stains will be obtained from pathology reports, if available, and documented. Any changes to medical history occurring between the Screening assessment and Day 1 will be updated prior to study drug administration. Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and BMI, 12-lead

electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, urinalysis and ADA and CIC assessments. Vaccination records will also be checked for compliance with national/local guidelines for pneumococcal and Hib vaccinations.

6.1.1. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). A patient who is unable to complete screening and run-in visits due to COVID-19 associated delays may be rescreened with approval of the Sponsor. A patient will be re-consented if rescreening occurs outside of the 120-day screening window. In this case, all screening procedures must be repeated.

6.1.2. Retesting

If in the Investigator's judgement, the laboratory abnormalities at Screening or in the run-in period are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale is to be documented. Laboratory values can be retested once during Screening or the run-in period as long as the patient can be evaluated for eligibility and randomized within the allowed Screening or run-in period. Two retests will be permitted for hematuria during Screening, if the first test is negative.

6.2. Run-in Period

During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): Hib and pneumococcal vaccinations (if required at Screening per national/local guidelines; vaccination should occur at least 14 days prior to randomization), vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine for proteinuria, and eGFR. Clinical laboratory tests will be performed centrally; however, eGFR may also be assessed locally at the end of the run-in period (Week -2) to facilitate assessment of patient eligibility and administer meningococcal vaccination on the same day. Meningococcal vaccines should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Sites are encouraged to discuss study information with the patients again at the end of the run-in period and to check key inclusion and exclusion criteria when run-in visits are delayed.

6.3. Baseline Assessments (Treatment Period)

Prior to dosing on Day 1, patients will be reassessed for eligibility, and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK, ADA and CIC.

In addition, prior to administration of study drug, the following assessments will be performed: full physical examination, body weight and height, vital signs, ECG, urine pregnancy test, eGFR assessment, and urinalysis.

Collection of blood and urine samples for PK analysis on Day 1 will be performed as outlined in Table 3.

6.4. Efficacy Assessments

6.4.1. Urine Protein/Creatinine Ratio

Primary efficacy will be assessed by determining the percent change from baseline in UPCR from a 24-hour urine sample after 32 weeks of treatment. 24-hour urine samples for determination of UPCR will be collected throughout the study as outlined in the Schedules of Assessments and will be analyzed by a central laboratory.

6.4.1.1. 24-Hour Urine Collection

Patients will be required to provide two separate valid 24-hour urine collections 2 weeks prior to randomization (to assess eligibility after the run-in period) and at Week 32 (to assess the primary endpoint). Patients will also be asked to provide a single valid 24-hour urine sample for other 24-hour urinary assessments outlined in the Schedule of Assessments. Both UPCR as well as UACR will be calculated in an aliquot of each 24-hour urine collection. Rigorous exercise and significant change in diet (in particular salt intake) should be avoided within 48 hours before collection of 24-hour urine samples, whenever possible. The two valid 24-hour urine samples may be collected within 2 weeks before assessment is due while the one valid 24-hour urine sample may be collected within one week before the assessment takes place. If any of the collections do not meet validity criteria outlined below, then repeat collections must be scheduled within the time frames outlined above to assure the minimum number of valid collections required for each of the study time points. The duration of collection and volume of urine in the collection will be recorded in the eCRF. In addition to protein, albumin, sodium and creatinine will also be quantified in each of the 24-hour urine samples.

A 24-hour urine collection will only be considered valid if the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.

Primary efficacy will be evaluated by comparing the percent change from baseline in 24-hour UPCR at Week 32 in patients treated with cemdisiran versus those treated with placebo.

Secondary and exploratory efficacy assessments include comparisons of the proportion of patients with partial or complete clinical remission, respectively, as measured by the amount of total protein in a 24-hour urine sample. Partial clinical remission is defined as having UP <1 g/24-hours and complete clinical remission is defined as UP <0.3 g/24-hours. Each will be assessed at Week 32.

Additionally, using 24-hour samples, the percent change from baseline in total protein will be evaluated as a secondary endpoint and the change from baseline in urine UACR at Week 32 as an exploratory endpoint.

6.4.1.2. Spot Urine Collection

Urinary protein, albumin and creatinine levels from spot urine collections prior to dosing will also be measured to assess the effect of cemdisiran on UPCR and UACR as outlined in the Schedule of Assessments.

The change from baseline in UPCR at Week 32 will be evaluated in spot urine samples. Spot urine samples will be collected at the time points outlined in the Schedule of Assessments (Table 1).

6.4.2. Hematuria

Hematuria from spot urine collections will also be evaluated to assess the effect of cemdisiran on disease course in patients with IgAN. The degree of hematuria will be assessed by microscopic examination of the spun urine sediment (RBC/hpf) and by urine dipstick. Single void collections for random urine sample for hematuria evaluation should be collected. If the investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated.

Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the Schedule of Assessments and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to study drug administration, if applicable.

6.4.3. Changes in Renal Function

Changes in renal function will be monitored using measurements of serum creatinine and eGFR (mL/min/1.73m^2) as outlined in the Schedule of Assessments. The calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for all patients. For assessment of eligibility at the last visit of run-in period, 2 weeks prior to randomization, local lab can be utilized. This will allow evaluation for eligibility on the same day. A sample will also be sent to central lab.

Renal function will also be estimated as creatinine clearance based on the 24-hour urine collection. The creatinine clearance is a widely used test to estimate the GFR using the following formula:

GFR = [UCr x V] / SCr

SCr is the serum creatinine concentration and the value assessed closest to collection of 24-hour urine collection will be utilized for purpose of above calculation. UCr is the urine creatinine concentration and V is the urine flow rate or volume.

Blood and urine samples for renal function assessments will be collected prior to administration of cemdisiran or placebo on dosing days, if applicable.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed for the treatment period and the entire study period (including the OLE).

6.4.4. Markers of Complement Activation, Inflammation and Renal Injury

Samples for measurement of markers of complement activation, inflammation and renal injury will be collected at the time points outlined in the Schedule of Assessments (Table 1) and analyzed by central laboratories. On dosing days, blood samples will be collected predose.

6.5. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at the time points outlined in the Schedule of Assessments (Table 1). Samples will be collected prior to administration of cemdisiran or placebo on dosing days.

Analysis of PD will include the impact of cemdisiran administration on plasma C5 protein levels (assessed by a mass spectrometry-based method) and serum complement activity (assessed by CAP enzyme linked immunosorbent assay [ELISA] and CCP ELISA). Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

6.6. Pharmacokinetic Assessments

Blood samples and urine samples will be collected for assessment of cemdisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples and urine samples for PK analysis is in Table 3.

The concentration of cemdisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests, including assessment of IgG/IgM/IgA ADA and CIC. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.7.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for at least

10 minutes. On Day 1, vital signs will be collected predose (no more than 4 hours prior to dosing) and 4 hours (±30 minutes) postdose. On all other dosing days, vital signs will be collected predose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral or tympanic method. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.7.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1 and Table 2; height at Screening only and dosing weight during the clinical study site visits) and will be recorded in the eCRF.

6.7.3. Physical Examination

Routine physical examinations will be conducted according to the Schedule of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

At Screening and Day 1 predose, a full physical examination will be performed. At all other time points, including Day 1 at 4 hours (±30 minutes) postdose, a directed physical examination will be performed.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Directed physical examinations will include examination of the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.7.4. Electrocardiogram

Twelve-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. A single 12-lead ECG will be performed at Screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings approximately 1 minute apart. 12-lead ECGs will be performed predose (on the same day as dosing); 60 minutes (±15 minutes) postdose; and 4 hours (±30 minutes) postdose in relation to the Day 1 and Week 32 cemdisiran or placebo doses.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.7.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, eGFR will also be assessed locally. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and include: hematology, serum chemistry and urinalysis parameters. Parameters will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5 which are measured locally should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions. If central laboratory tests are not feasible due to COVID-19 restrictions, local laboratory tests for safety monitoring can be performed with approval from the Sponsor.

Clinical laboratory assessments may be collected at the clinical study site or at a location other than the study site (eg, at home) by a trained healthcare professional. On dosing days blood samples will be collected predose.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the CKD-EPI formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide

Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH	Nitrite
Specific gravity	Blood
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.7.5.1)	
Antidrug antibodies	
Hepatic Tests (Screening Only)	
Hepatitis C, including: HCV RNA PCR – qualitative and quantitative assays	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Pregnancy Testing (Females of Child-bearing Potential Only) (see Section 6.7.5.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG= IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RNA=ribonucleic acid.

6.7.5.1. Immunogenicity

Blood samples will be collected to evaluate ADA and CIC. IgG/IgM/IgA ADA to total drug will be assessed at Screening and during the study. ADA samples will be tested in real time. Clinical study decision will be based on confirmed positive ADA results from the IgG/IgM/IgA assay. Confirmed positive ADA samples will be further characterized for cemdisiran domain specificity against the Tri-GalNAc component if a reliable method is established. Blood samples for ADA and CIC testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1 and Table 2). Blood samples to evaluate ADAs will be collected at Screening to assess study eligibility and at the Early Termination (ET) visit, if applicable. ADA

and CIC will be routinely monitored during the treatment period and throughout the open-label extension period and safety follow-up (ADA only), as indicated in the Schedule of Assessments. Finally, ADA and CIC samples will also be collected and analyses will be performed and prioritized if any clinical evidence of progression of IgAN disease and/or relevant safety findings. Patients who are confirmed positive for IgG/IgM/IgA ADA at baseline will be excluded from study treatment. In addition, patients who develop de novo ADAs will be discontinued from study drug but will be followed until EOS visit and during safety follow-up. These patients will also be monitored until ADA levels return to baseline.

Exploratory analysis of anti-Gd-IgA1 antibody levels will be conducted; serum samples for these analyses will be drawn when CIC samples are collected.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.7.6.7 for follow-up instructions).

6.7.5.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any liver function test (LFT) abnormalities. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 5, and other assessments or evaluations per Investigator discretion, as appropriate.

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
Herpes Zoster Virus IgM, IgG	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.7.6. Adverse Events

6.7.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at a location other than the study site (eg, at home), blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

Based on the biological target and the available nonclinical and clinical data, AEs of Clinical Interest (AECI) for this study are:

- Severe infections as judged by the investigator
- ALT or AST >3×ULN
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of cemdisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR.

For information on recording and reporting of AECIs, see Section 6.7.6.2 and Section 6.7.6.3 , respectively.

Adverse Event Severity

AEs are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.7.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording all SAEs and only AEs related to study procedures that are observed or reported by the patient during the run-in period (before the administration of the first dose of study drug) regardless of their relationship to study drug through the end of study. All AEs, including non-serious AEs, occurring after signing of the ICF and before study

drug administration will be captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study site and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.7.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AECIs (Section 6.7.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.7.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study site staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Investigator Site File.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.7.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.7.6.4.

6.7.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.7.7. COVID-19 Data Collection

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic and the patient's participation in the study will be collected.

6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with IgAN, as well as their responses to treatment.

To permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of cemdisiran, a set of biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2).

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, the samples will be collected as part of this study. Examples of potential exploratory investigations would include DNA, RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

The sample size of the study was determined based on the precision of the estimate of the treatment effect for the primary endpoint – the percent change from baseline in UPCR from a

24-hour urine sample at Week 32. It should be noted that geometric mean ratio of UPCR at Week 32 to baseline is statistically equivalent to mean of the change from baseline in logarithm of UPCR. Therefore, the effect size of the study is defined as the difference of change from baseline between cemdisiran and placebo in the logarithm of UPCR.

Based on the [Fellstrom 2017] study, we assume that in the placebo arm the geometric mean ratio of UPCR at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction, while the geometric mean ratio is 0.5, or a 50% reduction for the cemdisiran arm. Using these assumptions, sample size of 9 and 18 in the placebo and cemdisiran arms will provide a width of 0.80 (± 0.4) for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

Descriptive statistics including the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum values will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

Additional data summaries to help understand any impact of COVID-19 on PK/PD, efficacy and safety assessments will be outlined in the SAP.

7.2.1. Populations to be Analyzed

The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The primary population used to evaluate efficacy will be the mITT Population. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the mITT and Safety Analysis Set.

Baseline value for 24-hour UPCR will be calculated as the average of two valid 24-hour urine assessments before randomization (at the Week -2 visit).

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint of the study is the percentage change from baseline in 24-hour UPCR at Week 32. The 24-hour UPCR will be log transformed for analyses. The primary analysis will be performed using a restricted maximum likelihood (REML) based Mixed-Effect Model Repeated Measures (MMRM) approach. The outcome variable is change from baseline in 24-hour UPCR in log-scale at the Week 16 and Week 32 visits. Analysis will include fixed effects of treatment (cemdisiran vs. placebo), scheduled visits (Week 16 and Week 32), interaction term of treatment and scheduled visits, baseline 24-hour UPCR in log-scale (continuous), and patient as a random effect. The least square mean difference and its 90% confidence interval will be estimated . In addition, placebo-adjusted geometric mean percent change at the Week 32 visit and its 90% CI will be presented.

A sensitivity analysis for the impact of missing data and the normality assumptions on the log-transformed UPCR data will be performed. Details will be provided in the SAP.

7.2.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include percent change from baseline in 24-hour proteinuria (g/24 hours) at Week 32, percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in UP in 24-hour urine assessments and UPCR by spot urine at Week 32 will be analyzed similarly to the analysis of the primary variable as appropriate. The descriptive statistics for change from baseline in hematuria (urine dipstick) at Week 32 will be provided.

7.2.5.3. Exploratory Endpoints

Change from baseline in exploratory efficacy variables will be summarized. Percent of patients in full clinical remission and incidence of ADA will be tabulated by treatments.

The slope of eGFR for the double-blind period will be estimated for each treatment and the slope of eGFR for the entire study period including the OLE will be analyzed. Other inferential

statistics for exploratory efficacy variables may be presented as needed. Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Assessment of the PD effect of the treatment will be performed descriptively, including plotting graphically levels of serum C5 protein and CAP/CCP over time and relative to baseline levels. Inferential statistics may be generated as deemed necessary.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. Pharmacokinetic parameters include, but will not be limited to: AUC, C_{max}, T_{max}, t½, CL/F, V/F, cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe) in the urine of cemdisiran (25-mer) and 23-mer.

Other parameters may be calculated, if deemed necessary. Summary statistics and figures will be presented. Inferential statistics may be generated when deemed necessary.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized by treatment arm and overall.

AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary. All SAEs occurring before the first dose of study drug and AEs related to study procedures will be listed. The number and percentage of patients experiencing AEs after the first dose of the study drug or events that worsened in severity after dosing will be summarized. AEs will be presented by maximum severity and relationship to study medication. SAEs and AEs leading to discontinuation of treatment will also be tabulated.

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation.

Frequency of AEs of clinical interest will also be summarized and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

All safety analyses will be conducted using the Safety Analysis Set.

Additional data summaries to help understand any impact of COVID-19 on safety assessments will be outlined in the SAP.

7.2.9. Immunogenicity Analyses

Antidrug antibody, CIC and anti-Gd-IgA1 antibody results will be summarized descriptively.

7.2.10. Biomarker Analyses

Urine and serum complement activation products, inflammation and renal injury markers will be summarized descriptively.

7.2.11. Interim Analysis

No formal interim analysis is planned.

7.2.12. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.7.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study site periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee, immediately if contacted by a regulatory agency or an IRB/IEC about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 18 months after completion of the study at all sites. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Ashwell G,Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Advances in Enzymology and Related Areas of Molecular Biology, Volume 41. 2006:99-128.

Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney international. 2009;76(5):534-45.

Coppo R,D'amico G. Factors predicting progression of IgA nephropathies. Journal of nephrology. 2005;18(5):503-12.

Crew PE, Abara WE, McCulley L, Waldron PE, Kirkcaldy RD, Weston EJ, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. Clinical Infectious Diseases. 2018a.

Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC,Bersoff-Matcha SJ. Unusual Neisseria species as a cause of infection in patients taking eculizumab. Journal of Infection. 2018b.

Cugno M, Gualtierotti R, Possenti I, Testa S, Tel F, Griffini S, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. Journal of Thrombosis and Haemostasis. 2014;12(9):1440-8.

Elbashir SM, Lendeckel W,Tuschl T. RNA interference is mediated by 21-and 22-nucleotide RNAs. Genes & development. 2001;15(2):188-200.

Fellstrom BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017 May 27;389(10084):2117-27.

Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clinical journal of the American Society of Nephrology. 2007;2(6):1360-6.

Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nature genetics. 2014;46(11):1187.

Knoop T, Vikse BE, Mwakimonga A, Leh S,Bjørneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology Dialysis Transplantation. 2017;32(11):1841-50.

Knoppova B, Reily C, Maillard N, Rizk DV, Moldoveanu Z, Mestecky J, et al. The origin and activities of IgA1-containing immune complexes in IgA nephropathy. Frontiers in immunology. 2016;7:117.

Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. Journal of the American Society of Nephrology. 2016:ASN. 2016060640.

Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nature Reviews Disease Primers. 2016;2:16001.

Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy. Jama. 2017;318(5):432.

Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current understanding of the role of complement in IgA nephropathy. Journal of the American Society of Nephrology. 2015;26(7):1503-12.

McQuillen DP,Ram S. No good deed goes unpunished: eculizumab and invasive neisserial infections. Clinical Infectious Diseases. 2018.

Medjeral-Thomas NR, Troldborg A, Constantinou N, Lomax-Browne HJ, Hansen AG, Willicombe M, et al. Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin–Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H–Related Protein-5 (FHR5) Deposition. Kidney international reports. 2018;3(2):426-38.

Mestecky J, Novak J, Moldoveanu Z,Raska M. IgA nephropathy enigma. Clinical Immunology. 2016;172:72-7.

Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochemical Journal. 1989;264(1):1.

Novak J, Barratt J, Julian BA,Renfrow MB, editors. Aberrant Glycosylation of the IgA1 Molecule in IgA Nephropathy. Seminars in nephrology; 2018: Elsevier.

Ram S, Lewis LA,Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clinical microbiology reviews. 2010;23(4):740-80.

Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. New England Journal of Medicine. 2015;373(23):2225-36.

Reich HN, Troyanov S, Scholey JW,Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. Journal of the American Society of Nephrology. 2007;18(12):3177-83.

Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney international. 2009;76(5):546-56.

Ross SC,Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine. 1984;63(5):243-73.

Rosse WF. Variations in the red cells in paroxysmal nocturnal haemoglobinuria. British journal of haematology. 1973;24(3):327-42.

Sarcina C, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, et al. Changes in proteinuria and side effects of corticosteroids alone or in combination with azathioprine at different stages of IgA nephropathy. Clinical journal of the American Society of Nephrology. 2016;11(6):973-81.

Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004;432(7014):173-8.

Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. The Journal of clinical investigation. 2009;119(6):1668-77.

Woo K-T, Chan C-M, Chin YM, Choong H-L, Tan H-K, Foo M, et al. Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades. Nephron Clinical practice. 2010;116(4):c337-c46.

Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. Journal of the American Society of Nephrology. 1998;9(5):853-8.

Zimmermann TS, Lee AC, Akinc A, Bramlage B, Bumcrot D, Fedoruk MN, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006;441(7089):111-4.

10. APPENDICES

None.

ALN-CC5-005 PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES DATED 27 APRIL 2020

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

1. RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter (DIL) dated 06 April 2020. The USMs were implemented immediately by investigator sites on receipt of the DIL to minimize the serious risk caused by the COVID-19 pandemic to research participants in this trial. The changes focus on assuring the safety of trial participants while maintaining compliance with good clinical practice (GCP) and minimizing risks to trial integrity, and are in line with guidance published by the European Medicines Agency [EMA 2020] and the US Food and Drug Administration [FDA 2020]. The USMs are summarized in Section 1.1 and Table 1.

In order to reduce burden to investigator sites at this time of increased demands due to the COVID-19 pandemic, this protocol amendment also incorporates additional study changes that are not considered USMs. These changes are summarized in Section 1.2 and Table 2, and will only be implemented following receipt of appropriate Health Authority and Ethics Committee (EC) or Institutional Review Board (IRB) approval.

1.1. Urgent Safety Measures due to the Impact of the COVID-19 Pandemic

Urgent Safety Measures were implemented by the Sponsor, as mentioned above, to ensure the safety of study participants and the integrity of study data in response to the impact of the COVID-19 pandemic. The changes are outlined below, and a detailed summary of the USMs is provided in Section 2 in Table 1.

- **Screening Period (expansion of screening window and notification of Sponsor prior to screening of new trial participants)**

  The Screening window has been widened from 90 to 120 days ranging from Day-219 to Day-99 for completion of assessments.

  In addition, the Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and any new trial participant to comply with the protocol given COVID-19 limitations.

- **Run-in Period (completion of visits at a later time with the approval of the Medical Monitor)**

  If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period, as planned, the run-in period can be extended

as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.

Sites are encouraged to discuss study information with the patients again and to check key inclusion and exclusion criteria at the end of the run-in period if run-in visits are delayed.

Since the run-in period is designed to be observational and aims at ensuring a stable clinical state prior to the treatment period, allowing a delay in run-in visits is not expected to impact the study.

- **Study Visit Window (Treatment Period)**

  The visit window for the treatment period is expanded to ±14 days (previously ±3 days), but the interval between two doses may not be shorter than 14 days. If a dose is not administered within 14 days of the date determined by the schedule of assessments, then the dose is considered missed and should not be given.

  The change is being made to increase flexibility given transportation and scheduling challenges associated with COVID-19. A previous study of cemdisiran (ALN-CC5-001) established the safety of dosing at 14-day intervals, and hence this is set as the minimum interval between doses.

- **Cemdisiran Dosing Outside the Study Site**

  Following appropriate training on cemdisiran administration, dosing at a location other than the study site (eg, at home) may be arranged in place of in-site visits from Week 4 in the 36-week double-blinded Treatment Period, if feasible and approved by the Medical Monitor.

  Dosing at a location other than the study site (eg, at home) may be administered by a healthcare professional with the oversight of the Investigator. Administration by the patient or a caregiver is allowed following training with approval of the Investigator and Medical Monitor. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, patients' homes) for dosing.

- **All Study Assessments**
- Following appropriate training, study assessments may be conducted at site visits or at a location other than the study site (eg, at home) by a healthcare professional, as locally feasible.

- **PK Assessments**

  Blood samples for PK assessment will be collected at 1, 2, 4 and 6 hours postdose and, where locally feasible, at 8 and 24 hours postdose.

  This change is implemented to reduce study burden since it may not be practical to collect PK blood samples on all originally scheduled time points.

- **Assessment of Adverse Events through Verbal Contact**

  The Investigator or designee may remotely contact patients verbally to assess adverse events (AEs) and concomitant medications in situations where study drug is administered at a location other than the study site (eg, at home), or the dose is missed.

- **Collection of Information Related to COVID-19**

  Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient. Additional information regarding collection of this information, including completion of a new case report form specific to COVID-19, will be provided separately.

  This change is implemented to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to Study Administration**

  Text was updated to provide clarification on Investigator responsibilities regarding communication of new study information to patients and IRB/Independent Ethics Committees (IECs).

1.2. Changes Not Related to Urgent Safety Measures

The following changes are being made to the protocol. As noted above in Section 1 , these changes will not be implemented prior to approval from the concerned Health Authority and EC or IRB.

- Removal of creatinine-based criteria to assess 24-hour urinary creatinine sample validity. The protocol included creatinine-based criteria that were intended to assess the completeness of the 24-hour urine collection. However, based on a review of the references used in the protocol, [Fellstrom 2017; Rauen 2015] it is considered that these criteria are not appropriate for this use in the study as intended. Therefore, these criteria have been removed from the protocol, to avoid the rejection of valid samples.
- Exchange of primary and secondary endpoints for the evaluation of proteinuria, to use the UPCR rather than the total protein (g/24-hrs) as the primary endpoint. To mitigate against the risk of under/over collection of urine, which cannot be reliably controlled by the creatinine-based criteria (see above change), the assessment of proteinuria by total protein content will be changed from the primary, to the secondary endpoint. The UPCR normalizes the assessment of urinary protein and protects against variability from collection factors. To reflect this, the UPCR is being changed to the primary endpoint. The use of the UPCR from a timed sample as a primary endpoint is in line with published studies (NEFIGAN and STOP-IgAN) [Fellstrom 2017; Rauen 2015] and relevant EU guidance [EMA 2016].
- Including the use of urine dipstick for hematuria analyses for improved reliability. The inclusion criteria for hematuria previously required the presence of ≥10 red blood cells (RBCs) per high power field (HPF), based on microscopic analysis of urine at a

central laboratory. Delays inherent in transport of urine samples from local sites to the central laboratory can result in degradation of RBCs and falsely low measurement of RBCs. Measurement of hematuria by urine dipstick at the central laboratory is resilient to these effects of delays as it can detect both intact and degraded RBCs and has been performed in a standardized manner from the initiation of the study. Thus, the presence of ≥10 RBCs/HPF on microscopy or a positive urine dipstick (2+ [moderate] and above) measured by a central laboratory will be used to define hematuria for assessing inclusion criteria during Screening.

- Removal of pharmacokinetics (PK) periodic review by a Data Monitoring Committee (DMC). The DMC remains in place to perform periodic reviews of unblinded data (safety, tolerability, pharmacodynamics [PD], ADA, circulating immune complexes [CIC] and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Due to the short plasma exposure of cemdisiran, PK measurements are not considered informative for the assessment of safety or efficacy.

Additional changes are being implemented as outlined below.

- Reducing the prior exclusion for systemic steroid exposure or other immunosuppressant agents from 12 months to 6 months
- Clarifying the prohibition of dual RAS blockade in the eligibility criteria
- Clarification to specific eligibility criteria and safety assessment timeframes

A detailed summary of changes is provided in Table 2 of Section 2 . The following changes are not detailed: administrative changes, changes associated with administrative letters (between protocol amendments 2 and 3), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

References

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 2 (27/03/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-prevent-development/slow-progression-chronic-renal-insufficiency_en.pdf

Fellstrom BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter J W, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017;389:2117–27

Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. New England Journal of Medicine. 2015;373:2225-36

2. PROTOCOL AMENDMENT 3 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 3 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Table 1: Urgent Safety Measure COVID-19-related Changes to be Adopted Immediately

Purpose: To widen the Screening Period window from 90 to 120 days.

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up)

Revised text: The Screening Period window is now for a duration of **120** days ranging from Day-**219** to Day-99.

Sections also reflecting this change:

- Synopsis
- Figure 1, Study Design
- Section 3.1, Summary of Study Design
- Section 3.3, Duration of Study
- Section 6.1.1, Rescreening

Purpose: To widen the total time of study duration mainly due to the widening of the Screening Period window.

The primary change occurs in Section 3.3, Duration of Study

Revised text**:** The maximum estimated total time on study, inclusive of Screening (maximum of ~~90~~ **120** days), run in period (14 weeks), treatment period (36 weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is approximately ~~36~~ **43** months or 3 years **and 7 months**.

Section also reflecting this change:

- Synopsis

Purpose: To allow ongoing, safe administration of study drug by ensuring Sponsor notification before patient screening.

The primary change occurs in Section 3.1, Summary of Study Design

Revised text: **The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site and new trial participants to comply with the protocol given limitations during the COVID-19 pandemic.**

Sections also reflecting this change:

- Synopsis
- Section 6.1, Screening Assessments

Purpose: To allow rescreening of patients who are unable to complete screening and run-in visits.

The primary change occurs in Section 6.1.1, Rescreening

Revised text: A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). **A patient who is unable to complete screening and run-in visits due to COVID-19 associated delays may be rescreened with approval of the Sponsor.** A patient will be re-consented if rescreening occurs outside of the ~~90~~ **120**-day screening window. In this case, all screening procedures must be repeated.

Purpose: To allow the completion of visits at a later time during the run-in period following approval by the Medical Monitor

The primary change occurs in Section 6.2, Run-in Period

Revised text: ~~Patients will then return to the study center every 4 weeks after the start of study drug treatment period.~~ **If a run-in visit cannot proceed according to schedule, it may be delayed up to 28 days, with subsequent visits being rescheduled based on the new date. Visit windows, as indicated in the Schedule of Assessments (Table 1), are applied to the rescheduled date. Approval from the Medical Monitor is required prior to initiation of the treatment period. If a subject cannot proceed to the treatment period as planned, the run-in period can be extended as needed. If the final run-in visit will not be within 56 days of randomization, this visit will be repeated, and the new visit will serve as the Week -2 visit to determine eligibility for randomization.**

Sites are encouraged to discuss study information with the patients again at the end of the run-in period **and to check key inclusion and exclusion criteria when run-in visits are delayed**.

Sections also reflecting this change:

- Synopsis
- Schedule of Assessments (Table 1 footnotes)
- Section 3.1, Summary of Study Design

Purpose: To expand the visit window and to allow the study Investigator (or delegate) to verbally contact patients within the study visit window to assess for any adverse events

The primary change occurs in Section 5.2.3, Dose Modifications

Revised text: Dose modifications are not permitted.

The visit window for the treatment period is ±14 days, but the interval between two doses may not be shorter than 14 days. If a dose is not administered within 14 days of the date determined by the Schedule of Assessments (see Table 1), then the dose is considered missed and should not be given.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted. **In situations where study drug is administered at a location other than the study site (eg, at home), or the dose is missed, the study physician (or delegate) will verbally contact the patient to assess any AEs and concomitant medications.**

Section also reflecting this change:

- Table 1, Schedule of Assessments and footnotes

Purpose: To allow offsite and self-administration from Week 4 of the Treatment Period with the oversight of the Investigator and approval of the Medical Monitor.

The primary change occurs in Section 5.2.2, Dose and Administration

Revised text: **Study drug administration may be conducted by a healthcare professional at a location other than the study site (eg, at home) from Week 4 of the treatment period for patients that have demonstrated the ability to tolerate the study drug at the study site. If the patient is unable to come to the study site, and a visit by a healthcare professional for patients at a location other than the study site (eg, at home) is not possible due to circumstances related to the COVID-19 pandemic, cemdisiran may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or the caregiver must receive appropriate training on cemdisiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to a location other than the study site (eg, at home) for dosing.** ~~At home dosing may be administered by a healthcare professional~~. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy

Manual. **In addition, instructions and procedures related to administration of study drug by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.**

Sections also reflecting this change:

- Synopsis
- Schedule of Assessments (Table 1 footnotes)
- Section 3.1, Summary of Study Design
- Section 3.6, Blinding
- Section 5.4, Treatment Compliance

Purpose: To allow offsite administration during the open-label extension (OLE) period and safety follow-up.

The primary change occurs in Section 3.1, Summary of Study Design

Revised text: ~~Home visits~~ **Visits at a location other than the study site (eg, at home)**, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study site visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study site as judged necessary by the Investigator, or if ~~home~~ **visits at a location other than the study site (eg, at home)** cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study site for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. ~~Home visits~~ **Visits at a location other than the study site (eg, at home)**, where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Section also reflecting this change:

- Synopsis

Purpose: To allow offsite cemdisiran preparation, handling and storage by a health care professional or patient/caregiver

The primary change occurs in Section 5.2.4, Preparation, Handling, and Storage

Revised text: Staff at each clinical study site or the ~~home~~ healthcare professional **performing administration at a location other than the study site (eg, at home)** will be responsible for preparation of cemdisiran doses, according to procedures detailed in the Pharmacy Manual. **In cases where study drug is administered at a location other than the study site (eg, at home) by a**

patient/caregiver, dosing may be prepared and administered by the patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. ~~Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.~~

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual **and Patient/Caregiver Storage and Administration Instructions**.

Purpose: To allow study visit assessments to be performed offsite by a healthcare professional

The primary change occurs in Section 6, Study Assessments

Revised text: The Schedule of Assessments is provided in Table 1 and Table 2. **If a patient is unable to complete a site visit due to the COVID-19 pandemic impacting activities at the study site or patient ability or willingness to access the site, routine physical examination/body system assessment, height, weight, body mass index (BMI), vital signs and collection of blood and urine samples for efficacy, safety, PD, PK, and exploratory assessments may be conducted at a location other than the study site (eg, at home) by a trained healthcare professional as locally feasible (refer to instructions for home nurses in the Laboratory Manual).**

Section also reflecting this change:

- Schedule of Assessments (Table 1 footnotes)

Purpose: To collect PK samples, where locally feasible, at 8 and 24 hours postdose.

The primary change occurs in Table 3, Pharmacokinetic Time Points

Revised text: Blood samples for PK assessment will be collected at 1, 2, 4 and 6 hours postdose and, where locally feasible, at 8 and 24 hours postdose.

Purpose: To enable local laboratory tests to be performed if central laboratory tests are not feasible.

The primary change occurs in Section 6.7.5, Clinical Laboratory Assessments

Revised text: In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions. **If central laboratory tests are not feasible due to COVID-19 restrictions, local laboratory tests for safety monitoring can be performed with approval from the Sponsor.**

Clinical laboratory assessments may be collected at the clinical study site or at ~~home~~ **a location other than the study site (eg, at home)** by a trained healthcare professional. On dosing days blood samples will be collected predose.

Purpose: To reiterate that a serious adverse event can occur at a location other than the study site (eg, at home).

The primary change occurs in Section 6.7.6.1, Definitions

Revised text: An SAE is any untoward medical occurrence that at any dose:

- • Results in death
- • Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- • Requires in-patient hospitalization or prolongation of existing hospitalization
- • Results in persistent or significant disability or incapacity
- • Is a congenital anomaly or birth defect
- • Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at ~~home~~ **a location other than the study site (eg, at home)**, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Purpose: To outline additional data summaries on PK/PD, efficacy and safety assessments in the Statistical Analysis Plan (SAP).

The primary change occurs in Section 7.2, Statistical Methodology

Revised text: **Additional data summaries to help understand any impact of COVID-19 on PK/PD, efficacy and safety assessments will be outlined in the SAP.**

Section also reflecting this change:

- Section 7.2.8, Safety Analyses

Purpose: To communicate and document new information that becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study.

The primary change occurs in Section 8.1.1, Informed Consent

Revised text: **The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.**

Purpose: IRB or IEC approval of all patient materials for the study except those that support the need to remove an apparent immediate hazard to the patient.

The primary change occurs in Section 8.1.2, Ethical Review

Revised text: The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study **(except those that support the need to remove an apparent immediate hazard to the patient)**. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Purpose: To clarify lost to follow-up if a patient misses a required study visit.

The primary change occurs in Section 4.3.3, Lost to Follow-Up

Revised text: A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study site. The following actions must be taken if a patient **misses** ~~fails to return to the clinical for~~ a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

Purpose: Collect information related to the impact of the COVID-19 pandemic on patient participation in the study, to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data

The primary change occurs in Section 6.7.7, COVID-19 Data Collection

Added text: **Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic and the patient's participation in the study will be collected.**

Table 2: Changes Not Related to Urgent Safety Measures to be Implemented After EMA and FDA Approval

Purpose: Switched total protein to secondary endpoint and protein:creatinine ratio to primary endpoint.

The primary change occurs in Section 2, Objectives and Endpoints

Revised text: Objectives

Secondary:

- To evaluate the effect of cemdisiran on ~~remission~~ **additional measures** of proteinuria in adult patients with IgAN
- To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN
- To evaluate the safety and tolerability of cemdisiran

Exploratory:

- To evaluate the effect of cemdisiran on renal function parameters
- **To evaluate the effect of cemdisiran on full clinical remission and measures of albuminuria in adult patients with IgAN**
- To evaluate the pharmacodynamic (PD) effect of cemdisiran ~~in adult patients with IgAN~~ **ie, C5 level and CAP/CCP**
- To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN
- To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation
- To assess the incidence of antidrug antibodies (ADA)

Endpoints

Primary:

- Percent change from baseline in **urine protein/creatinine ratio (UPCR) as measured in** 24-hour ~~proteinuria (g/24 hours)~~ **urine** at Week 32

Secondary:

- **Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32**
- Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32

- Percent of patients with >50% reduction in 24-hour proteinuria at Week 32
- ~~Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32~~
- Change from baseline in UPCR as measured in a spot urine at Week 32
- Change from baseline in hematuria at Week 32 ~~(red blood cells per high powered field [RBC/hpf])~~
- Frequency of ~~adverse events (~~AEs~~)~~

Exploratory:

- The slope of eGFR computed for the first ~~32~~ **36** weeks using all assessments during the period

Sections also reflecting this change:

- Synopsis
- Section 1.3, Study Design Rationale
- Section 6.4.1, Urine Protein/Creatinine Ratio
- Section 6.4.1.1, 24-Hour Urine Collection
- Section 7.1, Determination of Sample Size
- Section 7.2.4, Baseline Evaluations
- Section 7.2.5, Efficacy Analyses
- Table 5, Clinical Laboratory Assessments

Purpose: Included the use of urine dipstick testing for the hematuria secondary analyses.

The primary change occurs in Section 7.2.5.2, Secondary Efficacy Endpoints

Revised text: The secondary efficacy endpoints include **percent change from baseline in 24-hour proteinuria (g/24 hours) at Week 32,** percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in ~~24-hour urine at Week 32, change from baseline in urine protein/creatinine ratio (UPCR) as measured in~~ a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in **UP in 24-hour** urine ~~protein / creatinine ration (~~**assessments and** UPCR~~)~~ **by spot urine at Week 32** will be analyzed similarly to the analysis of the primary variable as appropriate. ~~UPCR~~ **The descriptive statistics for change from baseline in hematuria (urine dipstick) at Week 32** will be ~~log transformed first before analysis~~ **provided**.

Purpose: Removed creatinine-based criteria to assess 24-hour urinary creatinine sample validity, and updated an inclusion criterion pertaining to and clarifying the validity of 24-hour urine collections.

The primary change occurs in Section 6.4.1.1, 24-Hour Urine Collection

Revised text: ~~Completeness of the 24-hour urine collection can be estimated from rate of creatinine excretion. Normal values of creatinine excretion vary with age and body weight. An aliquot of the 24-hour urine collection will be used to determine urinary creatinine content to determine if the 24-hour urine collections need to be repeated. Hence, a~~ **A** 24-hour urine collection will only be considered valid if ~~all~~ the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.
- ~~The 24-hour creatinine content is within 25% of expected range as estimated by the following formula: [(140-age) x weight]/5000, where weight is in kilograms. This result is multiplied by 0.85 in women.[Ix 2011]~~
- ~~In case of need of two valid samples, the maximum variation in total 24-hour urine creatinine between the two urine collections must be <25%.~~

Sections also reflecting this change:

- Synopsis
- Section 4.1, Inclusion Criteria – Criterion 4

Purpose: Removed the need for a periodic review of PK by a DMC.

The primary change occurs in Section 3.7, Data Monitoring Committee

Revised text: The DMC will perform periodic reviews of unblinded data (safety, tolerability, ~~PK,~~ pharmacodynamics (PD), ADA, circulating immune complexes (CIC) and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.

Purpose: Increased the window for patients to receive pneumococcal and Haemophilus influenzae type b (Hib) vaccination, if not previously vaccinated, based on local guidance for some countries which can be vaccination during Screening.

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up)

Revised text: The period window for patients to receive pneumococcal and Hib vaccination, if not previously vaccinated, based on local guidance for some countries which can be vaccination during Screening is now from the Screening visit to Week 8 in the treatment period, and should be administered **at least 14 days prior to randomization**.

Sections also reflecting this change:

- Section 5.3.2.2, Pneumococcal and Hib Vaccinations
- Section 6.2, Run-in Period

Purpose: Clarified when patients need to receive meningococcal vaccination.

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up)

Revised text: All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, ~~upon determination of eligibility~~ at ~~the end of run-in period, 2 weeks~~ **least 14 days** prior to **randomization** to cemdisiran or placebo, as per the Schedule of Assessments.

Sections also reflecting this change:

- Section 5.3.2.1, Meningococcal Vaccinations
- Section 6.2, Run-in Period

Purpose: Reduced prior exclusion for systemic steroid exposure or other immunosuppressant agents from 12 months to 6 months based on feedback from investigators, and literature.

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text:

- Criterion 10: Treatment with systemic steroids for more than 7 days or other immunosuppressant agents in the ~~12~~ **6** months prior to randomization

Section also reflecting this change:

- Synopsis

Purpose: Added an exclusion criterion to clarify that dual RAS blockade is prohibited.

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text:

- Criterion 11: **Treatment with dual RAS blockade in the 3 months prior to entry into the run-in phase**.

Section also reflecting this change:

- Synopsis

Purpose: Clarified an exclusion criterion on hepatitis B virus (HBV) and hepatitis C virus (HCV), and moved known human immunodeficiency virus (HIV), HBV and HCV infections under medical conditions.

The primary change occurs in Section 4.2, Exclusion Criteria

Revised text: Laboratory Assessments

- Criterion 9: ~~Known human immunodeficiency virus (HIV) infection~~ **Positive hepatitis B virus (HBV) surface antigen, HBV core antibody**, hepatitis C virus (HCV) ~~infection or hepatitis B virus (HBV) infection~~ **antibody (unless HCV viral load demonstrated negative)**

Medical Conditions

- Criterion 13: **Known human immunodeficiency virus (HIV) infection, HCV infection or HBV infection**

Purpose: Clarified predose and postdose timeframes for the collection of vital signs on Day 1.

The primary change occurs in Section 6.7.1, Vital Signs

Revised text: Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for **at least** 10 minutes. On Day 1, vital signs will be collected ~~at~~ predose **(no more than 4 hours prior to dosing)** and 4 hours (±**30** ~~15~~ minutes) postdose. On all other dosing days, vital signs will be collected predose.

Purpose: Clarified predose and postdose timeframes for the performance of 12-lead electrocardiograms on Day 1 and Week 32.

The primary change occurs in Section 6.7.4, Electrocardiogram

Revised text: 12 lead ECGs will be performed~~,~~ predose **(on the same day as dosing);** 60 minutes **(±15 minutes)** postdose; and 4 hours **(±30 minutes)** postdose in relation to the Day 1 and Week 32 cemdisiran or placebo doses.

Purpose: Clarified that antidrug antibodies will be monitored during the safety follow-up period.

The primary change occurs in Section 6.7.5.1, Immunogenicity

Revised text: ADA and CIC will be routinely monitored during the treatment period and throughout the open label extension **period** ~~phase~~ and safety follow-up **(ADA only)**, as indicated in the Schedule of Assessments.

Purpose: Clarified that a Randomization and Blinding Plan document will detail arrangements on blinding and unblinding.

The primary change occurs in Section 3.6, Blinding

Revised text: Further details on blinding and unblinding arrangements will be documented in a ~~separate plan/manual~~ **Randomization and Blinding Plan document**.

Section also reflecting this change:

- Section 3.6.1, Emergency Unblinding

Purpose: Administrative changes, changes associated with administrative letters (between protocol amendments 2 and 3), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-CC5-005

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy
Short Title:	A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy
Study Drug:	Cemdisiran (ALN-CC5)
EudraCT Number:	2018-002716-27
IND Number:	140087
Protocol Date:	Original protocol 10 September 2018 Amendment 1 [26 November 2018] Amendment 2 [20 September 2019]
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted] [redacted] Development

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

23 SEP 2019

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-CC5-005 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I 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 SYNOPSIS

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Short Title

A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Study Drug

Cemdisiran (ALN-CC5)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 30-40 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32

• To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• The slope of eGFR computed for the first 32 weeks using all assessments during the period • The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life ($t_{½}$), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, $t_{½}$, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. The standard of care is expected to remain unchanged during this run-in period. Patients will not receive study drug (cemdisiran or

placebo) during this time. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of subcutaneous (SC) cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study center at Week 40 and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only and who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by a Data Monitoring Committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years and ≤ 65 years of age) with a clinical diagnosis of primary immunoglobulin A (IgA) Nephropathy based on historical biopsy collected within 60 months of Screening, treated for IgA Nephropathy with stable, optimal pharmacological therapy including maximum allowed or tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for at least 3 months prior to the start of the run-in period. Eligible patients must have urine protein levels of ≥1 g/24-hour at Screening and mean urine protein ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization. In addition, eligible patients must have hematuria defined by ≥10 red blood cells per high powered field (RBC/hpf) at Screening. Eligible patients are required to have been previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or be willing to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care. In addition, patients not previously vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) must be willing to receive these vaccinations according to local guidelines.

Patients will be excluded from the study if eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization; treated with systemic steroids for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization; have a diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase; sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period measured in supine position after 10 minutes of rest; have received organ transplant (including hematologic transplant) or have secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease).

Study Drug, Dose, and Mode of Administration

Cemdisiran is a synthetic small interfering RNA (siRNA) targeting complement component 5 (C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand. Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. Doses of 600 mg of cemdisiran will be administered every 4 weeks during the 32-week treatment phase and the optional OLE period.

Placebo (normal saline 0.9% for SC administration) will be packaged and administered identically to cemdisiran.

Reference Treatment, Dose, and Mode of Administration

Angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) per physician and manufacturer‘s instructions.

Duration of Treatment and Study

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive SC doses of cemdisiran for a further 52 weeks in the optional OLE. The estimated total time on study, inclusive of Screening (90 days), run-in

period (14 weeks), treatment period (36 weeks), extension period (52 weeks) and safety follow-up (52 weeks), for patients is approximately 36 months or 3.0 years.

Statistical Methods

Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of 27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, approximately 30 patients are planned to be randomized stratified by baseline urine protein levels (≥1 g/24h and <2 g/24h versus ≥2 g/24h).

The analysis populations include:

- The modified Intent-to-treat (mITT) population will include all patients who receive any amount of study drug and have at least one post baseline 24-hour proteinuria assessment. Patients will be grouped by assigned treatments (ie, as randomized).
- The Safety Analysis Set will include all patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

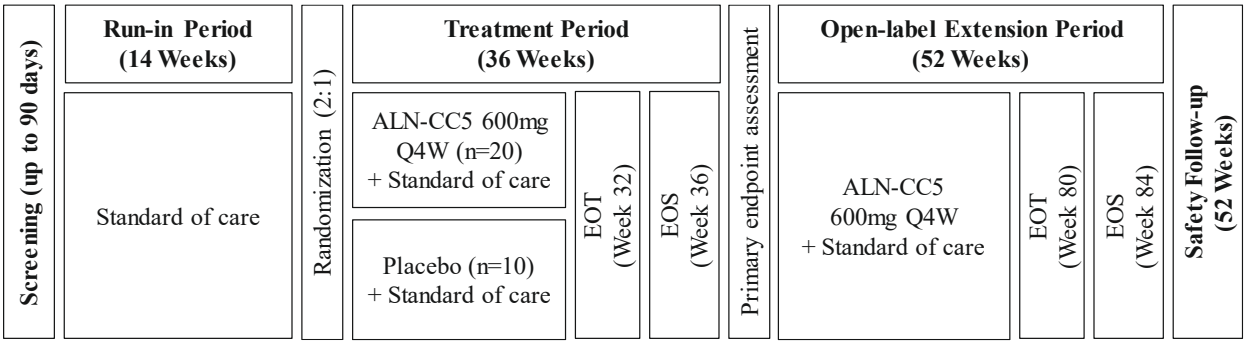
The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval (CI) will be estimated and then back transformed to original scale. In the end, the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and its 90% CI will be presented.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

The efficacy endpoints will be analyzed in the mITT population. PK and PD parameters will be analyzed in the PK and PD analysis sets, respectively.

Safety data will be summarized with descriptive statistics. Treatment-emergent adverse events will be summarized by SOC and PT (all events, related events, and serious events), in addition to being summarized by severity (all events). In addition, summaries will be provided for any AEs leading to discontinuation of study drug or death. Serious adverse events and procedure related adverse events in the run-in period will be listed.

Figure 1: Study Design



Abbreviations: Q4W=once every 4 weeks; EOS=end of study; EOT=end of treatment

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±3	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
Discuss Study Information and Collect Informed Consent	6.1 and 6.2	X				(X)									(X)					
Medical History	6.1	X																		
Demographics	6.1		X																	
Inclusion/Exclusion Criteria	4.1 and 4.2	X					X													
Routine Physical Exam	6.7.3		X				X		X						X	X		X		X
Height, Weight and BMI	6.7.2		X				X		X						X	X		X		X
Vital Signs	6.7.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4		X				X								X	X		X		X
Clinical Laboratory Assessment	6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	6.7.5.2		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±3	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
Review Routine Vaccination Status	6.1		X																	
Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccination, if not previously vaccinated and required per local guidance	5.3.2.2 and 6.2		X																	
Start of Meningitis Vaccination	5.3.2.1 and 6.2					X														
Confirmation of Meningococcal Vaccine Injection Schedule Compliance	As applicable and dependent on which vaccine will be used.						X	X	X	X	X	X	X	X						

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±3	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
Randomization							X													
Study Drug Administration	5.2.2						X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1					X									X					
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1		X								X							X		X
CAP/CCP Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
C5 Levels Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR Calculation	6.4.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±3	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1		X				X	X		X			X		X	X	X	X	X	X
Blood Samples for CIC and anti-Gd-IgA1 Antibody Assessment	6.7.5.1		X				X	X		X			X		X					
Exploratory Blood Sample	6.4.4						X		X		X		X		X					
Blood Sample for Exploratory Genetic Analysis	6.8.						X													
Exploratory Urine Sample	6.4.4.						X		X		X		X		X					
Plasma and Urine PK	See Table 3						X													
Optional Home Visit	Will be arranged																X		X	

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)									Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1 ±3	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
	where feasible during safety follow up at Weeks 49 and 75																		
Adverse Events	6.7.6.2						X												
Concomitant Medications	5.3	X	X	X															
Antibiotics Compliance (if applicable)	5.5.3						X												
IgAN standard of Care Compliance			X																

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Routine Physical Exam	6.7.3						X				X		X	X		X		X
Height, Weight and BMI	6.7.2						X				X			X		X		X
Vital Signs	6.7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4						X						X	X		X		X
Clinical Laboratory Assessment	6.7.5	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Pregnancy Test	6.7.5.2	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1													X				
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1						X				X					X		X
CAP/CCP Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
C5 Levels Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
eGFR Calculation	6.4.3	X	X		X		X		X		X		X	X	X	X	X	X

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5	X	X		X		X		X		X		X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2	X	X		X		X		X		X		X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1				X						X			X	X	X	X	X
Exploratory Blood Sample	6.4.4		X		X		X		X		X		X	X				
Exploratory Urine Sample	6.4.4		X		X		X		X		X		X	X				
Optional Home Visit	Will be arranged for cemdisiran administration in between 8-weekly study site visits at Weeks 44, 52, 60, 68 and 76 during the extension phase, and where feasible, during safety follow up at Weeks 97 and 123, unless patients are required to visit			X		X		X		X		X			X		X	

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
	the study center as judged necessary by the Investigator.																	
Adverse Events	See Section 6.7.6.2	X																
Concomitant Medications	See Section 5.3	X																
Antibiotics Compliance (if applicable)	See Section 5.5.3	X																
IgAN standard of Care Compliance		X																

Table 3: Pharmacokinetic Time Points

Phase	Study Day	Protocol Time Relative to Dosing (hh:mm)[a]	PK Blood	Pooled Urine[b]
Treatment phase	Day 1	Predose (within 60 mins)	X	
		00:00 (dose)		X
		01:00 (±5 mins)	X	
		02:00 (±15 mins)	X	
		04:00 (±15 mins)	X	
		06:00 (±15 mins)	X	
		08:00 (±30 mins)	X	X
		12:00 (±30 mins)		
		24:00 (±120 mins)	X	X

Abbreviations: hh=hours; mm=minutes; mins=minutes; PK=pharmacokinetics.

[a] The actual time of blood sample collection must be recorded.
[b] The pooled urine 6-12 hours and 12-24 hours can be collected as outpatient.

TABLE OF CONTENTS

SPONSOR PROTOCOL APPROVAL 2
INVESTIGATOR'S AGREEMENT 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 19
LIST OF TABLES 22
LIST OF FIGURES 23
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 24
1. INTRODUCTION 27
1.1. Disease Overview 27
1.2. Cemdisiran 29
1.3. Study Design Rationale 30
1.4. Dose Rationale 31
1.5. Benefit-Risk Assessment 32
2. OBJECTIVES AND ENDPOINTS 34
3. INVESTIGATIONAL PLAN 36
3.1. Summary of Study Design 36
3.2. Duration of Treatment 37
3.3. Duration of Study 37
3.3.1. Definition of End of Study for an Individual Patient 37
3.4. Number of Planned Patients 37
3.5. Method of Assigning Patients to Treatment Groups 37
3.6. Blinding 38
3.6.1. Emergency Unblinding 38
3.7. Data Monitoring Committee 38
4. SELECTION AND WITHDRAWAL OF PATIENTS 39
4.1. Inclusion Criteria 39
4.2. Exclusion Criteria 39
4.3. Removal from Therapy or Assessment 41
4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments 41
4.3.2. Stopping a Patient's Study Participation 42
4.3.2.1. Patient or Legal Guardian Stops Participation in the Study 42

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data 43
4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study....43
4.3.2.4. Recording Reason for Stopping a Patient's Study Participation 43
4.3.3. Lost to Follow-Up....43
4.3.4. Replacement of Study Patients 44
5. TREATMENTS AND OTHER REQUIREMENTS 45
5.1. Treatments Administered....45
5.2. Study Drug....45
5.2.1. Description....45
5.2.2. Dose and Administration 45
5.2.3. Dose Modifications....45
5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing....46
5.2.4. Preparation, Handling, and Storage 47
5.2.5. Packaging and Labeling....48
5.2.6. Accountability....48
5.3. Concomitant Medications and Procedures 48
5.3.1. Prohibited Concomitant Medications 48
5.3.2. Study-specific Vaccinations 49
5.3.2.1. Meningococcal Vaccinations....49
5.3.2.2. Pneumococcal and Hib Vaccinations 49
5.4. Treatment Compliance....50
5.5. Other Requirements 50
5.5.1. Contraception....50
5.5.2. Alcohol Restrictions 51
5.5.3. Antibiotic Compliance....51
6. STUDY ASSESSMENTS 52
6.1. Screening Assessments 52
6.1.1. Rescreening....52
6.1.2. Retesting 52
6.2. Run-in Period....52
6.3. Baseline Assessments (Treatment Period)....53
6.4. Efficacy Assessments 53

6.4.1. Proteinuria....53
6.4.1.1. 24-Hour Urine Collection....53
6.4.1.2. Spot Urine Collection....54
6.4.2. Hematuria....54
6.4.3. Changes in Renal Function....55
6.4.4. Markers of Complement Activation, Inflammation and Renal Injury....55
6.5. Pharmacodynamic Assessments....55
6.6. Pharmacokinetic Assessments....55
6.7. Safety Assessments....56
6.7.1. Vital Signs....56
6.7.2. Weight and Height....56
6.7.3. Physical Examination....56
6.7.4. Electrocardiogram....57
6.7.5. Clinical Laboratory Assessments....57
6.7.5.1. Immunogenicity....59
6.7.5.2. Pregnancy Testing....59
6.7.5.3. Additional Liver Function Assessments....59
6.7.6. Adverse Events....60
6.7.6.1. Definitions....60
6.7.6.2. Eliciting and Recording Adverse Events....62
6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee....63
6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee....63
6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities....64
6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee....64
6.7.6.7. Pregnancy Reporting....64
6.7.6.8. Overdose Reporting....64
6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository....65
7. STATISTICS....66
7.1. Determination of Sample Size....66
7.2. Statistical Methodology....66
7.2.1. Populations to be Analyzed....66
7.2.2. Examination of Subgroups....67

7.2.3. Handling of Missing Data....67
7.2.4. Baseline Evaluations....67
7.2.5. Efficacy Analyses....67
7.2.5.1. Primary Endpoint....67
7.2.5.2. Secondary Efficacy Endpoints....67
7.2.5.3. Exploratory Endpoints....67
7.2.6. Pharmacodynamic Analysis....68
7.2.7. Pharmacokinetic Analysis....68
7.2.8. Safety Analyses....68
7.2.9. Immunogenicity Analyses....69
7.2.10. Biomarker Analyses....69
7.2.11. Interim Analysis....69
7.2.12. Optional Additional Research....69
8. STUDY ADMINISTRATION....70
8.1. Ethical and Regulatory Considerations....70
8.1.1. Informed Consent....70
8.1.2. Ethical Review....70
8.1.3. Serious Breach of Protocol....71
8.1.4. Study Documentation, Confidentiality, and Records Retention....71
8.1.5. End of Study....71
8.1.6. Termination of the Clinical Study or Site Closure....71
8.2. Data Quality Control and Quality Assurance....72
8.2.1. Data Handling....72
8.2.2. Study Monitoring....72
8.2.3. Audits and Inspections....72
8.3. Publication Policy....72
9. LIST OF REFERENCES....74
10. APPENDICES....77

LIST OF TABLES

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up....10

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up 15
Table 3: Pharmacokinetic Time Points 18
Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified 47
Table 5: Clinical Laboratory Assessments 58
Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases 60

LIST OF FIGURES

Figure 1: Study Design....9

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibodies
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECI	Adverse event of clinical interest
aHUS	Atypical hemolytic uremic syndrome
ALN-CC5	Cemdisiran
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Aspartate transaminase
AUC	Area under the concentration curve
BMI	Body mass index
C3	Complement component 3
C3a	Activated complement 3
C5	Complement component 5
C5a	Activated complement component 5
CAP	Complement alternative pathway
CCP	Complement classical pathway
CFH	Complement factor H
CI	Confidence interval
CIC	Circulating immune complexes
CL/F	Clearance
C_{max}	Maximum concentration
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine

Abbreviation	Definition
GCP	Good Clinical Practice
Gd-IgA1	Galactose-deficient Immunoglobulin A 1
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
hpf	High powered field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgAN	IgA Nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function test
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRNA	Messenger RNA
NHP	Nonhuman primates
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
RAS	Renin-angiotensin system
RBC	Red blood cell

Abbreviation	Definition
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
T_{max}	Time to maximum concentration
TMF	Trial Master File
Tri-GalNAc	Triantennary N-acetylgalactosamine
UP	Urine protein
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein:creatinine ratio
V/F	Volume of distribution

1. INTRODUCTION

1.1. Disease Overview

Globally, immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure.[Lai 2016; Wyatt 1998] While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly O-glycosylated IgA1 (Gd-IgA1) and the presence of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule, resulting in the formation of pathogenic immune complexes. Some of these circulating complexes may deposit in glomeruli and induce renal injury.[Knoppova 2016] The lack of galactose exposes O-linked monosaccharide N-acetylgalactosamine (O-GalNAc) moeities in the hinge region of IgA1.[Novak 2018] While the binding of autoantibodies to Gd-IgA1 is dependent on the presence of multiple O-GalNAc residues, the IgA1 protein backbone and the spatial arrangement of O-GalNAc moieties are also thought to play a role in the specificity of autoantibodies to Gd-IgA1.[Mestecky 2016; Suzuki 2009]

Both the alternative and lectin complement pathways may be activated, leading to generation of the anaphylatoxins activated complement component 3 (C3a) and activated complement component 5 (C5a) and the membrane attack complex (MAC) C5b-9, with subsequent promotion of inflammatory mediators.[Maillard 2015] Emerging data indicate that mesangial-derived mediators that are released following deposition of IgA1 may lead to podocyte and tubulointerstitial injury.

Given that a biopsy specimen is required to diagnose IgAN, the clinical threshold for performing a biopsy will have a major impact on the prevalence of IgAN. Persistent microscopic hematuria alone and/or mild proteinuria alone are not commonly used as a per cause indication for biopsy in the United States. Thus, the prevalence of IgAN is modest in the United States (10 to 20% of primary glomerulonephritis), higher in some European countries (20 to 30%), and highest in developed countries in Asia (40 to 50%).[Woo 2010] This considerable geographical variability can be explained by several factors including the variation in access to primary care enabling early diagnosis and the differences in policies for performing renal biopsies as well as for early referrals. For example, in some countries, urine screening tests are conducted in schools or for military service or ahead of employment, explaining the apparent high incidence.[Imai 2007; Wyatt 1998] Ethnic differences can also contribute to the varying prevalence of IgAN. Genome-wide association studies have identified candidate genes as well as risk-associated and protective alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa.[Kiryluk 2014] These genes are involved in antigen presentation, mucosal defense system and notably the alternative complement pathway (complement factor H [CFH]/CFHR locus).[Kiryluk 2014] Finally, patients may present at any age with IgAN but there is a peak incidence in the second and third decades of life. Most cases of IgAN occur in sporadic (90 to 95%) rather than in familial patterns (5 to 10%).[Lai 2016]

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. The first indication for making a diagnosis comes after careful microscopic examination of a urine sample. The presence of red blood cell (RBC) casts and dysmorphic RBCs indicates glomerular bleeding. Varying degrees of proteinuria are present in patients with

IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio (UPCR) measurement. Hence, IgAN can only be diagnosed definitely upon renal biopsy and study of kidney tissue using immunofluorescence. The pathology of IgAN is characterized by deposition of pathogenic polymeric IgA1 immune complexes and C3 in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. A consensus on the pathologic classification of IgAN has been developed by the International IgA Nephropathy Network in collaboration with the Renal Pathology Society (Oxford classification).[Cattran 2009; Lai 2016; Roberts 2009]

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis which is often associated with severe hypertension, but between these extremes, most patients with IgAN pursue a chronic indolent course.[Lai 2016] Some patients present with more severe proteinuria, hypertension and renal progression over time, typically reaching end-stage renal disease (ESRD) over a span of 20 years. Thus, the severity of proteinuria upon presentation has significant prognostic implications. More importantly, the change in proteinuria over time is being regarded as the current best prognostic indicator: those who had heavy time averaged proteinuria and achieved a partial remission of <1 g/24-hours had a similar course to those who had <1 g/24-hours throughout and fared far better than those who never achieved partial remission.[Reich 2007] These observations support the notion that every effort should be made to reduce proteinuria in IgAN. In addition to the degree of proteinuria, baseline renal function and the degree of histological injury are of prognostic value. For example, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90 to 120 mL/min/1.73 m^2). The rate of glomerular filtration rate (GFR) decline also correlates with glomerulosclerosis and tubular atrophy or interstitial fibrosis on biopsy as outlined by Oxford-MEST-C classification. Spontaneous full recovery in IgAN is rare in adults, especially if associated with significant proteinuria (>0.5 g/24-hour).[Knoop 2017]

Patients with minor urine abnormalities, normal blood pressure, and normal GFR usually do well and require only monitoring. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. Thus, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease that can result in end-stage renal failure. The optimal role of immunosuppressive therapy is uncertain. The available studies are not conclusive since most are relatively small and have limited follow-up.[Lai 2016] STOP-IgAN, a German trial, randomly assigned adults with an eGFR of >30 mL/min/1.73 m^2 and persistent proteinuria of >0.75 g/24-hour despite 6 months of supportive care with RAS inhibitors to receive supportive care alone or supportive care plus immunosuppression (prednisone alone for those with initial GFR >60 mL/min and prednisone combined with cyclophosphamide then azathioprine with initial GFR 30-59 mL/min). This strategy did not significantly improve the renal outcome and was associated with increased adverse effects at 36 months.[Rauen 2015] The TESTING trial demonstrated some GFR effect of steroids in Chinese patients, but had to be stopped due to large number of serious adverse events (SAEs) in the steroid arm.[Lv 2017] The 2012 KDIGO guidelines recommend corticosteroids, albeit at very low level of evidence. Thus, steroids may be tried in some cases as

rescue therapy if proteinuria markedly increases or GFR rapidly falls. Further studies to address the role of steroids in IgAN are currently under way. Finally, Rituximab seems to be ineffective in the treatment of patients with progressive IgAN.[Lafayette 2016]

1.2. Cemdisiran

Alnylam Pharmaceuticals, Inc. is developing cemdisiran (ALN-CC5), a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of atypical hemolytic uremic syndrome (aHUS) and IgAN. Cemdisiran comprises a small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand.

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19-25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA.[Elbashir 2001] Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [Soutschek 2004], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo in animal models (including in rodents and nonhuman primates [NHP]) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations.[Soutschek 2004; Zimmermann 2006] Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a GalNAc carbohydrate ligand.[Ashwell 2006] Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

Cemdisiran (containing siRNA drug substance, ALN-62643, targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via subcutaneous (SC) injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the cemdisiran siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of MAC formation and C5a release. This in turn would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN resulting in renal function improvement.[Maillard 2015] Both lectin and alternative pathways of complement have been implicated in IgAN pathology. Cemdisiran-mediated silencing of C5 will inhibit MAC formation and C5a release regardless of the activating pathway and may be a superior approach in IgAN where the contribution of different pathways may be heterogenous between patients.[Medjeral-Thomas 2018]

The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities, other than an increased susceptibility to Neisserial infections, in subjects with known genetic C5 deficiencies.[Ross 1984] Subjects

with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. These infections include invasive meningococcal disease, disseminated gonococcal infections as well as diseases caused by typically commensal Neisseria species.[Crew 2018; Crew 2018; McQuillen 2018; Ram 2010] In addition, safety data on the treatment of healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH) with cemdisiran in Study ALN-CC5-001 indicate that cemdisiran is generally well-tolerated; the maximum tolerated dose was 900 mg. There were no serious adverse events (SAEs) or discontinuations due to adverse events (AEs) during this study, and most AEs were mild or moderate in severity. In Study ALN-CC5-001, the frequency of ADA was low. Two of 48 healthy volunteers (1 cemdisiran-treated and 1 placebo-treated) were ADA positive during the study. The cemdisiran-treated volunteer had transient ADA positivity, with a negative result later in the study and no impact on PK or PD. The placebo-treated volunteer was ADA positive at baseline (predose) and remained positive through Day 70.

A detailed description of the chemistry, pharmacology, nonclinical pharmacokinetics (PK) and toxicology, as well as preliminary efficacy, and safety of cemdisiran is provided in the current edition of the Investigator's Brochure (IB).

1.3. Study Design Rationale

In contrast to the RBC lysis which characterises the pathophysiology of PNH, which requires extremely high level of C5 inhibition for protection, endothelial cells and mesangial cells are the cellular targets of dysregulated complement in aHUS and IgAN, respectively. These cells are nucleated cells which possess complement regulatory proteins as well as the ability to shed membrane associated MAC to defend against MAC-mediated damage, a key step in thrombotic microangiopathy progression in aHUS and renal damage in IgAN. It is therefore hypothesized that a lesser degree of cemdisiran mediated C5 knockdown will be required for disease control in patients with IgAN and aHUS than in patients with PNH.[Morgan 1989; Rosse 1973] This hypothesis is supported by the observation that aHUS patients who achieve C5 inhibition maintain good disease control despite complement activity levels consistent with higher free C5 levels.[Cugno 2014] Therefore, cemdisiran monotherapy may be a viable treatment option in patients with IgAN at levels of C5 silencing achieved in Study ALN-CC5-001.

This therapeutic hypothesis will be tested in a multicenter, multinational, double-blind, placebo-controlled study to evaluate the effect of multiple doses of cemdisiran given by SC injection in patients with IgAN with persistent proteinuria (≥1 g/24-hours) despite the standard of care (angiotensin converting enzyme inhibitors [ACE] or angiotensin II receptor blockers [ARB]) and additional medications if necessary for blood pressure control followed by a treatment extension to evaluate long-term safety and clinical activity. The study population has been selected based on two major factors: 1) the severity of proteinuria upon presentation has significant prognostic implications.[Coppo 2005] IgAN patients with heavy proteinuria ≥1 g/24-hours have a significantly worse renal outcome than those who have proteinuria <1 g/24-hours.[Reich 2007] 2) For patients with persistent proteinuria, despite the nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, no disease-specific therapies are currently available, and an unmet need persists for novel interventions. Since proteinuria can result both from active inflammation as well as irreversible scarring of renal tissue and in lieu of a protocol biopsy, we enrich our patients for presence of potentially

reversible disease activity by requiring presence of hematuria and relatively preserved renal function with eGFR >30 mL/min. To ensure the selection of patients who are truly at risk of progression of kidney disease despite standard of care, the first period of the study consists of a run-in period during which patients will not receive study drug (cemdisiran or placebo). The run-in period will be an observational period during which patients' treatment with standard of care, blood pressure, kidney function, degree of hematuria, and proteinuria will be documented. The standard of care is expected to remain unchanged during this run-in period. Only patients whose

- proteinuria level remains ≥1 g/24-hours within 2 weeks before the end of the run-in period,
- continue to meet blood pressure and eGFR criteria

will be eligible to enroll in the 36-week treatment period portion of the study.

Randomization to cemdisiran or placebo will be performed in a 2:1 ratio so that more patients will receive cemdisiran. This will allow a more precise estimation of the effect of cemdisiran with only marginal loss of power. Inclusion of a placebo arm will allow better assessment of safety and interpretation of the efficacy of cemdisiran.

The primary endpoint for the study is percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32. This is justified for a phase 2 study given the slow progression of renal disease and the established role of proteinuria as a marker of disease progression.

1.4. Dose Rationale

In the Phase 1/2 Study (ALN-CC5-001), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). Treatment with cemdisiran was generally well tolerated in both healthy volunteers and patients with PNH. There were no SAEs and no discontinuations due to AEs during this study, including at the highest doses administered. Most AEs observed were mild or moderate in severity.

Dose selection for the current study is based on the expected level of C5 and complement activity inhibition necessary for efficacy in patients with IgAN and the extent to which different doses of cemdisiran can inhibit production of C5. C5 silencing is a novel approach for the treatment of IgAN and little clinical precedent exists for inhibiting the terminal complement pathway in this disease. Since complement regulation is not impaired in IgAN like it is in PNH, and the kidney glomerular cells are nucleated cells, it is expected that the level of silencing needed for efficacy in IgAN is lower than that needed for PNH (see IB Section 2.4). For this proof-of-concept study, a dose was selected that is expected to produce rapid and robust C5 suppression and complement activity inhibition across the patient population, allowing an unambiguous evaluation of whether C5 silencing results in proteinuria improvement in IgAN. In Study ALN-CC5-001, a single dose of 600 mg cemdisiran achieved a C5 level of 12.3±1.47 µg/mL by Day 14 and 2.3±0.76 µg/mL by Day 56, corresponding to 60.9% reduction in complement alternative pathway (CAP) activity and a 69.3% reduction in complement

classical pathway (CCP) activity by Day 14 and 90.2% and 91.4% reduction in CAP and CCP activities, respectively, by Day 56. Single and multiple biweekly doses of 600 mg were well-tolerated with an acceptable safety profile in healthy volunteers in Study ALN-CC5-001A. In this initial study, the cemdisiran dose of 600 mg that was safe and well-tolerated was chosen for evaluation. This dose will yield robust C5 silencing and will have maximal opportunity to produce a meaningful clinical effect in patients with IgAN. Since the relationship between C5 levels and complement activity is non-linear, with small C5 fluctuations resulting in a larger increase in complement activity, a monthly dose regimen was selected to maintain a constant level of C5 silencing. Additionally, a more consistent effect of cemdisiran on C5 protein and CCP level is predicted after monthly dosing when compared to quarterly dosing based on a modeling approach.

During the extension treatment phase, patients treated with both cemdisiran and placebo will have the option to receive a 600 mg dose of cemdisiran every four weeks for an additional 52 weeks.

IgAN can result in progressive renal impairment; however, patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2) who may have sustained irreversible damage to the kidney are not eligible for participation in this trial. As the kidney is not the major elimination pathway for cemdisiran and based on available nonclinical and clinical data obtained with cemdisiran (with 10.6 to 31.6% of the cemdisiran dose recovered in a 24-hour urine collection in the ALN-CC5-001 study), it is expected that moderate renal impairment (eGFR<60 mL/min/1.73 m^2) will not affect the PK of cemdisiran to the extent that a dose adjustment would be required. Therefore, patients with moderate renal impairment are eligible for study enrollment. More information on urine PK can be found in the IB.

1.5. Benefit-Risk Assessment

To date, no medications have been approved specifically for the treatment of IgAN. Therefore, there is a large unmet need for novel interventions, particularly in patients who are at risk of progressive renal disease such as those with persistent proteinuria despite treatment with RAS inhibitors. Available data from studies on the role of immunosuppressive therapy in IgAN are not conclusive as most are relatively small and have limited follow-up.[Lai 2016] Use of immunosuppressive drugs and high-dose steroids are also associated with increased AEs which is particularly common in patients with lower GFR.[Sarcina 2016]

Given the biological target of cemdisiran, the available nonclinical and clinical data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities and injection site reactions (ISRs). C5 inhibition is associated with increased susceptibility for Neisserial infections (including disseminated gonococcal infections) and the potential risk of other infections, particularly those due to encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), as well as *Aspergillus* in immunocompromised and neutropenic patients. Therefore, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine are required. Patients will be instructed to contact study site if any early signs of meningococcal infections are experienced. In addition, patients with functional or anatomic asplenia will be excluded and only patients previously vaccinated or who agree to receive vaccination for Hib and *Streptococcus pneumoniae* according to current national/local

vaccination guidelines, at Screening, will be enrolled. Investigators in Study ALN-CC5-005 should educate patients on the risk of disseminated gonococcal infection and encourage safe sex practices. All national/local screening recommendations for gonorrhea in the general population should also be followed. Finally, given the reported evidence of a higher risk of disseminated gonococcal infections with treatment with eculizumab, Investigators are encouraged to evaluate any patient who has a *Neisseria gonorrhoeae* infection for the signs and symptoms of disseminated infection.[Crew 2018; McQuillen 2018] No cases of Neisserial infection or other infections due to encapsulated bacteria were observed in healthy volunteers or in patients with PNH (Study ALN-CC5-001).

As cemdisiran is targeted for delivery to the liver, patients will be closely monitored for changes in LFTs and patients with a medical history or evidence of chronic liver disease or cirrhosis have been excluded. Criteria for dose withholding, and stopping of cemdisiran are provided in Section 5.2.3.1. Patients will also be monitored for the development of ISRs and rotation of injection site are recommended during the study.

Considering anti-glycan autoantibodies recognizing Gd-IgA1 are implicated in the pathogenesis of IgA nephropathy, exposure to the GalNAc moiety of cemdisiran may pose a theoretical risk of stimulating the production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy. This could presumably occur when antidrug antibodies (ADAs) to cemdisiran's triantennary GalNAc (Tri-GalNAc) cross-react with Gd-IgA1. The risk of developing these cross-reactive antibodies is likely low. This is based on the low incidence of ADA to cemdisiran in study ALN-CC5-001 (see Section 1.2) and the distinct difference in structure of the O-GalNAc moieties on a Gd-IgA1 glycoprotein and the Tri-GalNAc moiety in cemdisran. This low risk is further mitigated by excluding patients with confirmed pre-existing IgG/IgM/IgA ADAs to total drug and real time monitoring for development of de novo IgG/IgM/IgA ADAs after dosing with cemdisiran. Patients with confirmed de novo ADAs will be discontinued from study drug but will continue to be monitored until EOS visit and subsequent safety follow up. Patients who develop positive ADA will be followed until ADA titers return to baseline. Additional ADA samples will also be collected if any clinical evidence of progression of IgAN disease and/or relevant safety findings.

Detailed information about the known and expected benefits and risks of cemdisiran and additional information on the clinical and nonclinical data may be found in the current version of the IB.

Cumulatively, clinical data regarding the role of complement pathways in IgAN progression, robust nonclinical and clinical data with cemdisiran (see IB for more information), and prior and ongoing clinical experience with other RNAi therapeutics in humans suggest cemdisiran will have a favorable risk profile in the intended population and supports the initial clinical development of cemdisiran in IgAN. In addition, cemdisiran may address the unmet medical need for the first efficacious and disease-specific treatment for patients with IgAN.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 32 weeks using all assessments during the period • The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32

	• Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal half-life (t½), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, C_{max}, T_{max}, t½, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. Patients will not receive study drug (cemdisiran or placebo) during this time. The standard of care is expected to remain unchanged during this run-in period. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of SC cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains ≥1 g/24-hours within 2 weeks of the end of the run-in period, and who meet blood pressure and eGFR criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study center at Week 40 and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by an independent data monitoring committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

3.2. Duration of Treatment

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive 600 mg SC doses of cemdisiran for 52 weeks in the optional OLE.

3.3. Duration of Study

The maximum estimated total time on study, inclusive of Screening (maximum of 90 days), run-in period (14 weeks), treatment period (36 weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is approximately 36 months or 3.0 years.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the EOS visit (Week 36 for those patients who do not consent to continue to participate in the study in the OLE period and Week 84 for patients who enter the OLE period). Upon study completion (regardless if EOS visit is at Week 36 or Week 84) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.

For patients withdrawing from the study after receiving one dose of cemdisiran at a minimum (ET), all efforts should be made to conduct the EOS/ET assessments. Patients should then be encouraged to enter the safety follow up period.

3.4. Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the cemdisiran or placebo arms. Randomization will be stratified by baseline urine proteinuria levels (≥1 g/24h and <2 g/24h versus ≥2 g/24h).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at Screening and prior to randomization.

3.6. Blinding

All site personnel including sponsor delegated clinical research associates, data management CRO and patients will be blinded to study drug treatment during the efficacy period (up to Week 36). Sponsor personnel will not be blinded to study treatment. Cemdisiran and placebo will be packaged identically. The study drug will be administered under the supervision of the Investigator or at the patient's home by a healthcare professional (see Section 5.2.2). Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by a site pharmacist prior to administration by a healthcare professional. See the Pharmacy Manual for additional details. Further details on blinding and unblinding arrangements will be documented in a separate plan /manual.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the Trial Master File (TMF).

Further details on blinding and unblinding arrangements will be documented in a separate plan / manual.

3.7. Data Monitoring Committee

An independent DMC will perform regular reviews of safety, tolerability, and immunogenicity data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a Charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of unblinded data (safety, tolerability, PK, pharmacodynamics (PD), ADA, circulating immune complexes (CIC) and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Male or female ≥18 years and ≤65 years of age at the time of informed consent

Patient and Disease Characteristics

2. Clinical diagnosis of primary IgAN as demonstrated by historical biopsy collected within 60 months of Screening
3. Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB for at least 3 months prior to start of run-in period
4. Urine protein ≥1 g/24-hour at Screening and mean urine protein ≥1 g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization
5. Hematuria as defined by ≥10 RBCs per high powered field (RBC/hpf) at Screening
6. Females of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception 14 days before first dose, throughout study participation, and for 90 days after last dose administration
7. Previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or willingness to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care
8. Previously vaccinated or willingness to receive vaccinations for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines for vaccination use

Informed Consent

9. Patient is willing and able to provide written informed consent and to comply with the study requirements

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Concomitant significant renal disease other than IgAN
2. A diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase
3. Secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease)
4. Diagnosis of Henoch-Schonlein Purpura (IgA Vasculitis)

5. eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization (local results will be used for assessment of eligibility)

Laboratory Assessments

6. Has any of the following laboratory parameter assessments:
    a. Alanine transaminase (ALT) >1.5×upper limit of normal (ULN), International Normalized Ratio (INR) >2 (or >3.5 if on anticoagulants), or total bilirubin >1.5×ULN (unless bilirubin elevation is due to Gilbert's syndrome)
7. Confirmed positive IgG/IgM/IgA ADAs to cemdisiran at Screening
8. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
9. Known human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection or hepatitis B virus (HBV) infection

Prior/Concomitant Therapy

10. Treatment with systemic steroids for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization
11. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment

Medical Conditions

12. Malignancy (except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate cancer) within the last 5 years
13. Active psychiatric disorder, including, but not limited to schizophrenia, bipolar disorder, or severe depression despite current pharmacological intervention
14. Known medical history or evidence of chronic liver disease or cirrhosis
15. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
16. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc
17. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
18. Known contraindication to meningococcal vaccines (group ACWY conjugate and group B vaccines) required for this study. Refer to the most recent local product information for each vaccine for the current list of contraindications
19. Unable to take antibiotics for meningococcal prophylaxis, if required by local standard of care
20. Sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period, measured in supine position after 10 minutes of rest

21. Receipt of an organ transplant (including hematologic transplant)
22. History of meningococcal infection within 12 months before Screening
23. Patients with systemic bacterial or fungal infections that require systemic treatment with antibiotics or antifungals
24. Patients with functional or anatomic asplenia

Alcohol Use

25. Patients who consume more than 14 units of alcohol a week (unit 1 glass of wine [125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-adverse event), including confirmed positive test for ADA to cemdisiran
- Or, study is terminated by the Sponsor

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.7.5.2 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the Week 36/EOS or Week 84/OLE EOS visit and safety follow-up so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 2), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and adverse events, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.7.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) will be encouraged to remain on the study and complete assessments through Week 36; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 1).

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete the OLE EOS/ET assessments; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 2).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient/legal guardian considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Week 36 visit, including entering the 52-week safety follow-up. If a patient/legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 36-week treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the Week 36 EOS/ET visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an adverse event (AE), including serious adverse events (SAEs), the event should be followed as described in Section 6.7.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study during the 36-week treatment period or the OLE will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of cemdisiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to cemdisiran.

5.2.2. Dose and Administration

Patients will be administered cemdisiran (600 mg) or placebo (at the same volume as the active drug) as an SC injection once every 4 weeks in combination with standard of care in the 32-week treatment phase. During the 52-week OLE phase, patients will be administered cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. At-home dosing may be administered by a healthcare professional. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy Manual.

To maintain the blind during the treatment period, the syringes are to be masked prior to study drug withdrawal. A full description of the blinding procedure is included in the Pharmacy Manual.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing

1. LFT results (Table 5) from the previous visit should be reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 4.
3. For any ALT or AST elevation >3×ULN:
   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. Perform assessments per Table 4 and Table 6.
   c. If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 4

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least every two weeks: LFT and coagulation per Table 5
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold cemdisiran dosing until recovery to ≤1.5×ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least weekly: LFT and coagulation per Table 5 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of cemdisiran doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

Cemdisiran (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of a 0.5-mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

The standard of care treatment should be held stable throughout the run-in and treatment periods. Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 and Table 2). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

For other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug/placebo, for 7 days after the last dose of either study drug or placebo.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements (if started prior to Screening, then may continue during the study at the same dose)
- Hydroxychloroquine

5.3.2. Study-specific Vaccinations

5.3.2.1. Meningococcal Vaccinations

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, upon determination of eligibility at the end of run-in period, 2 weeks prior to randomization to cemdisiran or placebo, as per the Schedule of Assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions and according to the Advisory Committee on Immunization Practices (ACIP) or other locally applicable recommendations for patients with complement deficiencies. On days of vaccination, urinary samples should be collected prior to administration of vaccines.

Patients will be immunized against *Neisseria meningitidis* according to the following specifications:

- Patients who have previously completed the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) at least 14 days but no more than 3 years from randomization can start study assessments after confirming eligibility. Documented vaccine history must be available to, and verified by, study site staff at the time of Screening.
- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines if found eligible at the end of the run-in period.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the Schedule of Assessments if determined to be eligible for the study at the end of the run-in period.
- If required locally, patients will receive prophylactic antibiotics according to the local standard of care after randomization to cemdisiran or placebo.

5.3.2.2. Pneumococcal and Hib Vaccinations

Patients will receive vaccinations for Hib and *Streptococcus pneumoniae*, if not previously vaccinated, according to current national/local vaccination guidelines for vaccination use. Hib and pneumococcal vaccinations (if required at Screening per national/local guidelines;

vaccination should occur prior to Week-2. At Screening, patient vaccination records will be checked for compliance with local recommendations for the use of these vaccines.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration or until study completion.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries e.g. France, in order to comply with local requirements as described in the corresponding patient consent forms

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.7.5.2).

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. Antibiotic Compliance

Patients who require prophylactic antibiotics after randomization to cemdisiran or placebo (see Section 5.3.2.1) per local standard of care will undergo antibiotic compliance checks. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments. Antibiotic dose adjustments will be permitted in the case of renal impairment. All dose adjustments must comply with the manufacturer's instructions.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 and Table 2.

6.1. Screening Assessments

An ICF approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor; see Section 6.1.1.

Patient demographic data and medical history/disease history will be obtained. In particular, the MEST-C score and degree of IgG, IgA, IgM, C3, C1q, C4d and C5b-9 stains will be obtained from pathology reports, if available, and documented. Any changes to medical history occurring between the Screening assessment and Day 1 will be updated prior to study drug administration. Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, urinalysis and ADA and CIC assessments. Vaccination records will also be checked for compliance with national/local guidelines for pneumococcal and Hib vaccinations.

6.1.1. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). A patient will be re-consented if rescreening occurs outside of the 90-day screening window. In this case, all screening procedures must be repeated.

6.1.2. Retesting

If in the Investigator's judgement, the laboratory abnormalities at Screening or in the run-in period are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale is to be documented. Laboratory values can be retested once during Screening or the run-in period as long as the patient can be evaluated for eligibility and randomized within the allowed Screening or run-in period. Two retests will be permitted for hematuria during Screening, if the first test is negative.

6.2. Run-in Period

During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): Hib and pneumococcal vaccinations (if required at Screening per national/local guidelines; vaccination should occur prior to Week-2), vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine for proteinuria, and eGFR. Clinical laboratory tests will be performed centrally; however, eGFR will also be

assessed locally at the end of the run-in period (Week-2) to facilitate assessment of patient eligibility and administer meningococcal vaccination on the same day. Meningococcal vaccines should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

Sites are encouraged to discuss study information with the patients again at the end of the run-in period.

6.3. Baseline Assessments (Treatment Period)

Prior to dosing on Day 1, patients will be reassessed for eligibility and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK, ADA and CIC.

In addition, prior to administration of study drug, the following assessments will be performed: full physical examination, body weight and height, vital signs, ECG, urine pregnancy test, eGFR assessment, and urinalysis.

Collection of blood and urine samples for PK analysis on Day 1 will be performed as outlined in Table 3.

6.4. Efficacy Assessments

6.4.1. Proteinuria

Primary efficacy will be assessed by determining the percent change from baseline in 24 hour proteinuria (g/24-hour) after 32 weeks of treatment. 24 hour urine samples for determination of proteinuria will be collected throughout the study as outlined in the Schedules of Assessments and will be analyzed by a central laboratory.

6.4.1.1. 24-Hour Urine Collection

Patients will be required to provide two separate valid 24-hour urine collections 2 weeks prior to randomization (to assess eligibility after the run-in period) and at Week 32 (to assess the primary endpoint). Patients will also be asked to provide a single valid 24-hour urine sample for other 24-hour urinary assessments outlined in the Schedule of Assessments. Rigorous exercise and significant change in diet (in particular salt intake) should be avoided within 48 hours before collection of 24-hour urine samples, whenever possible. The two valid 24-hour urine samples may be collected within 2 weeks before assessment is due while the one valid 24-hour urine sample may be collected within one week before the assessment takes place. If any of the collections do not meet validity criteria outlined below, then repeat collections must be scheduled within the time frames outlined above to assure the minimum number of valid collections required for each of the study time points. The duration of collection and volume of urine in the collection will be recorded in the eCRF. In addition to protein, albumin, sodium and creatinine will also be quantified in each of the 24-hour urine samples. Both protein/creatinine (UPCR) as well as albumin/creatinine ratios (UACR) will also be calculated in an aliquot of the 24-hour urine collection.

Completeness of the 24-hour urine collection can be estimated from rate of creatinine excretion. Normal values of creatinine excretion vary with age and body weight. An aliquot of the 24-hour

urine collection will be used to determine urinary creatinine content to determine if the 24-hour urine collections need to be repeated. Hence, a 24-hour urine collection will only be considered valid if all the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.
- The 24-hour creatinine content is within 25% of expected range as estimated by the following formula: [(140-age) x weight]/5000, where weight is in kilograms. This result is multiplied by 0.85 in women.[Ix 2011]
- In case of need of two valid samples, the maximum variation in total 24-hour urine creatinine between the two urine collections must be <25%.

Primary efficacy will be evaluated by comparing the percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 in patients treated with cemdisiran versus those treated with placebo.

Secondary and exploratory efficacy assessments include comparisons of the proportion of patients with partial or complete clinical remission, respectively, as measured by the amount of urine protein (UP) in a 24-hour urine sample. Partial clinical remission is defined as having UP <1 g/24-hours and complete clinical remission is defined as UP <0.3 g/24-hours. Each will be assessed at Week 32.

Additionally, using 24-hour samples, the change from baseline in the UP/creatinine ratio (UPCR) will be evaluated as a secondary endpoint and the change from baseline in urine albumin/creatinine ratio (UACR) at Week 32 as an exploratory endpoint.

6.4.1.2. Spot Urine Collection

Urinary protein, albumin and creatinine levels from spot urine collections prior to dosing will also be measured to assess the effect of cemdisiran on urinary protein/creatinine (UPCR) and albumin/creatinine (UACR) as outlined in the Schedule of Assessments.

The change from baseline in UPCR at Week 32 will be evaluated in spot urine samples. Spot urine samples will be collected at the time points outlined in the Schedule of Assessments (Table 1).

6.4.2. Hematuria

Hematuria from spot urine collections will also be evaluated to assess the effect of cemdisiran on disease course in patients with IgAN. The degree of hematuria will be assessed by examination of the spun urine sediment by microscopy (RBC/hpf). Single void collections for random urine sample for hematuria evaluation should be collected. If the investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated.

Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the Schedule of Assessments and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to study drug administration, if applicable.

6.4.3. Changes in Renal Function

Changes in renal function will be monitored using measurements of serum creatinine and eGFR (mL/min/1.73m^2) as outlined in the Schedule of Assessments. The calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for all patients. For assessment of eligibility at the last visit of run-in period, 2 weeks prior to randomization, local lab can be utilized. This will allow evaluation for eligibility on the same day. A sample will also be sent to central lab.

Renal function will also be estimated as creatinine clearance based on the 24-hour urine collection. The creatinine clearance is a widely used test to estimate the GFR using the following formula:

GFR = [UCr x V] / SCr

SCr is the serum creatinine concentration and the value assessed closest to collection of 24-hour urine collection will be utilized for purpose of above calculation. UCr is the urine creatinine concentration and V is the urine flow rate or volume.

Blood and urine samples for renal function assessments will be collected prior to administration of cemdisiran or placebo on dosing days, if applicable.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed for the first 32 weeks and the entire study period (including the OLE).

6.4.4. Markers of Complement Activation, Inflammation and Renal Injury

Samples for measurement of markers of complement activation, inflammation and renal injury will be collected at the time points outlined in the Schedule of Assessments (Table 1) and analyzed by central laboratories. On dosing days, blood samples will be collected predose.

6.5. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at the time points outlined in the Schedule of Assessments (Table 1). Samples will be collected prior to administration of cemdisiran or placebo on dosing days.

Analysis of PD will include the impact of cemdisiran administration on plasma C5 protein levels (assessed by a mass spectrometry-based method) and serum complement activity (assessed by CAP enzyme linked immunosorbent assay [ELISA] and CCP ELISA). Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

6.6. Pharmacokinetic Assessments

Blood samples and urine samples will be collected for assessment of cemdisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples and urine samples for PK analysis is in Table 3.

The concentration of cemdisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests, including assessment of IgG/IgM/IgA ADA and CIC. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.7.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected at predose and 4 hours (±15 minutes) postdose. On all other dosing days, vital signs will be collected predose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral or tympanic method. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.7.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1 and Table 2; height at Screening only and dosing weight during the clinical study center visits) and will be recorded in the eCRF.

6.7.3. Physical Examination

Routine physical examinations will be conducted according to the Schedule of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

At Screening and Day 1 predose, a full physical examination will be performed. At all other time points, including Day 1 at 4 hours (±30 minutes) postdose, a directed physical examination will be performed.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Directed physical examinations will include examination of the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.7.4. Electrocardiogram

Twelve-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. A single 12-lead ECG will be performed at Screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings approximately 1 minute apart. 12-lead ECGs will be performed at predose; 60 minutes postdose; and 4 hours postdose in relation to the Day 1 and Week 32 cemdisiran or placebo doses.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.7.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, eGFR will also be assessed locally. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and include: hematology, serum chemistry and urinalysis parameters. Parameters will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. On dosing days blood samples will be collected predose.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the CKD-EPI formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.7.5.1)	
Antidrug antibodies	
Hepatic Tests (Screening Only)	
Hepatitis C, including: HCV RNA PCR – qualitative and quantitative assays	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Pregnancy Testing (Females of Child-bearing Potential Only) (see Section 6.7.5.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular

filtration rate; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG= IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid.

6.7.5.1. Immunogenicity

Blood samples will be collected to evaluate ADA and CIC. IgG/IgM/IgA ADA to total drug will be assessed at Screening and during the study. ADA samples will be tested in real time. Clinical study decision will be based on confirmed positive ADA results from the IgG/IgM/IgA assay. Confirmed positive ADA samples will be further characterized for cemdisiran domain specificity against the Tri-GalNAc component if a reliable method is established. Blood samples for ADA and CIC testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1 and Table 2). Blood samples to evaluate ADAs will be collected at Screening to assess study eligibility and at the Early Termination (ET) visit, if applicable. ADA and CIC will be routinely monitored during the treatment period and throughout the open-label extension phase and safety follow up, as indicated in the Schedule of Assessments. Finally, ADA and CIC samples will also be collected and analyses will be performed and prioritized if any clinical evidence of progression of IgAN disease and/or relevant safety findings. Patients who are confirmed positive for IgG/IgM/IgA ADA at baseline will be excluded from study treatment. In addition, patients who develop de novo ADAs will be discontinued from study drug but will be followed until EOS visit and during safety follow up. These patients will also be monitored until ADA levels return to baseline.

Exploratory analysis of anti-Gd-IgA1 antibody levels will be conducted; serum samples for these analyses will be drawn when CIC samples are collected.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.7.6.7 for follow-up instructions).

6.7.5.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any liver function test (LFT) abnormalities. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 5, and other assessments or evaluations per Investigator discretion, as appropriate.

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
Herpes Zoster Virus IgM, IgG	
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

6.7.6. Adverse Events

6.7.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

Based on the biological target and the available nonclinical and clinical data, AEs of Clinical Interest (AECI) for this study are:

- Severe infections as judged by the investigator
- ALT or AST >3×ULN
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of cemdisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR.

For information on recording and reporting of AECIs, see Section 6.7.6.2 and Section 6.7.6.3 , respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.7.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording all SAEs and only AEs related to study procedures that are observed or reported by the patient during the run-in period (before the administration of the first dose of study drug) regardless of their relationship to study drug through the end of study. All AEs, including non-serious AEs, occurring after signing of the ICF and before study

drug administration will be captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.7.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AECIs (Section 6.7.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.7.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Investigator Site File.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.7.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.7.6.4.

6.7.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with IgAN, as well as their responses to treatment.

To permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of cemdisiran, a set of biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2).

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, the samples will be collected as part of this study. Examples of potential exploratory investigations would include DNA, RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study. This is based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of 27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, approximately 30 patients are planned to be randomized stratified by baseline urine protein levels (≥1 g/24h and <2 g/24h versus ≥2 g/24h).

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The primary population used to evaluate efficacy will be the mITT Population. Sensitivity analyses for efficacy will be performed using the Per Protocol Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the mITT and Safety Analysis Set.

Baseline value for proteinuria will be calculated as the average of two valid 24-hour urine protein levels before randomization.

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The 24-hour urine protein will be log transformed for analyses. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval will be estimated and then back transformed to original scale.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

7.2.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in 24-hour urine at Week 32, change from baseline in urine protein/creatinine ratio (UPCR) as measured in a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in urine protein / creatinine ratio (UPCR) will be analyzed similarly to the analysis of the primary variable as appropriate. UPCR will be log transformed first before analysis.

7.2.5.3. Exploratory Endpoints

Change from baseline in exploratory efficacy variables will be summarized. Percent of patients in full clinical remission and incidence of ADA will be tabulated by treatments. Inferential

statistics for exploratory efficacy variables may be presented as needed. Details will be described in the SAP.

The slope of eGFR for the first 32 weeks will be estimated for each subject with the linear regression method using all assessment data during the period.

Descriptive statistics including the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum values will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

7.2.6. Pharmacodynamic Analysis

Assessment of the PD effect of the treatment will be performed descriptively, including plotting graphically levels of serum C5 protein and CAP/CCP over time and relative to baseline levels. Inferential statistics maybe generated as deemed necessary.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. Pharmacokinetic parameters include, but will not be limited to: AUC, C_{max}, T_{max}, t½, CL/F, V/F, cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe) in the urine of cemdisiran (25-mer) and 23-mer.

Other parameters may be calculated, if deemed necessary. Summary statistics and figures will be presented. Inferential statistics may be generated when deemed necessary.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized by dose level and overall.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary. All SAEs occurring before the first dose of study drug and AEs related to study procedures will be listed. The number and percentage of patients experiencing AEs after the first dose of the study drug or events that worsened in severity after dosing will be summarized. AEs will be presented by maximum severity and relationship to study medication. SAEs and AEs leading to discontinuation of treatment will also be tabulated.

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation.

Frequency of adverse events of clinical interest will also be summarized and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

All safety analyses will be conducted using the Safety Analysis Set.

7.2.9. Immunogenicity Analyses

Antidrug antibody, CIC and anti-Gd-IgA1 antibody results will be summarized descriptively.

7.2.10. Biomarker Analyses

Urine and serum complement activation products, inflammation and renal injury markers will be summarized descriptively.

7.2.11. Interim Analysis

No formal interim analysis is planned.

7.2.12. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.7.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the

decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee, immediately if contacted by a regulatory agency or an IRB/IEC about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 18 months after completion of the study at all centers. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at

least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Ashwell G,Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Advances in Enzymology and Related Areas of Molecular Biology, Volume 41. 2006:99-128.

Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney international. 2009;76(5):534-45.

Coppo R,D'amico G. Factors predicting progression of IgA nephropathies. Journal of nephrology. 2005;18(5):503-12.

Crew PE, Abara WE, McCulley L, Waldron PE, Kirkcaldy RD, Weston EJ, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. Clinical Infectious Diseases. 2018.

Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC,Bersoff-Matcha SJ. Unusual Neisseria species as a cause of infection in patients taking eculizumab. Journal of Infection. 2018.

Cugno M, Gualtierotti R, Possenti I, Testa S, Tel F, Griffini S, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. Journal of Thrombosis and Haemostasis. 2014;12(9):1440-8.

Elbashir SM, Lendeckel W,Tuschl T. RNA interference is mediated by 21-and 22-nucleotide RNAs. Genes & development. 2001;15(2):188-200.

Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clinical journal of the American Society of Nephrology. 2007;2(6):1360-6.

Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clinical journal of the American Society of Nephrology. 2011;6(1):184-91.

Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nature genetics. 2014;46(11):1187.

Knoop T, Vikse BE, Mwakimonga A, Leh S,Bjørneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology Dialysis Transplantation. 2017;32(11):1841-50.

Knoppova B, Reily C, Maillard N, Rizk DV, Moldoveanu Z, Mestecky J, et al. The origin and activities of IgA1-containing immune complexes in IgA nephropathy. Frontiers in immunology. 2016;7:117.

Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. Journal of the American Society of Nephrology. 2016:ASN. 2016060640.

Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nature Reviews Disease Primers. 2016;2:16001.

Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy. Jama. 2017;318(5):432.

Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current understanding of the role of complement in IgA nephropathy. Journal of the American Society of Nephrology. 2015;26(7):1503-12.

McQuillen DP,Ram S. No good deed goes unpunished: eculizumab and invasive neisserial infections. Clinical Infectious Diseases. 2018.

Medjeral-Thomas NR, Troldborg A, Constantinou N, Lomax-Browne HJ, Hansen AG, Willicombe M, et al. Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin–Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H–Related Protein-5 (FHR5) Deposition. Kidney international reports. 2018;3(2):426-38.

Mestecky J, Novak J, Moldoveanu Z,Raska M. IgA nephropathy enigma. Clinical Immunology. 2016;172:72-7.

Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochemical Journal. 1989;264(1):1.

Novak J, Barratt J, Julian BA,Renfrow MB, editors. Aberrant Glycosylation of the IgA1 Molecule in IgA Nephropathy. Seminars in nephrology; 2018: Elsevier.

Ram S, Lewis LA,Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clinical microbiology reviews. 2010;23(4):740-80.

Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. New England Journal of Medicine. 2015;373(23):2225-36.

Reich HN, Troyanov S, Scholey JW,Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. Journal of the American Society of Nephrology. 2007;18(12):3177-83.

Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney international. 2009;76(5):546-56.

Ross SC,Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine. 1984;63(5):243-73.

Rosse WF. Variations in the red cells in paroxysmal nocturnal haemoglobinuria. British journal of haematology. 1973;24(3):327-42.

Sarcina C, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, et al. Changes in proteinuria and side effects of corticosteroids alone or in combination with azathioprine at different stages of IgA nephropathy. Clinical journal of the American Society of Nephrology. 2016;11(6):973-81.

Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004;432(7014):173-8.

Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. The Journal of clinical investigation. 2009;119(6):1668-77.

Woo K-T, Chan C-M, Chin YM, Choong H-L, Tan H-K, Foo M, et al. Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades. Nephron Clinical practice. 2010;116(4):c337-c46.

Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. Journal of the American Society of Nephrology. 1998;9(5):853-8.

Zimmermann TS, Lee AC, Akinc A, Bramlage B, Bumcrot D, Fedoruk MN, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006;441(7089):111-4.

10. APPENDICES

None.

ALN-CC5-005 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 20 SEPTEMBER 2019

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to incorporate changes previously made to a regional protocol amendment (Amendment 1.1: Canada) into the global protocol. These changes ensure all relevant safety assessments (eg, safety laboratory, pregnancy tests) in the open-label extension (OLE) period mirror safety assessments made at initial treatment with study drug after randomization, because patients initially randomized to placebo will be treated with cemdisiran for the first time in the OLE period. The timing of this global protocol amendment ensures these changes are adopted prior to any patients crossing over to the OLE period. Additional changes include updates to specific eligibility criteria and certain safety assessment timeframes.

An overview of the changes made to the protocol include:

- Addition of timepoints for clinical laboratory and pregnancy tests such that patients are monitored every 4 weeks, from Week 36 until Week 64, in the OLE period
- Clarifying the blood sample collection for circulating immune complex (CIC) analysis and anti-Gd IgA1 antibody assessment at specified timepoints from Screening through Week 36
- Addition of a ±3 day window to Day 1 to make it easier to observe the mandatory 14-day minimum interval between completion of the meningococcal vaccinations series at Week-2 and randomization, and to allow study sites some flexibility around the scheduling of the Day 1 visit
- Removal of the optional blood sample B-cell function analysis during the Screening visit
- Removal of part of the inclusion criterion to screen for hematuria at the end of the run-in period, prior to randomization
- Removal of the dose-specific part of the exclusion criterion to screen for treatment with systemic steroids in the 12 months prior to randomization
- Clarifying the collection of vital signs on Day 1 at 4 hours (±15 minutes) postdose along with the addition of tympanic temperature measurement
- Clarifying routine physical examination on Day 1 at 4 hours (±30 minutes) postdose
- Correction to table number references for the monitoring of liver function test (LFT) and coagulation
- Removal of human immunodeficiency virus (HIV) testing from patients who experience elevated transaminases

- Clarifying that all adverse events, both serious and non-serious, are to be collected from the time of signing the ICF through the end of the study. Non-serious events not related to study procedures will be included in medical history

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between the protocol amendments 1 and 2) are not detailed.

Table 1: Protocol Amendment 2 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated the Schedule of Assessments (Table 2) to include safety laboratory tests every 4 weeks, from Week 36 until Week 64 in the OLE period

The primary change occurs in Table 2 (Schedule of Assessments – OLE period and safety follow-up)

Added text: "**X**" has been added against clinical laboratory assessments and pregnancy tests planned to be conducted during the OLE period every 4 weeks from Week 36 until Week 64. Previously, clinical laboratory assessments and pregnancy tests were included every 8 weeks after the first 4-week assessment starting at Week 36.

Purpose: Updated the Schedule of Assessments (Table 1) to clarify the blood sample collection for CIC analysis and serum sample collection for exploratory anti-Gd IgA1 antibody assessment at specified timepoints from Screening through Week 36

The primary change occurs in Table 1 - Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Added text: Blood Sample**s** for CIC ~~Analysis~~ and ~~Exploratory~~ **anti-**Gd IgA1 **Antibody** Assessment.

Sections also containing this change:

- Section 6.7.5.1 (Immunogenicity)
    - Exploratory analysis of **anti-**Gd-IgA1 **antibody** levels ~~and IgA-containing immune complexes may~~ **will** be conducted; ~~blood~~ **serum** samples for these analyses will be drawn when CIC samples are collected ~~to enable these assays~~.
- Section 7.2.9 (Immunogenicity Analyses)
    - Antidrug antibody**, CIC** and ~~CIC~~ **anti-Gd-IgA1 antibody** results will be summarized descriptively.

Purpose: Updated the Schedule of Assessments (Table 1) to include a ±3 day window to Day 1

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up)

Added text: "**±3**" has been added to Day 1 to make it easier to observe the mandatory 14-day minimum interval between completion of the meningococcal vaccinations series at Week-2 and randomization, and to allow study sites some flexibility around the scheduling of the Day 1 visit

Purpose: Updated the Schedule of Assessments (Table 1) to remove the optional blood sample B-cell function analysis during the Screening visit

The primary change occurs in Table 1 - Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Deleted text: ~~Optional Blood Sample for B-cell function Analysis~~
"**X**" was removed from the Screening visit.

Section also containing this change:

- Section 6.7.5.1 (Immunogenicity)
  - ~~For US patients only, an optional blood sample may be collected at screening to evaluate any potential for B-cell stimulation by cemdisiran, at the Sponsor's discretion~~.

Purpose: Updated inclusion criterion to remove screening for hematuria at the end of the run-in period

The primary changes occur in Section 4, Selection and Withdrawal of Patients

- Section 4.1 (Inclusion Criteria)
  - Criterion 5: Hematuria as defined by ≥10 RBCs per high powered field (RBC/hpf) at ~~s~~**S**creening ~~and either ≥10 RBC/hpf or a positive urinary dipstick (1+ and above) at the end of the run-in period, prior to randomization (local result accepted for assessment of eligibility at the end of the run-in period)~~

Sections also containing these changes

- Synopsis (Study Design)
    - Patients whose proteinuria level remains ~~>~~≥1 g/24-hours within 2 weeks of the end of the run-in period, ~~who continue to have hematuria,~~ and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 36-week treatment period.
- Synopsis (Diagnosis and Main Eligibility Criteria)
    - Eligible patients must have urine protein levels of ≥1g/24-hour at ~~s~~**S**creening and mean urine protein ≥ 1g/24 hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization. In addition, eligible patients must have hematuria defined by ≥ 10 red blood cells per high powered field (RBC/hpf) at ~~s~~**S**creening ~~and either ≥10 RBC/hpf or a positive urinary dipstick (1+ and above) at the end of the run-in period.~~
- Section 1.3 (Study Design Rationale)

  The standard of care is expected to remain unchanged during this run-in period. Only patients whose
    - proteinuria level remains ~~above~~ ≥1 g/24-hours within 2 weeks before the end of the run-in period,
    - continue to ~~have hematuria, and~~ meet blood pressure and eGFR criteria
- Section 3.1 (Summary of Study Design)
    - Patients whose proteinuria level remains ~~>~~≥1 g/24-hours within 2 weeks of the end of the run-in period, ~~who continue to have hematuria,~~ and who meet blood pressure and eGFR criteria will be eligible to enroll in the 36-week treatment period.
- Section 6.2 (Run-in Period)
    - Clinical laboratory tests will be performed centrally; however, ~~hematuria and~~ eGFR will also be assessed locally at the end of the run-in period (Week-2) to facilitate assessment of patient eligibility and administer meningococcal vaccination on the same day.
- Section 6.4.2 (Hematuria)
    - ~~To allow evaluation of eligibility on the same day at the end of the run in period, 2 weeks prior to randomization, the single void can be split in two containers, one evaluated by local lab and another by central lab. The local hematuria evaluation by microscopy or urinary dipstick will be utilized to determine eligibility for the study at the end of the run-in period.~~
- Section 6.7.5 (Clinical Laboratory Assessments)

- The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, ~~hematuria and~~ eGFR will also be assessed locally.

Purpose: Updated exclusion criterion pertaining to the treatment with systemic steroids to remove the ambiguity around the permitted duration of doses <20 mg/day of prednisone-equivalent for more than 7 days in the 12 months prior to randomization

The primary changes occur in Section 4, Selection and Withdrawal of Patients

- Section 4.2 (Exclusion Criteria)
  - Criterion 10: Treatment with systemic steroids ~~at dosages exceeding 20 mg prednisone equivalent~~ for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization

Section also containing this change

- Synopsis (Diagnosis and Main Eligibility Criteria)
  - Patients will be excluded from the study if eGFR <30 mL/min/1.73 m2 2 weeks prior to randomization; treated with systemic steroids ~~at dosages exceeding 20 mg prednisone equivalent~~ for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization

---

Purpose: Updated retesting wording to clarify that laboratory tests may be repeated if laboratory abnormalities at Screening or the run-in period are likely to be transient. In addition, 2 retests will be permitted for hematuria during Screening, if the first test is negative

The primary changes occur in Section 6.1, Screening Assessments

- Section 6.1.2 (Retesting)
  - If in the Investigator's judgement, the ~~screening~~ laboratory abnormalities **at Screening or in the run-in period** are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale is to be documented. Laboratory values can be retested once during Screening **or the run-in period** as long as the patient can be evaluated for eligibility and randomized within the allowed Screening **or run-in period. Two retests will be permitted for hematuria during Screening, if the first test is negative**.

Purpose: Updated physical examination wording to add more clarity to the routine physical examination assessment row in the Schedule of Assessments tables

The primary changes occur in Section 6.7, Safety Assessments

- Section 6.7.3 (Physical Examination)
    - **Routine** ~~Full~~ physical examinations will be conducted according to the Schedule of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing.

      At Screening and Day 1 predose, a full physical examination will be performed. At all other time points, including Day 1 at 4 hours (±30 minutes) postdose, a directed physical examination will be performed. ~~On Day 1, routine physical examination will be performed at predose and 4 hours (±30 minutes) postdose. On all other dosing days, the routine physical examination will be performed predose.~~

Purpose: Updated safety assessments to clarify the collection of vital signs and the conduct of routine physical examination on Day 1 at 4 hours postdose and to include tympanic temperature measurement

The primary change occurs in Section 6.7, Safety Assessments

- Section 6.7.1 (Vital Signs)

Added text: Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, ~~oral~~ body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected at predose and 4 hours **(±15 minutes)** postdose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral **or tympanic** method.

- Section 6.7.3 (Physical Examination)

Added text: **At Screening and Day 1 predose, a full physical examination will be performed. At all other time points, including Day 1 at 4 hours (±30 minutes) postdose, a directed physical examination will be performed.** ~~On Day 1, routine physical examination will be performed at predose and 4 hours postdose.~~

Purpose: Corrected table number references for the monitoring of LFT and coagulation

The primary changes occur in Table 4 - Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase level >3× to 5× ULN:	Monitor at least every two weeks: LFT and coagulation per **Table 5** ~~Table 6~~

Transaminase level >5× to 8× ULN:	Monitor at least weekly: LFT and coagulation per **Table 5** ~~Table 6~~ until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

Purpose: Updated the hepatic assessments in patients who experience elevated transaminases (Table 6) to remove HIV testing

The primary change occurs in Table 6 - Hepatic Assessments in Patients Who Experience Elevated Transaminases

Deleted text: ~~HIV-1 and 2[a]~~

"~~HIV=human immunodeficiency virus~~" and footnote [a] "~~HIV testing will not be performed where prohibited by local regualtions~~" were removed from the footnotes of Table 6.

Purpose: Updated primary endpoint efficacy analyses wording to remove the presentation of the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and its 90% confidence interval

The primary changes occur in Section 7.2.5, Efficacy Analyses

- Section 7.2.5.1 (Primary Endpoint)
    - The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The 24-hour urine protein will be log transformed for analyses. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval will be estimated and then back transformed to original scale. ~~In the end the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and its 90% confidence interval will be presented.~~

Purpose: Updated adverse events wording to clarify that all adverse events, including serious and non-serious, will be collected from the time of signing the ICF through the end of the study

The primary changes occur in Section 6.7.6, Adverse Events

- Section 6.7.6.2 (Eliciting and Recording Adverse Events)
    - ~~Events~~ **All AEs, including non-serious AEs,** occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non serious AEs will be followed until the end of study.

CLINICAL STUDY PROTOCOL
ALN-CC5-005

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy
Short Title:	A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy
Study Drug:	Cemdisiran (ALN-CC5)
EudraCT Number:	2018-002716-27
IND Number:	140087
Protocol Date:	Original protocol 10 September 2018 Amendment 1.0 [26 November 2018]
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

27 NOV 2018

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-CC5-005 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I 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 SYNOPSIS

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Short Title

A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Study Drug

Cemdisiran (ALN-CC5)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 30-40 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 32 weeks using all assessments during the period

• To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal half-life (t1/2), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, Cmax, Tmax, t1/2, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. The standard of care is expected

to remain unchanged during this run-in period. Patients will not receive study drug (cemdisiran or placebo) during this time. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of subcutaneous (SC) cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains >1 g/24-hours within 2 weeks of the end of the run-in period, who continue to have hematuria, and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study center at Week 40 and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only and who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by a Data Monitoring Committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

Number of Planned Patients
Approximately 30 patients are planned for randomization in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years and ≤ 65 years of age) with a clinical diagnosis of primary immunoglobulin A (IgA) Nephropathy based on historical biopsy collected within 60 months of Screening, treated for IgA Nephropathy with stable, optimal pharmacological therapy including maximum allowed or tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for at least 3 months prior to the start of the run-in period. Eligible patients must have urine protein levels of ≥1g/24-hour at screening and mean urine protein ≥ 1g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization. In addition, eligible patients must have hematuria defined by ≥ 10 red blood cells per high powered field (RBC/hpf) at screening and either ≥10 RBC/hpf or a positive urinary dipstick (1+ and above) at the end of the run-in period. Eligible patients are required to have been previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or be willing to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care. In addition, patients not previously vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) must be willing to receive these vaccinations according to local guidelines.

Patients will be excluded from the study if eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization; treated with systemic steroids at dosages exceeding 20 mg prednisone-equivalent for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization; have a diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase; sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period measured in supine position after 10 minutes of rest; have received organ transplant (including hematologic transplant) or have secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease).

Study Drug, Dose, and Mode of Administration
Cemdisiran is a synthetic small interfering RNA (siRNA) targeting complement component 5 (C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand. Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. Doses of 600 mg of cemdisiran will be administered every 4 weeks during the 32-week treatment phase and the optional OLE period.

Placebo (normal saline 0.9% for SC administration) will be packaged and administered identically to cemdisiran.

Reference Treatment, Dose, and Mode of Administration

Angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) per physician and manufacturer‘s instructions.

Duration of Treatment and Study

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive SC doses of cemdisiran for a further 52 weeks in the the optional OLE. The estimated total time on study, inclusive of Screening (90 days), run-in

period (14 weeks), treatment period (36 weeks), extension period (52 weeks) and safety follow-up (52 weeks), for patients is approximately 36 months or 3.0 years.

Statistical Methods

Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of 27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, approximately 30 patients are planned to be randomized stratified by baseline urine protein levels (≥ 1g/24h and <2g/24h versus >=2g/24h).

The analysis populations include:

- The modified Intent-to-treat (mITT) population will include all patients who receive any amount of study drug and have at least one post baseline 24-hour proteinuria assessment. Patients will be grouped by assigned treatments (ie, as randomized).
- The Safety Analysis Set will include all patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

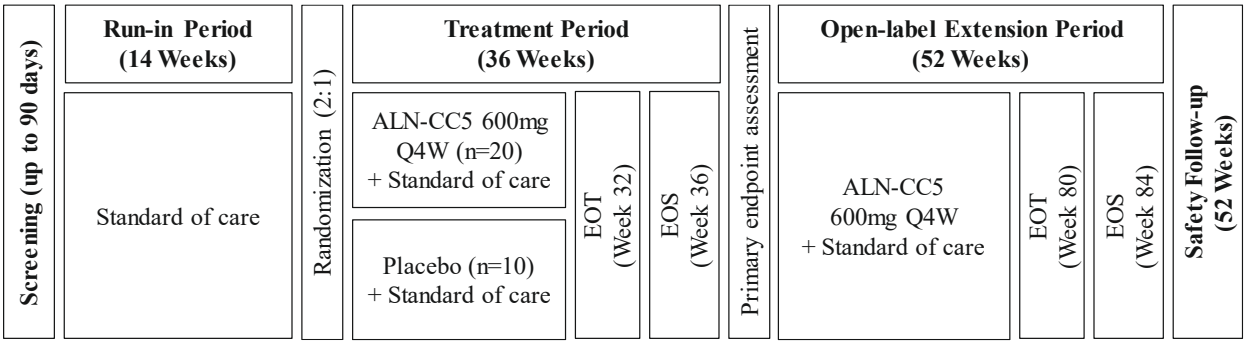
The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval (CI) will be estimated and then back transformed to original scale. In the end, the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and its 90% CI will be presented.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

The efficacy endpoints will be analyzed in the mITT population. PK and PD parameters will be analyzed in the PK and PD analysis sets, respectively.

Safety data will be summarized with descriptive statistics. Treatment-emergent adverse events will be summarized by SOC and PT (all events, related events, and serious events), in addition to being summarized by severity (all events). In addition, summaries will be provided for any AEs leading to discontinuation of study drug or death. Serious adverse events and procedure related adverse events in the run-in period will be listed.

Figure 1: Study Design



Abbreviations: Q4W=once every 4 weeks; EOS=end of study; EOT=end of treatment

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up

Study Visit (Day/Week)		Screening		Run-in Period (14 weeks)			Treatment Period (36 weeks)										Safety Follow up			
			Screening visit	Week -14	Week -8	Week -2	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 (EOT)	Week 36 (EOS/ET)	Week 49	Week 62	Week 75	Week 88
	Notes For details, see Section	D-189 to D-99	D-112 ±7	D-98 ±7	D-56 ±7	D-14 ±3	D1	D28 ±3	D56 ±3	D84 ±3	D112 ±3	D140 ±3	D168 ±3	D196 ±3	D224 ±3	D252±3	D343±14	D434±14	D525±14	D616±14
Discuss Study Information and Collect Informed Consent	6.1 and 6.2	X				(X)									(X)					
Medical History	6.1	X																		
Demographics	6.1		X																	
Inclusion/Exclusion Criteria	4.1 and 4.2	X					X													
Routine Physical Exam	6.7.3		X				X		X						X	X		X		X
Height, Weight and BMI	6.7.2		X				X		X						X	X		X		X
Vital Signs	6.7.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4		X				X								X	X		X		X
Clinical Laboratory Assessment	6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	6.7.5.2		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Routine Vaccination Status	6.1		X																	

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (36 weeks)**									**Safety Follow up**			
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32 (EOT)**	**Week 36 (EOS/ET)**	**Week 49**	**Week 62**	**Week 75**	**Week 88**
	Notes For details, see Section	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**	**D252±3**	**D343±14**	**D434±14**	**D525±14**	**D616±14**
Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccination, if not previously vaccinated and required per local guidance	5.3.2.2 and 6.2		X																	
Start of Meningitis Vaccination	5.3.2.1 and 6.2					X														
Confirmation of Meningococcal Vaccine Injection Schedule Compliance	As applicable and dependent on which vaccine will be used.						X	X	X	X	X	X	X	X						
Randomization							X													
Study Drug Administration	5.2.2						X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1					X									X					

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (36 weeks)**										**Safety Follow up**			
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32 (EOT)**	**Week 36 (EOS/ET)**	**Week 49**	**Week 62**	**Week 75**	**Week 88**
	Notes For details, see Section	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**	**D252±3**	**D343±14**	**D434±14**	**D525±14**	**D616±14**
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1		X								X							X		X
CAP/CCP Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
C5 Levels Blood Sample	6.5						X	X	X	X	X	X	X	X	X	X	X	X	X	X
eGFR Calculation	6.4.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1		X				X	X		X			X		X	X	X	X	X	X
Blood Sample for CIC Analysis and Exploratory Gd-IgA1 Assessment	6.7.5.1		X				X	X		X			X		X					
Optional Blood Sample for B-cell function Analysis	6.7.5.1		X																	
Exploratory Blood Sample	6.4.4						X		X		X		X		X					

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (36 weeks)**										**Safety Follow up**			
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32 (EOT)**	**Week 36 (EOS/ET)**	**Week 49**	**Week 62**	**Week 75**	**Week 88**
	Notes For details, see Section	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**	**D252±3**	**D343±14**	**D434±14**	**D525±14**	**D616±14**
Blood Sample for Exploratory Genetic Analysis	6.8.						X													
Exploratory Urine Sample	6.4.4.						X		X		X		X		X					
Plasma and Urine PK	See Table 3						X													
Optional Home Visit	Will be arranged where feasible during safety follow up at Weeks 49 and 75																X		X	
Adverse Events	6.7.6.2						X													
Concomitant Medications	5.3	X	X	X																
Antibiotics Compliance (if applicable)	5.5.3						X													
IgAN standard of Care Compliance			X																	

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Routine Physical Exam	6.7.3						X				X		X	X		X		X
Height, Weight and BMI	6.7.2						X				X			X		X		X
Vital Signs	6.7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	6.7.4						X						X	X		X		X
Clinical Laboratory Assessment	6.7.5	X	X		X		X		X		X		X	X	X	X	X	X
Pregnancy Test	6.7.5.2	X	X		X		X		X		X		X	X	X	X	X	X
Study Drug Administration	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	6.4.1.1													X				
24-hours Urine Proteinuria Assessment (from a single valid collection)	6.4.1.1						X				X					X		X
CAP/CCP Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
C5 Levels Blood Sample	6.5	X	X		X		X		X		X		X	X	X	X	X	X
eGFR Calculation	6.4.3	X	X		X		X		X		X		X	X	X	X	X	X

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (OLE EOT)	Week 84 (OLE EOS/ET)	Week 97	Week 110	Week 123	Week 136
	Notes For details, see Section	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Urine Sample for Urinalysis and Microscopy	6.4.2 and 6.7.5	X	X		X		X		X		X		X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	6.4.1.2	X	X		X		X		X		X		X	X	X	X	X	X
Blood Sample for Antidrug Antibodies	6.7.5.1				X						X			X	X	X	X	X
Exploratory Blood Sample	6.4.4		X		X		X		X		X		X	X				
Exploratory Urine Sample	6.4.4		X		X		X		X		X		X	X				
Optional Home Visit	Will be arranged for cemdisiran administration in between 8-weekly study site visits at Weeks 44, 52, 60, 68 and 76 during the extension phase, and where feasible, during safety follow up at Weeks 97 and 123, unless patients are required to visit the study center as judged necessary by the Investigator.			X		X		X		X		X			X		X	

Study Visit (Day/Week)		**Open-Label Extension Period (52 weeks)**													**Safety Follow up**			
		Week 36	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80 (OLE EOT)**	**Week 84 (OLE EOS/ET)**	**Week 97**	**Week 110**	**Week 123**	**Week 136**
	Notes For details, see Section	**D252 ±7**	**D280 ±7**	**D308 ±7**	**D336 ±7**	**D364 ±7**	**D392 ±7**	**D420 ±7**	**D448 ±7**	**D476 ±7**	**D504 ±7**	**D532 ±7**	**D560 ±7**	**D588 ±7**	**D679 ±14**	**D770 ±14**	**D861±14**	**D952 ±14**
Adverse Events	See Section 6.7.6.2	X																
Concomitant Medications	See Section 5.3	X																
Antibiotics Compliance (if applicable)	See Section 5.5.3	X																
IgAN standard of Care Compliance		X																

Table 3: Pharmacokinetic Time Points

Phase	Study Day	Protocol Time Relative to Dosing (hh:mm)[a]	PK Blood	Pooled Urine[b]
Treatment phase	Day 1	Predose (within 60 mins)	X	
		00:00 (dose)		X
		01:00 (±5 mins)	X	
		02:00 (±15 mins)	X	
		04:00 (±15 mins)	X	
		06:00 (±15 mins)	X	
		08:00 (±30 mins)	X	X
		12:00 (±30 mins)		
		24:00 (±120 mins)	X	X

Abbreviations: hh=hours; mm=minutes; mins=minutes; PK=pharmacokinetics.

[a] The actual time of blood sample collection must be recorded.
[b] The pooled urine 6-12 hours and 12-24 hours can be collected as outpatient.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 18
LIST OF TABLES 21
LIST OF FIGURES 22
1. INTRODUCTION 25
1.1. Disease Overview 25
1.2. Cemdisiran 27
1.3. Study Design Rationale 28
1.4. Dose Rationale 29
1.5. Benefit-Risk Assessment 30
2. OBJECTIVES AND ENDPOINTS 32
3. INVESTIGATIONAL PLAN 34
3.1. Summary of Study Design 34
3.2. Duration of Treatment 35
3.3. Duration of Study 35
3.3.1. Definition of End of Study for an Individual Patient 35
3.4. Number of Planned Patients 35
3.5. Method of Assigning Patients to Treatment Groups 35
3.6. Blinding 36
3.6.1. Emergency Unblinding 36
3.7. Data Monitoring Committee 36
4. SELECTION AND WITHDRAWAL OF PATIENTS 37
4.1. Inclusion Criteria 37
4.2. Exclusion Criteria 37
4.3. Removal from Therapy or Assessment 39
4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments 39
4.3.2. Stopping a Patient's Study Participation 40
4.3.2.1. Patient or Legal Guardian Stops Participation in the Study 40
4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data 41
4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study 41
4.3.2.4. Recording Reason for Stopping a Patient's Study Participation 41

4.3.3. Lost to Follow-Up....41
4.3.4. Replacement of Study Patients....42
5. TREATMENTS AND OTHER REQUIREMENTS....43
5.1. Treatments Administered....43
5.2. Study Drug....43
5.2.1. Description....43
5.2.2. Dose and Administration....43
5.2.3. Dose Modifications....43
5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing....44
5.2.4. Preparation, Handling, and Storage....45
5.2.5. Packaging and Labeling....46
5.2.6. Accountability....46
5.3. Concomitant Medications and Procedures....46
5.3.1. Prohibited Concomitant Medications....46
5.3.2. Study-specific Vaccinations....47
5.3.2.1. Meningococcal Vaccinations....47
5.3.2.2. Pneumococcal and Hib Vaccinations....47
5.4. Treatment Compliance....48
5.5. Other Requirements....48
5.5.1. Contraception....48
5.5.2. Alcohol Restrictions....49
5.5.3. Antibiotic Compliance....49
6. STUDY ASSESSMENTS....50
6.1. Screening Assessments....50
6.1.1. Rescreening....50
6.1.2. Retesting....50
6.2. Run-in Period....50
6.3. Baseline Assessments (Treatment Period)....51
6.4. Efficacy Assessments....51
6.4.1. Proteinuria....51
6.4.1.1. 24-Hour Urine Collection....51
6.4.1.2. Spot Urine Collection....52
6.4.2. Hematuria....52

6.4.3. Changes in Renal Function 53
6.4.4. Markers of Complement Activation, Inflammation and Renal Injury 53
6.5. Pharmacodynamic Assessments 53
6.6. Pharmacokinetic Assessments 53
6.7. Safety Assessments 54
6.7.1. Vital Signs 54
6.7.2. Weight and Height 54
6.7.3. Physical Examination 54
6.7.4. Electrocardiogram 55
6.7.5. Clinical Laboratory Assessments 55
6.7.5.1. Immunogenicity 57
6.7.5.2. Pregnancy Testing 57
6.7.5.3. Additional Liver Function Assessments 57
6.7.6. Adverse Events 58
6.7.6.1. Definitions 58
6.7.6.2. Eliciting and Recording Adverse Events 60
6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee 61
6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee 61
6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities 62
6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee 62
6.7.6.7. Pregnancy Reporting 62
6.7.6.8. Overdose Reporting 62
6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository 63
7. STATISTICS 64
7.1. Determination of Sample Size 64
7.2. Statistical Methodology 64
7.2.1. Populations to be Analyzed 64
7.2.2. Examination of Subgroups 65
7.2.3. Handling of Missing Data 65
7.2.4. Baseline Evaluations 65
7.2.5. Efficacy Analyses 65
7.2.5.1. Primary Endpoint 65

7.2.5.2. Secondary Efficacy Endpoints....65
7.2.5.3. Exploratory Endpoints....66
7.2.6. Pharmacodynamic Analysis....66
7.2.7. Pharmacokinetic Analysis....66
7.2.8. Safety Analyses....66
7.2.9. Immunogenicity Analyses....67
7.2.10. Biomarker Analyses....67
7.2.11. Interim Analysis....67
7.2.12. Optional Additional Research....67
8. STUDY ADMINISTRATION....68
8.1. Ethical and Regulatory Considerations....68
8.1.1. Informed Consent....68
8.1.2. Ethical Review....68
8.1.3. Serious Breach of Protocol....69
8.1.4. Study Documentation, Confidentiality, and Records Retention....69
8.1.5. End of Study....69
8.1.6. Termination of the Clinical Study or Site Closure....69
8.2. Data Quality Control and Quality Assurance....70
8.2.1. Data Handling....70
8.2.2. Study Monitoring....70
8.2.3. Audits and Inspections....70
8.3. Publication Policy....70
9. LIST OF REFERENCES....72
10. APPENDICES....75

LIST OF TABLES

Table 1: Schedule of Assessments Run-in and Treatment Periods (Screening through Week 36) including Safety Follow up....10
Table 2: Schedule of Assessments Open-Label Extension Period and Safety Follow up....14
Table 3: Pharmacokinetic Time Points....17

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified 45
Table 5: Clinical Laboratory Assessments 56
Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases 58

LIST OF FIGURES

Figure 1: Study Design....9

List of Abbreviations and Definitions of Terms

Abbreviation	**Definition**
ADA	Antidrug antibodies
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECI	Adverse event of clinical interest
aHUS	Atypical hemolytic uremic syndrome
ALN-CC5	Cemdisiran
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Aspartate transaminase
AUC	Area under the concentration curve
BMI	Body mass index
C3	Complement component 3
C3a	Activated complement 3
C5	Complement component 5
C5a	Activated complement component 5
CAP	Complement alternative pathway
CCP	Complement classical pathway
CFH	Complement factor H
CI	Confidence interval
CIC	Circulating immune complexes
CL/F	Clearance
Cmax	Maximum concentration

Abbreviation	Definition
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
Gd-IgA1	Galactose-deficient Immunoglobulin A 1
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hib	Haemophilus influenzae type b
HIV	Human immunodeficiency virus
hpf	High powered field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgAN	IgA Nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function test
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mITT	Modified intent-to-treat
mRNA	Messenger RNA
NHP	Nonhuman primates
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
RAS	Renin-angiotensin system
RBC	Red blood cell
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
Tmax	Time to maximum concentration
TMF	Trial Master File
Tri-GalNAc	Triantennary N-acetylgalactosamine
UP	Urine protein
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein:creatinine ratio
V/F	Volume of distribution

1. INTRODUCTION

1.1. Disease Overview

Globally, immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure.[Lai 2016; Wyatt 1998] While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly O-glycosylated IgA1 (Gd-IgA1) and the presence of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule, resulting in the formation of pathogenic immune complexes. Some of these circulating complexes may deposit in glomeruli and induce renal injury.[Knoppova 2016] The lack of galactose exposes O-linked monosaccharide N-acetylgalactosamine (O-GalNAc) moeities in the hinge region of IgA1.[Novak 2018] While the binding of autoantibodies to Gd-IgA1 is dependent on the presence of multiple O-GalNAc residues, the IgA1 protein backbone and the spatial arrangement of O-GalNAc moieties are also thought to play a role in the specificity of autoantibodies to Gd-IgA1.[Mestecky 2016; Suzuki 2009]

Both the alternative and lectin complement pathways may be activated, leading to generation of the anaphylatoxins activated complement component 3 (C3a) and activated complement component 5 (C5a) and the membrane attack complex (MAC) C5b-9, with subsequent promotion of inflammatory mediators.[Maillard 2015] Emerging data indicate that mesangial-derived mediators that are released following deposition of IgA1 may lead to podocyte and tubulointerstitial injury.

Given that a biopsy specimen is required to diagnose IgAN, the clinical threshold for performing a biopsy will have a major impact on the prevalence of IgAN. Persistent microscopic hematuria alone and/or mild proteinuria alone are not commonly used as a per cause indication for biopsy in the United States. Thus, the prevalence of IgAN is modest in the United States (10 to 20% of primary glomerulonephritis), higher in some European countries (20 to 30%), and highest in developed countries in Asia (40 to 50%).[Woo 2010] This considerable geographical variability can be explained by several factors including the variation in access to primary care enabling early diagnosis and the differences in policies for performing renal biopsies as well as for early referrals. For example, in some countries, urine screening tests are conducted in schools or for military service or ahead of employment, explaining the apparent high incidence.[Imai 2007; Wyatt 1998] Ethnic differences can also contribute to the varying prevalence of IgAN. Genome-wide association studies have identified candidate genes as well as risk-associated and protective alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa.[Kiryluk 2014] These genes are involved in antigen presentation, mucosal defense system and notably the alternative complement pathway (complement factor H [CFH]/CFHR locus).[Kiryluk 2014] Finally, patients may present at any age with IgAN but there is a peak incidence in the second and third decades of life. Most cases of IgAN occur in sporadic (90 to 95%) rather than in familial patterns (5 to 10%).[Lai 2016]

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. The first indication for making a diagnosis comes after careful microscopic examination of a urine sample. The presence of red blood cell (RBC) casts and dysmorphic RBCs indicates glomerular bleeding. Varying degrees of proteinuria are present in patients with

IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio (UPCR) measurement. Hence, IgAN can only be diagnosed definitely upon renal biopsy and study of kidney tissue using immunofluorescence. The pathology of IgAN is characterized by deposition of pathogenic polymeric IgA1 immune complexes and C3 in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. A consensus on the pathologic classification of IgAN has been developed by the International IgA Nephropathy Network in collaboration with the Renal Pathology Society (Oxford classification).[Cattran 2009; Lai 2016; Roberts 2009]

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis which is often associated with severe hypertension, but between these extremes, most patients with IgAN pursue a chronic indolent course.[Lai 2016] Some patients present with more severe proteinuria, hypertension and renal progression over time, typically reaching end-stage renal disease (ESRD) over a span of 20 years. Thus, the severity of proteinuria upon presentation has significant prognostic implications. More importantly, the change in proteinuria over time is being regarded as the current best prognostic indicator: those who had heavy time averaged proteinuria and achieved a partial remission of <1 g/24-hours had a similar course to those who had <1 g/24-hours throughout and fared far better than those who never achieved partial remission.[Reich 2007] These observations support the notion that every effort should be made to reduce proteinuria in IgAN. In addition to the degree of proteinuria, baseline renal function and the degree of histological injury are of prognostic value. For example, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90 to 120 mL/min/1.73 m^2). The rate of glomerular filtration rate (GFR) decline also correlates with glomerulosclerosis and tubular atrophy or interstitial fibrosis on biopsy as outlined by Oxford-MEST-C classification. Spontaneous full recovery in IgAN is rare in adults, especially if associated with significant proteinuria (>0.5 g/24-hour).[Knoop 2017]

Patients with minor urine abnormalities, normal blood pressure, and normal GFR usually do well and require only monitoring. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. Thus, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease that can result in end-stage renal failure. The optimal role of immunosuppressive therapy is uncertain. The available studies are not conclusive since most are relatively small and have limited follow-up.[Lai 2016] STOP-IgAN, a German trial, randomly assigned adults with an eGFR of >30 mL/min/1.73 m^2 and persistent proteinuria of >0.75 g/24-hour despite 6 months of supportive care with RAS inhibitors to receive supportive care alone or supportive care plus immunosuppression (prednisone alone for those with initial GFR >60 mL/min and prednisone combined with cyclophosphamide then azathioprine with initial GFR 30-59 mL/min). This strategy did not significantly improve the renal outcome and was associated with increased adverse effects at 36 months.[Rauen 2015] The TESTING trial demonstrated some GFR effect of steroids in Chinese patients, but had to be stopped due to large number of serious adverse events (SAEs) in the steroid arm.[Lv 2017] The 2012 KDIGO guidelines recommend corticosteroids, albeit at very low level of evidence. Thus, steroids may be tried in some cases as

rescue therapy if proteinuria markedly increases or GFR rapidly falls. Further studies to address the role of steroids in IgAN are currently under way. Finally, Rituximab seems to be ineffective in the treatment of patients with progressive IgAN.[Lafayette 2016]

1.2. Cemdisiran

Alnylam Pharmaceuticals, Inc. is developing cemdisiran (ALN-CC5), a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of atypical hemolytic uremic syndrome (aHUS) and IgAN. Cemdisiran comprises a small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand.

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19-25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA.[Elbashir 2001] Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [Soutschek 2004], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo in animal models (including in rodents and nonhuman primates [NHP]) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations.[Soutschek 2004; Zimmermann 2006] Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a GalNAc carbohydrate ligand.[Ashwell 2006] Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

Cemdisiran (containing siRNA drug substance, ALN-62643, targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via subcutaneous (SC) injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the cemdisiran siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of MAC formation and C5a release. This in turn would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN resulting in renal function improvement.[Maillard 2015] Both lectin and alternative pathways of complement have been implicated in IgAN pathology. Cemdisiran-mediated silencing of C5 will inhibit MAC formation and C5a release regardless of the activating pathway and may be a superior approach in IgAN where the contribution of different pathways may be heterogenous between patients.[Medjeral-Thomas 2018]

The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities, other than an increased susceptibility to Neisserial infections, in subjects with known genetic C5 deficiencies.[Ross 1984] Subjects

with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. These infections include invasive meningococcal disease, disseminated gonococcal infections as well as diseases caused by typically commensal Neisseria species.[Crew 2018; Crew 2018; McQuillen 2018; Ram 2010] In addition, safety data on the treatment of healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH) with cemdisiran in Study ALN-CC5-001 indicate that cemdisiran is generally well-tolerated; the maximum tolerated dose was 900 mg. There were no serious adverse events (SAEs) or discontinuations due to adverse events (AEs) during this study, and most AEs were mild or moderate in severity. In Study ALN-CC5-001, the frequency of ADA was low. Two of 48 healthy volunteers (1 cemdisiran-treated and 1 placebo-treated) were ADA positive during the study. The cemdisiran-treated volunteer had transient ADA positivity, with a negative result later in the study and no impact on PK or PD. The placebo-treated volunteer was ADA positive at baseline (predose) and remained positive through Day 70.

A detailed description of the chemistry, pharmacology, nonclinical pharmacokinetics (PK) and toxicology, as well as preliminary efficacy, and safety of cemdisiran is provided in the current edition of the Investigator's Brochure (IB).

1.3. Study Design Rationale

In contrast to the RBC lysis which characterises the pathophysiology of PNH, which requires extremely high level of C5 inhibition for protection, endothelial cells and mesangial cells are the cellular targets of dysregulated complement in aHUS and IgAN, respectively. These cells are nucleated cells which possess complement regulatory proteins as well as the ability to shed membrane associated MAC to defend against MAC-mediated damage, a key step in thrombotic microangiopathy progression in aHUS and renal damage in IgAN. It is therefore hypothesized that a lesser degree of cemdisiran mediated C5 knockdown will be required for disease control in patients with IgAN and aHUS than in patients with PNH.[Morgan 1989; Rosse 1973] This hypothesis is supported by the observation that aHUS patients who achieve C5 inhibition maintain good disease control despite complement activity levels consistent with higher free C5 levels.[Cugno 2014] Therefore, cemdisiran monotherapy may be a viable treatment option in patients with IgAN at levels of C5 silencing achieved in Study ALN-CC5-001.

This therapeutic hypothesis will be tested in a multicenter, multinational, double-blind, placebo-controlled study to evaluate the effect of multiple doses of cemdisiran given by SC injection in patients with IgAN with persistent proteinuria (>1 g/24-hours) despite the standard of care (angiotensin converting enzyme inhibitors [ACE] or angiotensin II receptor blockers [ARB]) and additional medications if necessary for blood pressure control followed by a treatment extension to evaluate long-term safety and clinical activity. The study population has been selected based on two major factors: 1) the severity of proteinuria upon presentation has significant prognostic implications.[Coppo 2005] IgAN patients with heavy proteinuria >1 g/24-hours have a significantly worse renal outcome than those who have proteinuria <1 g/24-hours.[Reich 2007] 2) For patients with persistent proteinuria, despite the nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, no disease-specific therapies are currently available, and an unmet need persists for novel interventions. Since proteinuria can result both from active inflammation as well as irreversible scarring of renal tissue and in lieu of a protocol biopsy, we enrich our patients for presence of potentially

reversible disease activity by requiring presence of hematuria and relatively preserved renal function with eGFR >30 mL/min. To ensure the selection of patients who are truly at risk of progression of kidney disease despite standard of care, the first period of the study consists of a run-in period during which patients will not receive study drug (cemdisiran or placebo). The run-in period will be an observational period during which patients' treatment with standard of care, blood pressure, kidney function, degree of hematuria, and proteinuria will be documented. The standard of care is expected to remain unchanged during this run-in period. Only patients whose

- proteinuria level remains above 1 g/24-hours within 2 weeks before the end of the run-in period,
- continue to have hematuria, and meet blood pressure and eGFR criteria

will be eligible to enroll in the 36-week treatment period portion of the study.

Randomization to cemdisiran or placebo will be performed in a 2:1 ratio so that more patients will receive cemdisiran. This will allow a more precise estimation of the effect of cemdisiran with only marginal loss of power. Inclusion of a placebo arm will allow better assessment of safety and interpretation of the efficacy of cemdisiran.

The primary endpoint for the study is percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32. This is justified for a phase 2 study given the slow progression of renal disease and the established role of proteinuria as a marker of disease progression.

1.4. Dose Rationale

In the Phase 1/2 Study (ALN-CC5-001), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). Treatment with cemdisiran was generally well tolerated in both healthy volunteers and patients with PNH. There were no SAEs and no discontinuations due to AEs during this study, including at the highest doses administered. Most AEs observed were mild or moderate in severity.

Dose selection for the current study is based on the expected level of C5 and complement activity inhibition necessary for efficacy in patients with IgAN and the extent to which different doses of cemdisiran can inhibit production of C5. C5 silencing is a novel approach for the treatment of IgAN and little clinical precedent exists for inhibiting the terminal complement pathway in this disease. Since complement regulation is not impaired in IgAN like it is in PNH, and the kidney glomerular cells are nucleated cells, it is expected that the level of silencing needed for efficacy in IgAN is lower than that needed for PNH (see IB Section 2.4). For this proof-of-concept study, a dose was selected that is expected to produce rapid and robust C5 suppression and complement activity inhibition across the patient population, allowing an unambiguous evaluation of whether C5 silencing results in proteinuria improvement in IgAN. In Study ALN-CC5-001, a single dose of 600 mg cemdisiran achieved a C5 level of 12.3±1.47 µg/mL by Day 14 and 2.3±0.76 µg/mL by Day 56, corresponding to 60.9% reduction in complement alternative pathway (CAP) activity and a 69.3% reduction in complement

classical pathway (CCP) activity by Day 14 and 90.2% and 91.4% reduction in CAP and CCP activities, respectively, by Day 56. Single and multiple biweekly doses of 600 mg were well-tolerated with an acceptable safety profile in healthy volunteers in Study ALN-CC5-001A. In this initial study, the cemdisiran dose of 600 mg that was safe and well-tolerated was chosen for evaluation. This dose will yield robust C5 silencing and will have maximal opportunity to produce a meaningful clinical effect in patients with IgAN. Since the relationship between C5 levels and complement activity is non-linear, with small C5 fluctuations resulting in a larger increase in complement activity, a monthly dose regimen was selected to maintain a constant level of C5 silencing. Additionally, a more consistent effect of cemdisiran on C5 protein and CCP level is predicted after monthly dosing when compared to quarterly dosing based on a modeling approach.

During the extension treatment phase, patients treated with both cemdisiran and placebo will have the option to receive a 600 mg dose of cemdisiran every four weeks for an additional 52 weeks.

IgAN can result in progressive renal impairment; however, patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2) who may have sustained irreversible damage to the kidney are not eligible for participation in this trial. As the kidney is not the major elimination pathway for cemdisiran and based on available nonclinical and clinical data obtained with cemdisiran (with 10.6 to 31.6% of the cemdisiran dose recovered in a 24-hour urine collection in the ALN-CC5-001 study), it is expected that moderate renal impairment (eGFR<60 mL/min/1.73 m^2) will not affect the PK of cemdisiran to the extent that a dose adjustment would be required. Therefore, patients with moderate renal impairment are eligible for study enrollment. More information on urine PK can be found in the IB.

1.5. Benefit-Risk Assessment

To date, no medications have been approved specifically for the treatment of IgAN. Therefore, there is a large unmet need for novel interventions, particularly in patients who are at risk of progressive renal disease such as those with persistent proteinuria despite treatment with RAS inhibitors. Available data from studies on the role of immunosuppressive therapy in IgAN are not conclusive as most are relatively small and have limited follow-up.[Lai 2016] Use of immunosuppressive drugs and high-dose steroids are also associated with increased AEs which is particularly common in patients with lower GFR.[Sarcina 2016]

Given the biological target of cemdisiran, the available nonclinical and clinical data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities and injection site reactions (ISRs). C5 inhibition is associated with increased susceptibility for Neisserial infections (including disseminated gonococcal infections) and the potential risk of other infections, particularly those due to encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), as well as *Aspergillus* in immunocompromised and neutropenic patients. Therefore, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine are required. Patients will be instructed to contact study site if any early signs of meningococcal infections are experienced. In addition, patients with functional or anatomic asplenia will be excluded and only patients previously vaccinated or who agree to receive vaccination for Hib and *Streptococcus pneumoniae* according to current national/local

vaccination guidelines, at screening, will be enrolled. Investigators in Study ALN-CC5-005 should educate patients on the risk of disseminated gonococcal infection and encourage safe sex practices. All national/local screening recommendations for gonorrhea in the general population should also be followed. Finally, given the reported evidence of a higher risk of disseminated gonococcal infections with treatment with eculizumab, Investigators are encouraged to evaluate any patient who has a *Neisseria gonorrhoeae* infection for the signs and symptoms of disseminated infection.[Crew 2018; McQuillen 2018] No cases of Neisserial infection or other infections due to encapsulated bacteria were observed in healthy volunteers or in patients with PNH (Study ALN-CC5-001).

As cemdisiran is targeted for delivery to the liver, patients will be closely monitored for changes in LFTs and patients with a medical history or evidence of chronic liver disease or cirrhosis have been excluded. Criteria for dose withholding, and stopping of cemdisiran are provided in Section 5.2.3.1. Patients will also be monitored for the development of ISRs and rotation of injection site are recommended during the study.

Considering anti-glycan autoantibodies recognizing Gd-IgA1 are implicated in the pathogenesis of IgA nephropathy, exposure to the GalNAc moiety of cemdisiran may pose a theoretical risk of stimulating the production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy. This could presumably occur when antidrug antibodies (ADAs) to cemdisiran's triantennary GalNAc (Tri-GalNAc) cross-react with Gd-IgA1. The risk of developing these cross-reactive antibodies is likely low. This is based on the low incidence of ADA to cemdisiran in study ALN-CC5-001 (see Section 1.2) and the distinct difference in structure of the O-GalNAc moieties on a Gd-IgA1 glycoprotein and the Tri-GalNAc moiety in cemdisran. This low risk is further mitigated by excluding patients with confirmed pre-existing IgG/IgM/IgA ADAs to total drug and real time monitoring for development of de novo IgG/IgM/IgA ADAs after dosing with cemdisiran. Patients with confirmed de novo ADAs will be discontinued from study drug but will continue to be monitored until EOS visit and subsequent safety follow up. Patients who develop positive ADA will be followed until ADA titers return to baseline. Additional ADA samples will also be collected if any clinical evidence of progression of IgAN disease and/or relevant safety findings.

Detailed information about the known and expected benefits and risks of cemdisiran and additional information on the clinical and nonclinical data may be found in the current version of the IB.

Cumulatively, clinical data regarding the role of complement pathways in IgAN progression, robust nonclinical and clinical data with cemdisiran (see IB for more information), and prior and ongoing clinical experience with other RNAi therapeutics in humans suggest cemdisiran will have a favorable risk profile in the intended population and supports the initial clinical development of cemdisiran in IgAN. In addition, cemdisiran may address the unmet medical need for the first efficacious and disease-specific treatment for patients with IgAN.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 32 weeks using all assessments during the period • The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32

	• Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal half-life (t1/2), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, Cmax, Tmax, t1/2, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. Patients will not receive study drug (cemdisiran or placebo) during this time. The standard of care is expected to remain unchanged during this run-in period. The second study period is a 36-week treatment period which will evaluate the efficacy and safety of SC cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains >1 g/24-hours within 2 weeks of the end of the run-in period, who continue to have hematuria, and who meet blood pressure and eGFR criteria will be eligible to enroll in the 36-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Approximately 30 patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of treatment at Week 32.

At the end of treatment (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 36. Patients will return to the study center at Week 40 and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 (OLE EOT) and an end of study (EOS) or early termination (ET) visit will be completed at Week 84 (OLE EOS/ET). For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS/ET visit will be at Week 36.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at 13 and 39 weeks after the EOS/ET visit (regardless if EOS/ET visit is at Week 36 or Week 84).

Regular reviews of safety and tolerability data will be performed by an independent data monitoring committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

3.2. Duration of Treatment

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive 600 mg SC doses of cemdisiran for 52 weeks in the optional OLE.

3.3. Duration of Study

The maximum estimated total time on study, inclusive of Screening (maximum of 90 days), run-in period (14 weeks), treatment period (36 weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is approximately 36 months or 3.0 years.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the EOS visit (Week 36 for those patients who do not consent to continue to participate in the study in the OLE period and Week 84 for patients who enter the OLE period). Upon study completion (regardless if EOS visit is at Week 36 or Week 84) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.

For patients withdrawing from the study after receiving one dose of cemdisiran at a minimum (ET), all efforts should be made to conduct the EOS/ET assessments. Patients should then be encouraged to enter the safety follow up period.

3.4. Number of Planned Patients

Approximately 30 patients are planned for randomization in this study.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the cemdisiran or placebo arms. Randomization will be stratified by baseline urine proteinuria levels (≥ 1g/24h and <2g/24h versus >=2g/24h).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at screening and prior to randomization.

3.6. Blinding

All site personnel including sponsor delegated clinical research associates, data management CRO and patients will be blinded to study drug treatment during the efficacy period (up to Week 36). Sponsor personnel will not be blinded to study treatment. Cemdisiran and placebo will be packaged identically. The study drug will be administered under the supervision of the Investigator or at the patient's home by a healthcare professional (see Section 5.2.2). Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by a site pharmacist prior to administration by a healthcare professional. See the Pharmacy Manual for additional details. Further details on blinding and unblinding arrangements will be documented in a separate plan /manual.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the Trial Master File (TMF).

Further details on blinding and unblinding arrangements will be documented in a separate plan / manual.

3.7. Data Monitoring Committee

An independent DMC will perform regular reviews of safety, tolerability, and immunogenicity data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a Charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of unblinded data (safety, tolerability, PK, pharmacodynamics (PD), ADA, circulating immune complexes (CIC) and efficacy of cemdisiran) during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Male or female ≥18 years and ≤65 years of age at the time of informed consent

Patient and Disease Characteristics

2. Clinical diagnosis of primary IgAN as demonstrated by historical biopsy collected within 60 months of screening
3. Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB for at least 3 months prior to start of run-in period
4. Urine protein ≥1g/24-hour at screening and mean urine protein ≥1g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization
5. Hematuria as defined by ≥10 RBCs per high powered field (RBC/hpf) at screening and either ≥10 RBC/hpf or a positive urinary dipstick (1+ and above) at the end of the run-in period, prior to randomization (local result accepted for assessment of eligibility at the end of the run-in period)
6. Females of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception 14 days before first dose, throughout study participation, and for 90 days after last dose administration
7. Previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or willingness to receive these vaccinations as well as prophylactic antibiotic treatment, if required by local standard of care
8. Previously vaccinated or willingness to receive vaccinations for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines for vaccination use

Informed Consent

9. Patient is willing and able to provide written informed consent and to comply with the study requirements

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Concomitant significant renal disease other than IgAN
2. A diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase
3. Secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease)

4. Diagnosis of Henoch-Schonlein Purpura (IgA Vasculitis)
5. eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization (local results will be used for assessment of eligibility)

Laboratory Assessments

6. Has any of the following laboratory parameter assessments:
   a. Alanine transaminase (ALT) >1.5×upper limit of normal (ULN), International Normalized Ratio (INR) >2 (or >3.5 if on anticoagulants), or total bilirubin >1.5×ULN (unless bilirubin elevation is due to Gilbert's syndrome)
7. Confirmed positive IgG/IgM/IgA ADAs to cemdisiran at Screening
8. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
9. Known human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection or hepatitis B virus (HBV) infection

Prior/Concomitant Therapy

10. Treatment with systemic steroids at dosages exceeding 20 mg prednisone-equivalent for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization
11. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment

Medical Conditions

12. Malignancy (except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate cancer) within the last 5 years
13. Active psychiatric disorder, including, but not limited to schizophrenia, bipolar disorder, or severe depression despite current pharmacological intervention
14. Known medical history or evidence of chronic liver disease or cirrhosis
15. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
16. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc
17. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
18. Known contraindication to meningococcal vaccines (group ACWY conjugate and group B vaccines) required for this study. Refer to the most recent local product information for each vaccine for the current list of contraindications
19. Unable to take antibiotics for meninigococcal prophylaxis, if required by local standard of care

20. Sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period, measured in supine position after 10 minutes of rest
21. Receipt of an organ transplant (including hematologic transplant)
22. History of meningococcal infection within 12 months before Screening
23. Patients with systemic bacterial or fungal infections that require systemic treatment with antibiotics or antifungals
24. Patients with functional or anatomic asplenia

Alcohol Use

25. Patients who consume more than 14 units of alcohol a week (unit 1 glass of wine [125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-adverse event), including confirmed positive test for ADA to cemdisiran
- Or, study is terminated by the Sponsor

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.7.5.2 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments

through the Week 36/EOS or Week 84/OLE EOS visit and safety follow-up so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 2), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and adverse events, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.7.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 36-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 36 assessments) will be encouraged to remain on the study and complete assessments through Week 36; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 1).

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete the OLE EOS/ET assessments; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks thereafter (see Table 2).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient/legal guardian considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Week 36 visit, including entering the 52-week safety follow-up. If a patient/legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 36-week treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the Week 36 EOS/ET visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an adverse event (AE), including serious adverse events (SAEs), the event should be followed as described in Section 6.7.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study during the 36-week treatment period or the OLE will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of cemdisiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to cemdisiran.

5.2.2. Dose and Administration

Patients will be administered cemdisiran (600 mg) or placebo (at the same volume as the active drug) as an SC injection once every 4 weeks in combination with standard of care in the 32-week treatment phase. During the 52-week OLE phase, patients will be administered cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. At-home dosing may be administered by a healthcare professional. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy Manual.

To maintain the blind during the treatment period, the syringes are to be masked prior to study drug withdrawal. A full description of the blinding procedure is included in the Pharmacy Manual.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing

1. LFT results (Table 5) from the previous visit should be reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 4.
3. For any ALT or AST elevation >3×ULN:
   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. Perform assessments per Table 4 and Table 6.
   c. If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 4

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least every two weeks: LFT and coagulation per Table 6
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold cemdisiran dosing until recovery to ≤1.5×ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of cemdisiran doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

Cemdisiran (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of a 0.5-mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

The standard of care treatment should be held stable throughout the run-in and treatment periods. Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 and Table 2). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

For other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug/placebo, for 7 days after the last dose of either study drug or placebo.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements (if started prior to screening, then may continue during the study at the same dose)
- Hydroxychloroquine

5.3.2. Study-specific Vaccinations

5.3.2.1. Meningococcal Vaccinations

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, upon determination of eligibility at the end of run-in period, 2 weeks prior to randomization to cemdisiran or placebo, as per the Schedule of Assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions and according to the Advisory Committee on Immunization Practices (ACIP) or other locally applicable recommendations for patients with complement deficiencies. On days of vaccination, urinary samples should be collected prior to administration of vaccines.

Patients will be immunized against *Neisseria meningitidis* according to the following specifications:

- Patients who have previously completed the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) at least 14 days but no more than 3 years from randomization can start study assessments after confirming eligibility. Documented vaccine history must be available to, and verified by, study site staff at the time of Screening.
- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines if found eligible at the end of the run-in period.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the Schedule of Assessments if determined to be eligible for the study at the end of the run-in period.
- If required locally, patients will receive prophylactic antibiotics according to the local standard of care after randomization to cemdisiran or placebo.

5.3.2.2. Pneumococcal and Hib Vaccinations

Patients will receive vaccinations for Hib and *Streptococcus pneumoniae*, if not previously vaccinated, according to current national/local vaccination guidelines for vaccination use. Hib and pneumococcal vaccinations (if required at screening per national/local guidelines;

vaccination should occur prior to Week-2. At screening, patient vaccination records will be checked for compliance with local recommendations for the use of these vaccines.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration or until study completion.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries e.g. France, in order to comply with local requirements as described in the corresponding patient consent forms

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.7.5.2).

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. Antibiotic Compliance

Patients who require prophylactic antibiotics after randomization to cemdisiran or placebo (see Section 5.3.2.1) per local standard of care will undergo antibiotic compliance checks. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments. Antibiotic dose adjustments will be permitted in the case of renal impairment. All dose adjustments must comply with the manufacturer's instructions.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 and Table 2.

6.1. Screening Assessments

An ICF approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor; see Section 6.1.1.

Patient demographic data and medical history/disease history will be obtained. In particular, the MEST-C score and degree of IgG, IgA, IgM, C3, C1q, C4d and C5b-9 stains will be obtained from pathology reports, if available, and documented. Any changes to medical history occurring between the Screening assessment and Day 1 will be updated prior to study drug administration. Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, urinalysis and ADA and CIC assessments. Vaccination records will also be checked for compliance with national/local guidelines for pneumococcal and Hib vaccinations.

6.1.1. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). A patient will be re-consented if rescreening occurs outside of the 90-day screening window. In this case, all screening procedures must be repeated.

6.1.2. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale is to be documented. Laboratory values can be retested once during Screening as long as the patient can be evaluated for eligibility and randomized within the allowed Screening period.

6.2. Run-in Period

During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): Hib and pneumococcal vaccinations (if required at screening per national/local guidelines; vaccination should occur prior to Week-2), vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine for proteinuria, and eGFR. Clinical laboratory tests will be performed centrally; however, hematuria and eGFR will also be assessed locally at the end of the run-in period (Week-2) to facilitate assessment of patient eligibility and administer meningococcal vaccination on the same day. Meningococcal

vaccines should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

Sites are encouraged to discuss study information with the patients again at the end of the run-in period.

6.3. Baseline Assessments (Treatment Period)

Prior to dosing on Day 1, patients will be reassessed for eligibility and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK, ADA and CIC.

In addition, prior to administration of study drug, the following assessments will be performed: full physical examination, body weight and height, vital signs, ECG, urine pregnancy test, eGFR assessment, and urinalysis.

Collection of blood and urine samples for PK analysis on Day 1 will be performed as outlined in Table 3.

6.4. Efficacy Assessments

6.4.1. Proteinuria

Primary efficacy will be assessed by determining the percent change from baseline in 24 hour proteinuria (g/24-hour) after 32 weeks of treatment. 24 hour urine samples for determination of proteinuria will be collected throughout the study as outlined in the Schedules of Assessments and will be analyzed by a central laboratory.

6.4.1.1. 24-Hour Urine Collection

Patients will be required to provide two separate valid 24-hour urine collections 2 weeks prior to randomization (to assess eligibility after the run-in period) and at Week 32 (to assess the primary endpoint). Patients will also be asked to provide a single valid 24-hour urine sample for other 24-hour urinary assessments outlined in the Schedule of Assessments. Rigorous exercise and significant change in diet (in particular salt intake) should be avoided within 48 hours before collection of 24-hour urine samples, whenever possible. The two valid 24-hour urine samples may be collected within 2 weeks before assessment is due while the one valid 24-hour urine sample may be collected within one week before the assessment takes place. If any of the collections do not meet validity criteria outlined below, then repeat collections must be scheduled within the time frames outlined above to assure the minimum number of valid collections required for each of the study time points. The duration of collection and volume of urine in the collection will be recorded in the eCRF. In addition to protein, albumin, sodium and creatinine will also be quantified in each of the 24-hour urine samples. Both protein/creatinine (UPCR) as well as albumin/creatinine ratios (UACR) will also be calculated in an aliquot of the 24-hour urine collection.

Completeness of the 24-hour urine collection can be estimated from rate of creatinine excretion. Normal values of creatinine excretion vary with age and body weight. An aliquot of the 24-hour urine collection will be used to determine urinary creatinine content to determine if the 24-hour

urine collections need to be repeated. Hence, a 24-hour urine collection will only be considered valid if all the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.
- The 24-hour creatinine content is within 25% of expected range as estimated by the following formula: [(140-age) x weight]/5000, where weight is in kilograms. This result is multiplied by 0.85 in women.[Ix 2011]
- In case of need of two valid samples, the maximum variation in total 24-hour urine creatinine between the two urine collections must be <25%.

Primary efficacy will be evaluated by comparing the percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 in patients treated with cemdisiran versus those treated with placebo.

Secondary and exploratory efficacy assessments include comparisons of the proportion of patients with partial or complete clinical remission, respectively, as measured by the amount of urine protein (UP) in a 24-hour urine sample. Partial clinical remission is defined as having UP <1 g/24-hours and complete clinical remission is defined as UP <0.3 g/24-hours. Each will be assessed at Week 32.

Additionally, using 24-hour samples, the change from baseline in the UP/creatinine ratio (UPCR) will be evaluated as a secondary endpoint and the change from baseline in urine albumin/creatinine ratio (UACR) at Week 32 as an exploratory endpoint.

6.4.1.2. Spot Urine Collection

Urinary protein, albumin and creatinine levels from spot urine collections prior to dosing will also be measured to assess the effect of cemdisiran on urinary protein/creatinine (UPCR) and albumin/creatinine (UACR) as outlined in the Schedule of Assessments.

The change from baseline in UPCR at Week 32 will be evaluated in spot urine samples. Spot urine samples will be collected at the time points outlined in the Schedule of Assessments (Table 1).

6.4.2. Hematuria

Hematuria from spot urine collections will also be evaluated to assess the effect of cemdisiran on disease course in patients with IgAN. The degree of hematuria will be assessed by examination of the spun urine sediment by microscopy (RBC/hpf). Single void collections for random urine sample for hematuria evaluation should be collected. If the investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated. Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the Schedule of Assessments and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to study drug administration, if applicable.

To allow evaluation of eligibility on the same day at the end of the run in period, 2 weeks prior to randomization, the single void can be split in two containers, one evaluated by local lab and

another by central lab. The local hematuria evaluation by microscopy or urinary dipstick will be utilized to determine eligibility for the study at the end of the run-in period.

6.4.3. Changes in Renal Function

Changes in renal function will be monitored using measurements of serum creatinine and eGFR (mL/min/1.73m^2) as outlined in the Schedule of Assessments. The calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for all patients. For assessment of eligibility at the last visit of run-in period, 2 weeks prior to randomization, local lab can be utilized. This will allow evaluation for eligibility on the same day. A sample will also be sent to central lab.
Renal function will also be estimated as creatinine clearance based on the 24-hour urine collection. The creatinine clearance is a widely used test to estimate the GFR using the following formula:
GFR = [UCr x V] / SCr
SCr is the serum creatinine concentration and the value assessed closest to collection of 24-hour urine collection will be utilized for purpose of above calculation. UCr is the urine creatinine concentration and V is the urine flow rate or volume.
Blood and urine samples for renal function assessments will be collected prior to administration of cemdisiran or placebo on dosing days, if applicable.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed for the first 32 weeks and the entire study period (including the OLE).

6.4.4. Markers of Complement Activation, Inflammation and Renal Injury

Samples for measurement of markers of complement activation, inflammation and renal injury will be collected at the time points outlined in the Schedule of Assessments (Table 1) and analyzed by central laboratories. On dosing days, blood samples will be collected predose.

6.5. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at the time points outlined in the Schedule of Assessments (Table 1). Samples will be collected prior to administration of cemdisiran or placebo on dosing days.

Analysis of PD will include the impact of cemdisiran administration on plasma C5 protein levels (assessed by a mass spectrometry-based method) and serum complement activity (assessed by CAP enzyme linked immunosorbent assay [ELISA] and CCP ELISA). Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

6.6. Pharmacokinetic Assessments

Blood samples and urine samples will be collected for assessment of cemdisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples and urine samples for PK analysis is in Table 3.

The concentration of cemdisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests, including assessment of IgG/IgM/IgA ADA and CIC. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.7.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected at predose and 4 hours postdose. On all other dosing days, vital signs will be collected predose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral method. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.7.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1 and Table 2; height at Screening only and dosing weight during the clinical study center visits) and will be recorded in the eCRF.

6.7.3. Physical Examination

Full physical examinations will be conducted according to the Schedule of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. On Day 1, routine physical examination will be performed at predose and 4 hours postdose. On all other dosing days, the routine physical examination will be performed predose.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Directed physical examinations will include examination of the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.7.4. Electrocardiogram

Twelve-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia-corrected QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. A single 12-lead ECG will be performed at Screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings approximately 1 minute apart. 12-lead ECGs will be performed at predose; 60 minutes postdose; and 4 hours postdose in relation to the Day 1 and Week 32 cemdisiran or placebo doses.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.7.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, hematuria and eGFR will also be assessed locally. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and include: hematology, serum chemistry and urinalysis parameters. Parameters will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. On dosing days blood samples will be collected predose.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the CKD-EPI formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.7.5.1)	
Antidrug antibodies	
Hepatic Tests (Screening Only)	
Hepatitis C, including: HCV RNA PCR – qualitative and quantitative assays	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Pregnancy Testing (Females of Child-bearing Potential Only) (see Section 6.7.5.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBsAg=hepatitis B virus surface antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG= IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid.

6.7.5.1. Immunogenicity

Blood samples will be collected to evaluate ADA and CIC. IgG/IgM/IgA ADA to total drug will be assessed at screening and during the study. ADA samples will be tested in real time. Clinical study decision will be based on confirmed positive ADA results from the IgG/IgM/IgA assay. Confirmed positive ADA samples will be further characterized for cemdisiran domain specificity against the Tri-GalNAc component if a reliable method is established. Blood samples for ADA and CIC testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1 and Table 2). Blood samples to evaluate ADAs will be collected at Screening to assess study eligibility and at the Early Termination (ET) visit, if applicable. ADA and CIC will be routinely monitored during the treatment period and throughout the open-label extension phase and safety follow up, as indicated in the Schedule of Assessments. Finally, ADA and CIC samples will also be collected and analyses will be performed and prioritized if any clinical evidence of progression of IgAN disease and/or relevant safety findings. Patients who are confirmed positive for IgG/IgM/IgA ADA at baseline will be excluded from study treatment. In addition, patients who develop de novo ADAs will be discontinued from study drug but will be followed until EOS visit and during safety follow up. These patients will also be monitored until ADA levels return to baseline.

Exploratory analysis of Gd-IgA1 levels and IgA-containing immune complexes may be conducted; blood samples for these analyses will be drawn when CIC samples are collected to enable these assays.

For US patients only, an optional blood sample may be collected at screening to evaluate any potential for B-cell stimulation by cemdisiran, at the Sponsor's discretion.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.7.6.7 for follow-up instructions).

6.7.5.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any liver function test (LFT) abnormalities. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one

time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 5, and other assessments or evaluations per Investigator discretion, as appropriate.

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2a	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

[a] HIV testing will not be performed where prohibited by local regulations.

6.7.6. Adverse Events

6.7.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational

subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

Based on the biological target and the available nonclinical and clinical data, AEs of Clinical Interest (AECI) for this study are:

- Severe infections as judged by the investigator
- ALT or AST >3×ULN
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of cemdisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR.

For information on recording and reporting of AECIs, see Section 6.7.6.2 and Section 6.7.6.3 , respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.7.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording all SAEs and only AEs related to study procedures that are observed or reported by the patient during the run-in period (before the administration of the first dose of study drug) regardless of their relationship to study drug through the end of study. Events occurring after signing of the ICF and before study drug administration will be

captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.7.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AECIs (Section 6.7.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.7.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Investigator Site File.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.7.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.7.6.4.

6.7.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with IgAN, as well as their responses to treatment.

To permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of cemdisiran, a set of biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2).

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, the samples will be collected as part of this study. Examples of potential exploratory investigations would include DNA, RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Approximately 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study. This is based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of 27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, approximately 30 patients are planned to be randomized stratified by baseline urine protein levels (≥ 1g/24h and <2g/24h versus >=2g/24h).

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The primary population used to evaluate efficacy will be the mITT Population. Sensitivity analyses for efficacy will be performed using the Per Protocol Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the mITT and Safety Analysis Set.

Baseline value for proteinuria will be calculated as the average of two valid 24-hour urine protein levels before randomization.

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The 24-hour urine protein will be log transformed for analyses. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval will be estimated and then back transformed to original scale. In the end the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and its 90% confidence interval will be presented.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

7.2.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in 24-hour urine at Week 32, change from baseline in urine protein/creatinine ratio (UPCR) as measured in a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in urine protein / creatinine ratio (UPCR) will be analyzed similarly to the analysis of the primary variable as appropriate. UPCR will be log transformed first before analysis.

7.2.5.3. Exploratory Endpoints

Change from baseline in exploratory efficacy variables will be summarized. Percent of patients in full clinical remission and incidence of ADA will be tabulated by treatments. Inferential statistics for exploratory efficacy variables may be presented as needed. Details will be described in the SAP.

The slope of eGFR for the first 32 weeks will be estimated for each subject with the linear regression method using all assessment data during the period.

Descriptive statistics including the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum values will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

7.2.6. Pharmacodynamic Analysis

Assessment of the PD effect of the treatment will be performed descriptively, including plotting graphically levels of serum C5 protein and CAP/CCP over time and relative to baseline levels. Inferential statistics maybe generated as deemed necessary.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. Pharmacokinetic parameters include, but will not be limited to: AUC, C_{max}, T_{max}, T½, CL/F, V/F, cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe) in the urine of cemdisiran (25-mer) and 23-mer.

Other parameters may be calculated, if deemed necessary. Summary statistics and figures will be presented. Inferential statistics may be generated when deemed necessary.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized by dose level and overall.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary. All SAEs occurring before the first dose of study drug and AEs related to study procedures will be listed. The number and percentage of patients experiencing AEs after the first dose of the study drug or events that worsened in severity after dosing will be summarized. AEs will be presented by maximum severity and relationship to study medication. SAEs and AEs leading to discontinuation of treatment will also be tabulated.

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation.

Frequency of adverse events of clinical interest will also be summarized and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory

shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

All safety analyses will be conducted using the Safety Analysis Set.

7.2.9. Immunogenicity Analyses

Antidrug antibody and CIC results will be summarized descriptively.

7.2.10. Biomarker Analyses

Urine and serum complement activation products, inflammation and renal injury markers will be summarized descriptively.

7.2.11. Interim Analysis

No formal interim analysis is planned.

7.2.12. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.7.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the

decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee, immediately if contacted by a regulatory agency or an IRB/IEC about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 18 months after completion of the study at all centers. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at

least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Ashwell G,Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Advances in Enzymology and Related Areas of Molecular Biology, Volume 41. 2006:99-128.

Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney international. 2009;76(5):534-45.

Coppo R,D'amico G. Factors predicting progression of IgA nephropathies. Journal of nephrology. 2005;18(5):503-12.

Crew PE, Abara WE, McCulley L, Waldron PE, Kirkcaldy RD, Weston EJ, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. Clinical Infectious Diseases. 2018.

Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC,Bersoff-Matcha SJ. Unusual Neisseria species as a cause of infection in patients taking eculizumab. Journal of Infection. 2018.

Cugno M, Gualtierotti R, Possenti I, Testa S, Tel F, Griffini S, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. Journal of Thrombosis and Haemostasis. 2014;12(9):1440-8.

Elbashir SM, Lendeckel W,Tuschl T. RNA interference is mediated by 21-and 22-nucleotide RNAs. Genes & development. 2001;15(2):188-200.

Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clinical journal of the American Society of Nephrology. 2007;2(6):1360-6.

Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clinical journal of the American Society of Nephrology. 2011;6(1):184-91.

Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nature genetics. 2014;46(11):1187.

Knoop T, Vikse BE, Mwakimonga A, Leh S,Bjørneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology Dialysis Transplantation. 2017;32(11):1841-50.

Knoppova B, Reily C, Maillard N, Rizk DV, Moldoveanu Z, Mestecky J, et al. The origin and activities of IgA1-containing immune complexes in IgA nephropathy. Frontiers in immunology. 2016;7:117.

Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. Journal of the American Society of Nephrology. 2016:ASN. 2016060640.

Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nature Reviews Disease Primers. 2016;2:16001.

Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy. Jama. 2017;318(5):432.

Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current understanding of the role of complement in IgA nephropathy. Journal of the American Society of Nephrology. 2015;26(7):1503-12.

McQuillen DP,Ram S. No good deed goes unpunished: eculizumab and invasive neisserial infections. Clinical Infectious Diseases. 2018.

Medjeral-Thomas NR, Troldborg A, Constantinou N, Lomax-Browne HJ, Hansen AG, Willicombe M, et al. Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H Related Protein-5 (FHR5) Deposition. Kidney international reports. 2018;3(2):426-38.

Mestecky J, Novak J, Moldoveanu Z,Raska M. IgA nephropathy enigma. Clinical Immunology. 2016;172:72-7.

Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochemical Journal. 1989;264(1):1.

Novak J, Barratt J, Julian BA,Renfrow MB, editors. Aberrant Glycosylation of the IgA1 Molecule in IgA Nephropathy. Seminars in nephrology; 2018: Elsevier.

Ram S, Lewis LA,Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clinical microbiology reviews. 2010;23(4):740-80.

Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. New England Journal of Medicine. 2015;373(23):2225-36.

Reich HN, Troyanov S, Scholey JW,Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. Journal of the American Society of Nephrology. 2007;18(12):3177-83.

Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney international. 2009;76(5):546-56.

Ross SC,Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine. 1984;63(5):243-73.

Rosse WF. Variations in the red cells in paroxysmal nocturnal haemoglobinuria. British journal of haematology. 1973;24(3):327-42.

Sarcina C, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, et al. Changes in proteinuria and side effects of corticosteroids alone or in combination with azathioprine at different stages of IgA nephropathy. Clinical journal of the American Society of Nephrology. 2016;11(6):973-81.

Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004;432(7014):173-8.

Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. The Journal of clinical investigation. 2009;119(6):1668-77.

Woo K-T, Chan C-M, Chin YM, Choong H-L, Tan H-K, Foo M, et al. Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades. Nephron Clinical practice. 2010;116(4):c337-c46.

Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. Journal of the American Society of Nephrology. 1998;9(5):853-8.

Zimmermann TS, Lee AC, Akinc A, Bramlage B, Bumcrot D, Fedoruk MN, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006;441(7089):111-4.

10. APPENDICES

None.

ALN-CC5-005 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 26 NOVEMBER 2018

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Rationale for Protocol Amendment

The main purpose of this protocol amendment is to incorporate changes requested by a Health Authority. The primary changes pertain to safety monitoring and risk mitigation measures within the protocol to address two risks possibly associated with cemdisiran treatment of the target patient population: 1) the theoretical risk of increased production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy associated with exposure to the N-Acetylgalactosamine (GalNAc) moiety of cemdisiran, and 2) an increase in susceptibility to encapsulated bacterial infections other than Neisserial infections.

An overview of the changes made to this protocol in response to Health Authority feedback includes:

- Exclusion of patients with confirmed pre-existing IgG/IgM/IgA anti-drug antibodies (ADA) to cemdisiran at screening
- Discontinuation of dosing in patients who develop de novo confirmed IgG/IgM/IgA ADA
- Collection of an additional blood sample for ADA testing 4 weeks after the last dose of treatment (Week 36) for any subject who does not continue in the open-label extension period.
- Inclusion of the theoretical risk of other types of infections, particularly those due to encapsulated bacteria, and measures to mitigate this risk including vaccination, according to national/local guidelines.

Additional changes have also been made based on the results of feasibility assessments and to improve clarity.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 1 Detailed Summary of Changes

The primary sections of the protocol affected by the changes in Protocol Amendment 1 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Updated to include the theoretical risk of increased production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy associated with exposure to the GalNAc moiety of cemdisiran

The primary change occurs in Section 1.1, Disease Overview

Formerly read: While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly glycosylated IgA1 and the development of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule.

Now reads: While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly **O-**glycosylated IgA1 **(Gd-IgA1)** and the ~~development~~ **presence** of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule, **resulting in the formation of pathogenic immune complexes. Some of these circulating complexes may deposit in glomeruli and induce renal injury.[Knoppova 2016] The lack of galactose exposes O-linked monosaccharide N-acetylgalactosamine (O-GalNAc) moeities in the hinge region of IgA1.[Novak 2018] While the binding of autoantibodies to Gd-IgA1 is dependent on the presence of multiple O-GalNAc residues, the IgA1 protein backbone and the spatial arrangement of O-GalNAc moieties are also thought to play a role in the specificity of autoantibodies to Gd-IgA1.[Mestecky 2016; Suzuki 2009]**

Sections also changed include:

- Section 1.5 (Benefit-Risk Assessment)
    - **Considering anti-glycan autoantibodies recognizing Gd-IgA1 are implicated in the pathogenesis of IgA nephropathy, exposure to the GalNAc moiety of cemdisiran may pose a theoretical risk of stimulating the production of pathogenic autoantibodies and immune complexes in patients with IgA nephropathy. This could presumably occur when antidrug antibodies (ADAs) to cemdisiran's triantennary GalNAc (Tri-GalNAc) cross-react with Gd IgA1. The risk of developing these cross-reactive antibodies is likely low. This is based on the low incidence of ADA to cemdisiran in study ALN-CC5-001 (see Section 1.2) and the distinct difference in structure of the O GalNAc moieties on a Gd IgA1 glycoprotein and the Tri-GalNAc moiety in cemdisran. This low risk is further mitigated by excluding patients with confirmed pre-existing IgG/IgM/IgA ADAs to total drug and real time monitoring for development of de novo IgG/IgM/IgA ADAs after dosing with cemdisiran. Patients with confirmed de novo ADAs will be discontinued from study drug but will continue to be monitored until EOS visit and subsequent safety follow up. Patients who develop positive ADA will be followed until ADA titers return to baseline. Additional ADA samples will also be collected if any clinical evidence of progression of IgAN disease and/or relevant safety findings.**
- Section 1.2 (Cemdisiran): Updated to include the results of ADA analyses in Study ALN-CC5-001
    - **In Study ALN-CC5-001, the frequency of ADA was low. Two of 48 healthy volunteers (1 cemdisiran-treated and 1 placebo-treated) were ADA positive during the study. The cemdisiran-treated volunteer had transient ADA positivity, with a negative result later in the study and no impact on PK or PD. The placebo-treated volunteer was ADA positive at baseline (predose) and remained positive through Day 70.**
- Section 3.7 (Data Monitoring Committee): Updated to include mitigation measures for the risk of autoantibody development
    - An independent DMC will perform regular reviews of safety**,** tolerability**, and immunogenicity** data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a Charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of **unblinded** data **(safety, tolerability, PK, pharmacodynamics (PD), ADA, CIC and efficacy of cemdisiran)** during the clinical trial, and on an ad hoc basis review emergent safety data. Details are provided in the DMC Charter.
- Schedule of Assessments:
    - Added more time points for blood sample collection for the analysis of ADAs (Table 1 and Table 2)
        - "**X**" was added to "**Blood** Sample for Antidrug Antibodies" at the Screening visit, Week 36 and Safety Follow up visits at Weeks 49, 62, 75, 88 (Table 1); and Weeks 97, 110, 123, 136 (Table 2)
    - Added time points for blood sample collection for the analysis of CIC (Table 1)
        - A new row was added for the collection of blood samples for circulating immune complexes at all timepoints where ADA samples are collected. During the Treatment Period (Table 1), "**X**" was added at the Screening visit, Day 1 and at Weeks 4, ~~8,~~ 12, 24 and 32.

  - Added a time point for an optional blood sample collection for B-cell function analysis (Table 1)
    - A new row was added for an optional collection of blood samples for B-cell function analysis. During the Treatment Period (Table 1), "**X**" was added at the Screening visit.

- Section 4.2 (Exclusion Criteria): Updated to include a risk mitigation measure for ADA (excluding patients with confirmed positive IgG/IgM/IgA ADA at screening)
  - New Criterion 7: **Confirmed positive IgG/IgM/IgA ADAs to cemdisiran at Screening**
- Sections 6.1, 6.3 and 6.7: Updated to include the assessment of ADA and/or CIC.
  - Section 6.1 (Screening Assessments)
    - Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, ~~and~~ urinalysis **and ADA and CIC assessments**.
  - Section 6.3 (Baseline Assessments – Treatment Period)
    - Prior to dosing on Day 1, patients will be reassessed for eligibility and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK, ADA and ~~ADA.~~**CIC**.
  - Section 6.7 (Safety Assessments)
    - The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests, **including assessment of IgG/IgM/IgA ADA and CIC**.
- Sections 6.7.5.1 and 7.2.9: Updated to clarify immunogenicity testing and analyses
  - Section 6.7.5.1 (Immunogenicity)
    - Blood samples will be collected to evaluate ADA~~. Blood samples for antidrug antibody~~ **and CIC. IgG/IgM/IgA ADA to total drug will be assessed at screening and during the study. ADA samples will be tested in real time. Clinical study decision will be based on confirmed positive ADA results from the IgG/IgM/IgA assay. Confirmed positive ADA samples will be further characterized for cemdisiran domain specificity against the Tri-GalNAc component if a reliable method is established. Blood samples for ADA and CIC** testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1 and Table 2). ~~A blood sample~~**Blood samples** to evaluate ~~antidrug antibodies~~**ADAs** will be collected **at Screening to assess study eligibility and** at the Early Termination **(ET)** visit, if applicable. **ADA and CIC will be routinely monitored during the treatment period and throughout the open-label extension phase and safety follow up, as indicated in the Schedule of Assessments. Finally, ADA and CIC samples will also be collected and analyses will be performed and prioritized if any clinical evidence of progression of IgAN disease and/or relevant safety findings. Patients who are confirmed positive for IgG/IgM/IgA**

ADA at baseline will be excluded from study treatment. In addition, patients who develop de novo ADAs will be discontinued from study drug but will be followed until EOS visit and during safety follow up. These patients will also be monitored until ADA levels return to baseline.
Exploratory analysis of Gd-IgA1 levels and IgA-containing immune complexes may be conducted; blood samples for these analyses will be drawn when CIC samples are collected to enable these assays.
For US patients only, an optional blood sample may be collected at screening to evaluate any potential for B-cell stimulation by cemdisiran, at the Sponsor's discretion.

- Section 7.2.9 (Immunogenicity Analyses)
  - Antidrug antibody **and CIC** results will be summarized descriptively.

Purpose: Updated the benefit risk section in recognition of an increase in susceptibility to infections by encapsulated bacteria other than N. meninigitidis

The primary change occurs in Section 1.5, Benefit-Risk Assessment

Added text:

Given the biological target of cemdisiran, the available nonclinical and clinical data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities and injection site reactions (ISRs). ~~Since~~ C5 inhibition is associated with increased susceptibility for Neisserial infections **(including disseminated gonococcal infections) and the potential risk of other infections, particularly those due to encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), as well as Aspergillus in immunocompromised and neutropenic patients. Therefore**, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine are required. Patients will be instructed to contact study site if any early signs of meningococcal infections are experienced. **In addition, patients with functional or anatomic asplenia will be excluded and only patients previously vaccinated or who agree to receive vaccination for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines, at screening, will be enrolled. Investigators in Study ALN-CC5-005 should educate patients on the risk of disseminated gonococcal infection and encourage safe sex practices. All national/local screening recommendations for gonorrhea in the general population should also be followed. Finally, given the reported evidence of a higher risk of disseminated gonococcal infections with treatment with eculizumab, Investigators are encouraged to evaluate any patient who has a *Neisseria gonorrhoeae* infection for the signs and symptoms of disseminated infection.[Crew 2018; McQuillen 2018] No cases of Neisserial infection or other infections due to encapsulated bacteria were observed in healthy volunteers or in patients with PNH (Study ALN CC5-001).**

Other sections changed include:

- Section 1.2 (Cemdisiran)
    - Added text: The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities**, other than an increased susceptibility to Neisserial infections**, in subjects with known genetic C5 deficiencies.[Ross 1984] Subjects with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. **These infections include invasive meningococcal disease, disseminated gonococcal infections as well as diseases caused by typically commensal Neisseria species.[Crew 2018; Crew 2018; McQuillen 2018; Ram 2010]**
- Schedule of Assessments (Table 1)
    - *Purpose: Updated to include a vaccination record check for pneumococcal and Hib vaccines*
        - Added text: A new row was added "**Review Routine Vaccination Status**" at the Screening visit (D-112±7).
    - *Purpose: Updated to include pneumococcal and Hib vaccination, if required per local guidance, for patients who have not been previously vaccinated*

- Added text: A new row was added "**Pneumococcal and Haemophilus influenzae type b (Hib) vaccination, if not previously vaccinated and required per local guidance.**" "**X**" was added in the Schedule of Assessments (Table 1) for the procedure to occur between D-112 and Day-56

- Section 4 (Selection and Withdrawal of Patients)
  - Section 4.1 (Inclusion Criteria)
    - New Criterion 8: **Previously vaccinated or willingness to receive vaccinations for Hib and *Streptococcus pneumoniae* according to current national/local vaccination guidelines for vaccination use**
      - Other section including change is the Synopsis (Diagnosis and Main Eligibility Criteria)
  - Section 4.2 (Exclusion Criteria)
    - Criterion 19: Unable to take antibiotics for meninigococcal prophylaxis, **if required by local standard of care**
    - Criterion 23: Patients with systemic bacterial or fungal infections~~, as demonstrated by a positive culture result,~~ that require systemic treatment with antibiotics or antifungals
    - New Criterion 24: **Patients with functional or anatomic asplenia**
- Section 5.3.2.2
  - *Purpose: Included a new section on pneumoccal and Hib vaccinations (Section 5.3.2.2)*
    - Added text: **Section 5.3.2.2 Pneumococcal and Hib Vaccinations**
      - **Patients will receive vaccinations for Hib and *Streptococcus pneumoniae*, if not previously vaccinated, according to current national/local vaccination guidelines for vaccination use. Hib and pneumococcal vaccinations (if required at screening per national/local guidelines; vaccination should occur prior to Week-2. At screening, patient vaccination records will be checked for compliance with local recommendations for the use of these vaccines.**
- Section 6.1 (Screening Assessments)
  - Added text: **Vaccination records will also be checked for compliance with national/local guidelines for pneumococcal and Hib vaccinations**.
- Section 6.2 (Run-in Period)
  - Added text:
    - During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): **Hib and pneumococcal vaccination (if required at screening per national/local guidelines; vaccination should occur prior to Week-2)**, vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine for proteinuria, and eGFR.

- Clinical laboratory tests will be performed centrally; however, hematuria and eGFR will also be assessed locally at the end of the run-in period (**Week-2**) to facilitate assessment of patient eligibility and administer **meningococcal** vaccination on the same day. ~~During this period, patients will begin the recommended meningitis vaccination regimen if eligible for the study. Vaccines~~ **Meningococcal vaccines** should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

Purpose: Updated the number of clinical study centers

The primary change occurs in the Synopsis

Added text: The study will be conducted at approximately 30**-40** clinical study centers worldwide

Purpose: Updated to improve clarity

The primary change occurs in the Synopsis (Diagnosis and Main Eligibility Criteria)

Added text: Eligible patients must have **urine protein levels of ≥1g/24-hour at screening and** mean urine protein ≥ 1g/24 hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization.

Purpose: Updated the Schedule of Assessments (Table 1) to include safety follow up visits for patients who do not enter the OLE phase, for clarification

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods [Screening through Week 36])

Added columns for visit Weeks 49, 62, 75 and 88. "**X**" has been added against all assessments planned to be conducted during safety follow-up consistent with Table 2. Previously, safety follow up assessments were only provided in Table 2.

Purpose: Added a row for "Optional Home Visit" in the Schedule of Assessments (Table 1)

The primary change occurs in Table 1 (Schedule of Assessments – Run-in and Treatment Periods [Screening through Week 36])

Added text: A new row was added for "Optional Home Visit" during safety follow-up for patients who do not enter the OLE phase. "**X**" was added at Weeks 49 and 75.

Purpose: Corrected the note on "Optional Home Visit" in the Schedule of Assessments (Table 2) to reflect that cemdisiran is not administered during safety follow-up

The primary change occurs in Table 2 (Schedule of Assessments – Open-Label Extension Period) – Optional home visit

Added text: Will be arranged for cemdisiran administration in between 8-weekly study site visits at Weeks 44, 52, 60, 68 **and** 76~~, 97 and 123~~ during the extension phase**, and where feasible, during safety follow up at Weeks 97 and 123,** unless patients are required to visit the study center as judged necessary by the Investigator.

Purpose: Corrected one footnote in Table 3 (Pharmacokinetic Time Points) to align with the timing of pooled urine in the table

The primary change occurs in Table 3 footnote b

Added text: The pooled urine ~~8~~**6**-12 hours and 12-24 hours can be collected as outpatient.

Purpose: Corrected the start visit for the OLE period of the study to align with the schedule of assessments

The primary change occurs in Section 3.1 (Study Design)

Added text: The first study drug administration of the OLE will be administered at Week ~~32~~**36**. Patients will return to the study center at Week~~s~~ ~~36~~**40** and every 8 weeks thereafter during the OLE.

Other section including the change is the Synopsis (Study Design)

Purpose: For patients who do not consent to participate in the OLE period, added Week 36 as the EOS visit instead of a joint EOT and EOS visit at Week 32

The primary change occurs in Section 3.1 (Study Design)

Added text: Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/ET visit (regardless if EOS/**ET** visit is at Week **36** or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at ~~visit~~ 13 and 39 weeks after the EOS visit (**regardless if EOS/ET visit is at Week 36 or Week 84**)~~Weeks 97 (13 weeks after the EOS visit) and 123 (39 weeks after the EOS visit)~~.

Other sections changed include:

- Synopsis (Study Design; see also Figure 1)
- Schedule of Assessments (Table 1)
- Section 3.3 (Duration of Study) including corresponding section in the Synopsis
  - ~~o~~ The maximum estimated total time on study, inclusive of Screening (maximum of 90 days), run-in period (14 weeks), treatment period (~~32~~**36** weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is ~~up to~~ approximately 36 months or 3.0 years.
  - ~~o~~ A patient is considered to have reached the end of the study if the patient has completed the EOS ~~(Week 84)~~ visit ~~or the~~ **(**Week ~~32~~ **36** for those patients who do not consent to continue to participate in the study in the OLE period **and Week 84 for patients who enter the OLE period**). Upon study completion (regardless if EOS visit is at Week ~~32~~ **36** or Week 84) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.
- Section 3.6 (Blinding)
- Section 4.3.1
- Section 4.3.2.1

Purpose: Clarified the end of treatment (EOT), end of study (EOS) and early termination (ET) visit for patients who only consent to participate in the treatment period of the study (EOT/EOS/ET) versus those who consent to continue in the OLE period (OLE EOT/EOS/ET)

The primary change occurs in Section 3.1 (Study Design)

Added text: An end of treatment (EOT) visit will occur at Week 80 **(OLE EOT**) and an end of study (EOS) **or early termination** (**ET**) visit will be completed at Week 84 (**OLE EOS/ET**). For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the **EOS/ET** visit will be at Week ~~32~~ **36**.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS/**ET** visit (regardless if EOS/**ET** visit is at Week ~~32~~ **36** or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at ~~visit Weeks 97 (13 weeks after the EOS visit)~~ 13 and ~~123~~ 39 weeks after the **EOS/ET** visit (regardless if **EOS/ET** visit is at Week 36 or Week 84).

Other sections changed include:

- Synopsis (Study Design)
- Schedule of Assessments (Table 1 and Table 2)
- Section 3.3.1
- Section 4.3.1

Purpose: Updated to include blinding of data management CRO

The primary change occurs in Section 3.6 (Blinding)

Added text: All site personnel including sponsor delegated clinical research associates**, data management CRO** and patients will be blinded to study drug treatment during the efficacy period (up to Week **36)**.

Purpose: Updated to remove direct renin-inhibitors from the list of allowed standard of care and include another method of assessment for hematuria.

The primary changes occur in Section 4 (Selection and Withdrawal of Patients)

Added text:

Inclusion Criteria (Section 4.1)

- Criterion 3: Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB ~~or a direct renin inhibitor~~ for at least 3 months prior to start of run-in period
    - This change also occurs in the Synopsis (Diagnosis and Main Eligibility Criteria)
- Criterion 5: Hematuria **as defined by** ≥10 RBCs per high powered field (RBC/hpf) at screening **and either ≥10 RBC/hpf or a positive urinary dipstick (1+ and above)** at the end of the run-in period, prior to randomization (local result accepted for assessment of eligibility at the end of the run-in period)
    - This change also occurs in the Synopsis (Diagnosis and Main Eligibility Criteria) and in Section 1.3 (Study Design Rationale)

Other section including the update in the method of assessment of hematuria is Section 6.4.2

Added text: The local hematuria evaluation **by microscopy or urinary dipstick** will be utilized to determine eligibility for **the** study **at the end of the end of the run-in period**.

Purpose: Corrected information on study discontinuation

The primary change occurs in Section 4.3.1 (Discontinuation of Study Drug or Declining Procedural Assessments)

Added text:

Reasons for discontinuation of study drug include any of the following:

- Other reason (non-adverse event), **including confirmed positive test for ADA to cemdisiran**

Deleted text: ~~The Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient~~.

Purpose: Updated for clarification

The primary change occurs in Section 5.3.1 (Prohibited Concomitant Medications)

Added text:

- Fish oil supplements **(if started prior to screening, then may continue during the study at the same dose)**

Purpose: Updated to clarify the timing of meningococcal vaccination and its administration based on local recommendations

The primary change occurs in Section **5.3.2.1**

Added text:

Section 5.3.2.1 (Meningococcal Vaccinations)

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, upon determination of eligibility at the end of run-in period, **2 weeks prior to administering cemdisiran**, as per the Schedule of Assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions **and according to the Advisory Committee on Immunization Practices (ACIP) or other locally applicable recommendations for patients with complement deficiencies**. On days of vaccination, urinary samples should be collected prior to administration of vaccines.

- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines if found eligible at the end of the run-in period. ~~Patients who complete the vaccination series after starting cemdisiran will receive prophylactic antibiotics according to local standard of care for at least 2 weeks after completing the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) or longer, if required by local standard of care.~~
- ~~Patients who either completed the recommended series of meningococcal vaccines less than 14 days from initiation of treatment with cemdisiran or those who have an incomplete meningococcal vaccination series will receive prophylactic antibiotic treatment according to local standard of care for at least 2 weeks after completing the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) or longer, if required by local standard of care~~.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the Schedule of Assessments if determined to be eligible for the study at the end of the run-in period. ~~Patients who complete the vaccine series after receiving cemdisiran will receive prophylactic antibiotics according to the local standard of care for at least 2 weeks after completing the recommended series of meningococcal vaccinations or longer, if required by local standard of care~~.
- **If required locally, patients will receive prophylactic antibiotics according to the local standard of care after randomization to cemdisiran or placebo**.

Purpose: Updated to reflect the use of highly effective methods of contraception in line with European Guidance (Clinical Trial Facilitation Group, 'Recommendations related to contraception and pregnancy testing in clinical trials'; September 2014).

The primary change occurs in Section 5.5.1

Added text: Females of child-bearing potential must be willing to use ~~acceptable methods~~ **a highly effective method** of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration **or until study completion**.

Birth control methods which are considered ~~acceptable~~ **highly effective** include:

- Established use of oral (**except low-dose gestagens**), implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- ~~If hormonal methods of contraception are medically contraindicated due to their underlying disease, a double barrier method (combination of male condom with cap, diaphragm, or sponge, in conjunction with spermicide) is also considered an acceptable method of contraception.~~

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

For male patients, no contraception is required. However, use by males of contraception (condom) may be required in some countries e.g. France, in order to comply with local requirements as described in the corresponding patient consent forms.

Purpose: Corrected to reflect start of antibiotic prophylaxis after the start of cemdisiran treatment, if required per local guidance

The primary change occurs in Section 5.5.3

Added text: Patients who require prophylactic antibiotics ~~following study specific vaccinations~~**after randomization to cemdisiran or placebo** (see Section **5.3.2.1**) per local standard of care will undergo antibiotic compliance checks.

Purpose:Added text (previously included in Table 1) encouraging sites to re-discuss study information at the end of the run-in period

The primary change occurs in Sections 6.2 (Run-in Period)

Added text: **Sites are encouraged to discuss study information with the patients again at the end of the run-in period.**

Purpose: Clarified change from baseline in urine albumin/creatinine ratio (UACR) at Week 32 as an exploratory endpoint in line with Section 2

The primary change occurs in Sections 6.4.1.1

Added text: Additional**ly** ~~secondary endpoints that will be evaluated~~ using 24-hour samples ~~include~~ the change from baseline in the UP/creatinine ratio (UPCR) **will be evaluated as a secondary** endpoint and the change from baseline in the **urine** ~~UP/albumin~~ **albumin/creatinine** ratio (UACR) at Week 32 **as an exploratory endpoint**.

Purpose: Updated to clarify study treatment

The primary change occurs in Section 6.4.3

Added text: Blood and urine samples for renal function assessments will be collected prior to administration of cemdisiran **or placebo** on dosing days, if applicable.

Other sections changed include: Section 6.5 and Section 6.7.4

Purpose: Moved text from the notes section in the Schedule of Assessments to the relevant section in the body of the protocol

The primary change occurs in Section 6.2 (Run-in Period) and Section 6.7.5 (Clinical Laboratory Assessments)

Added text:

Section6.2: **Sites are encouraged to discuss study information with the patients again at the end of the run-in period.**

Section 6.7.5: Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional. **On dosing days blood samples will be collected predose**.

Purpose: Updated to clarify the sample size and stratification by baseline proteinuria

The primary change occurs in Section 7.1

Added text: ~~Thirty~~**Approximately** 30 patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study.

To account for potential dropouts, **approximately** 30 patients are planned to be randomized **stratified by baseline urine protein levels (≥ 1g/24h and <2g/24h versus >=2g/24h)**.

Other sections including the change are:

- Synopsis
- Section 3.1
- Section 3.4

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-CC5-005

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy
Short Title:	A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy
Study Drug:	Cemdisiran (ALN-CC5)
EudraCT Number:	2018-002716-27
IND Number:	140087
Protocol Date:	Original protocol 10 September 2018
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

[redacted]

11 Sept 2018

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-CC5-005 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I 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 SYNOPSIS

Protocol Title

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Short Title

A Phase 2 Study of Cemdisiran in Adult Patients with IgA Nephropathy

Study Drug

Cemdisiran (ALN-CC5)

Phase

Phase 2

Study Center(s)

The study will be conducted at approximately 30 clinical study centers worldwide.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 32 weeks using all assessments during the period

• To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal half-life (t1/2), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, Cmax, Tmax, t1/2, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. The standard of care is expected

to remain unchanged during this run-in period. Patients will not receive study drug (cemdisiran or placebo) during this time. The second study period is a 32-week treatment period which will evaluate the efficacy and safety of subcutaneous (SC) cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains >1 g/24-hours within 2 weeks of the end of the run-in period, who continue to have hematuria, and who meet blood pressure and estimated glomerular filtration rate (eGFR) criteria will be eligible to enroll in the 32-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Thirty patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of the treatment period at Week 32.

At the end of the treatment period (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 32. Patients will return to the study center at Weeks 36, 40, and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 and an end of study (EOS) visit will be completed at Week 84. For patients who complete the treatment period only and who do not consent to continue to participate in the study in the OLE period, the EOS will be at Week 32.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS visit (regardless if EOS visit is at Week 32 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at visit Weeks 97 (13 weeks after the EOS visit) and 123 (39 weeks after the EOS visit).

Regular reviews of safety and tolerability data will be performed by a Data Monitoring Committee (DMC) throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

Number of Planned Patients
Thirty patients are planned for randomization in this study.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years and ≤ 65 years of age) with a clinical diagnosis of primary immunoglobulin A (IgA) Nephropathy based on historical biopsy collected within 60 months of Screening, treated for IgA Nephropathy with stable, optimal pharmacological therapy including maximum allowed or tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) or a direct renin-inhibitor for at least 3 months prior to the start of the run-in period. Eligible patients must have mean urine protein ≥ 1g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization. In addition, eligible patients must have hematuria ≥ 10 red blood cells per high powered field (RBC/hpf) at screening and at the end of the run-in period, 2 weeks prior to randomization. Eligible patients are required to have been previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or be willing to receive these vaccinations as well as prophylactic antibiotic treatment if required.

Patients will be excluded from the study if eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization; treated with systemic steroids at dosages exceeding 20 mg prednisone-equivalent for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization; have a diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase; sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period measured in supine position after 10 minutes of rest; have received organ transplant (including hematologic transplant) or have secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease).

Study Drug, Dose, and Mode of Administration

Cemdisiran is a synthetic small interfering RNA (siRNA) targeting complement component 5 (C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand. Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. Doses of 600 mg of cemdisiran will be administered every 4 weeks during the 32-week treatment phase and the optional OLE period.

Placebo (normal saline 0.9% for SC administration) will be packaged and administered identically to cemdisiran.

Reference Treatment, Dose, and Mode of Administration

Angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB) or direct renin inhibitors per physician and manufacturer‘s instructions.

Duration of Treatment and Study

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive SC doses of cemdisiran for a further 52 weeks in the the optional OLE. The estimated total time on study, inclusive of Screening (90 days), run-in period (14 weeks), treatment period (32 weeks), extension period (52 weeks) and safety follow-up (52 weeks), for patients is up to approximately 36 months or 3.0 years.

Statistical Methods

Thirty patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of

27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran – placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, 30 patients are planned to be randomized.

The modified Intent-to-treat (mITT) population will include all patients who receive any amount of study drug and have at least one post baseline 24-hour proteinuria assessment. Patients will be grouped by assigned treatments (ie, as randomized). The Safety Analysis Set will include all patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm. Patients in the Safety Analysis Set will be grouped by treatment received. PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration. PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

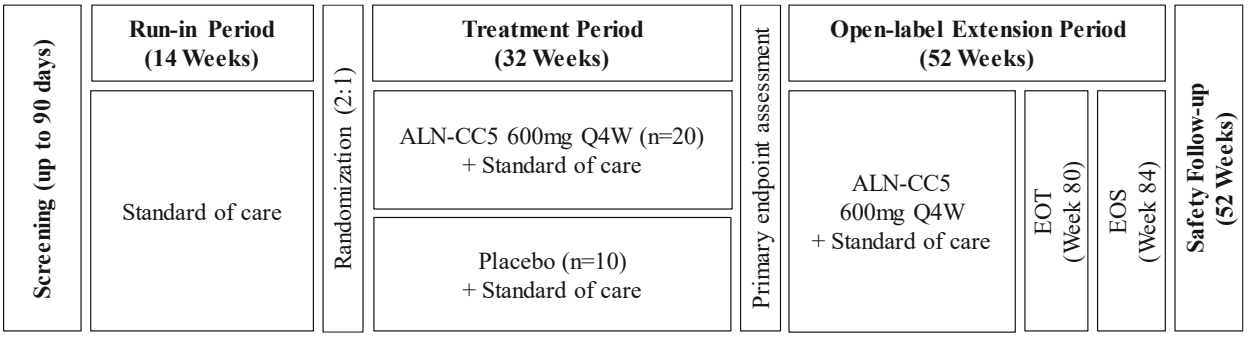
The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval (CI) will be estimated and then back transformed to original scale. In the end, the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and 90% CI will be presented.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

The efficacy endpoints will be analyzed in the mITT population. PK and PD parameters will be analyzed in the PK and PD analysis sets, respectively.

Safety data will be summarized with descriptive statistics. Treatment-emergent adverse events will be summarized by SOC and PT (all events, related events, and serious events), in addition to being summarized by severity (all events). In addition, summaries will be provided for any AEs leading to discontinuation of study drug or death. Serious adverse events and procedure related adverse events in the run-in period will be listed.

Figure 1: Study Design



Abbreviations: Q4W=once every 4 weeks; EOS=end of study; EOT=end of treatment

Table 1: Schedule of Assessments – Run-in and Treatment Periods (Screening through Week 32 Assessments)

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (32 weeks)**								
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**
	Notes	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**
Discuss Study Information and Collect Informed Consent	Sites are encouraged to discuss the study information with the patients again at the end of the run-in period.	X				(X)									(X)
Medical History		X													
Demographics			X												
Inclusion/Exclusion Criteria		X					X								
Routine Physical Exam	See Section 6.7.3.		X				X		X						X
Height, Weight and BMI	See Section 6.7.2.		X				X		X						X
Vital Signs	See Section 6.7.1.		X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	See Section 6.7.4.		X				X								X
Clinical Laboratory Assessment	On dosing days blood samples will be collected predose; see Section 6.7.5.		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	See Section 6.7.5.2.		X			X	X	X	X	X	X	X	X	X	X
Start of Meningitis Vaccination	Sites to use locally approved vaccines and follow the manufacturer's instructions applicable to patients with persistent complement component					X									

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (32 weeks)**								
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**
	Notes	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**
	deficiency; see Section 5.3.2 and Section 6.2.														
Confirmation of Vaccine Injection Schedule Compliance	As applicable and dependent on which vaccine will be used.						X	X	X	X	X	X	X	X	
Randomization							X								
Study Drug Administration	See Section 5.2.2.						X	X	X	X	X	X	X	X	X
24-hours Urine Proteinuria Assessment (from 2 valid collections)	Collected within two weeks before the assessment is due to take place; see Section 6.4.1.1.					X									X
24-hours Urine Proteinuria Assessment (from a single valid collection)	Collected within one week before the assessment is due to take place; see Section 6.4.1.1.		X								X				
CAP/CCP Blood Sample	Samples will be collected predose; see Section 6.5.						X	X	X	X	X	X	X	X	X
C5 Levels Blood Sample	Samples will be collected predose; see Section 6.5.						X	X	X	X	X	X	X	X	X
eGFR Calculation	See Section 6.4.3.		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Urinalysis	See Section 6.4.1.1.		X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	See Section 6.4.1.2.		X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visit (Day/Week)		**Screening**		**Run-in Period (14 weeks)**			**Treatment Period (32 weeks)**								
			Screening visit	**Week -14**	**Week -8**	**Week -2**	**Day 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**
	Notes	**D-189 to D-99**	**D-112 ±7**	**D-98 ±7**	**D-56 ±7**	**D-14 ±3**	**D1**	**D28 ±3**	**D56 ±3**	**D84 ±3**	**D112 ±3**	**D140 ±3**	**D168 ±3**	**D196 ±3**	**D224 ±3**
Antidrug Antibodies	Antidrug antibodies samples will be collected predose; see Section 6.7.5.1.						X	X		X			X		X
Exploratory Blood Sample	See Section 6.4.4.						X		X		X		X		X
Blood Sample for Exploratory Genetic Analysis	See Section 6.8.						X								
Exploratory Urine Sample	See Section 6.4.4.						X		X		X		X		X
Plasma and Urine PK	Blood samples for PK will be collected at timepoints noted in Table 3.						X								
Adverse Events	See Section 6.7.6.2. All SAEs and only AEs related to study procedures will be collected during the run-in period.						X								
Concomitant Medications	See Section 5.3.	X	X	X											
Antibiotics Compliance (if applicable)	See Section 5.5.3.					X									
IgAN standard of Care Compliance			X												

Table 2: Schedule of Assessments – Open-Label Extension Period and Safety Follow up

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (EOT)	Week 84 (EOS)	Week 97	Week 110	Week 123	Week 136
	Notes	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
Routine Physical Exam	See Section 6.7.3.						X				X		X	X		X		X
Height, Weight and BMI	See Section 6.7.2.						X				X			X		X		X
Vital Signs	See Section 6.7.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	See Section 6.7.4.						X						X	X		X		X
Clinical Laboratory Assessment	On dosing days blood samples will be collected predose; see Section 6.7.5.	X	X		X		X		X		X		X	X	X	X	X	X
Pregnancy Test	See Section 6.7.5.2.	X	X		X		X		X		X		X	X	X	X	X	X
Study Drug Administration	See Section 5.2.2.	X	X	X	X	X	X	X	X	X	X	X	X					
24-hours Urine Proteinuria Assessment (from 2 valid collections)	See Section 6.4.1.1.													X				
24-hours Urine Proteinuria Assessment (from a single valid collection)	Collected within one week before the assessment is due to take place; see Section 6.4.1.1.						X				X					X		X
CAP/CCP Blood Sample	On dosing days samples will be	X	X		X		X		X		X		X	X	X	X	X	X

Study Visit (Day/Week)		Open-Label Extension Period (52 weeks)													Safety Follow up			
		Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80 (EOT)	Week 84 (EOS)	Week 97	Week 110	Week 123	Week 136
	Notes	D252 ±7	D280 ±7	D308 ±7	D336 ±7	D364 ±7	D392 ±7	D420 ±7	D448 ±7	D476 ±7	D504 ±7	D532 ±7	D560 ±7	D588 ±7	D679 ±14	D770 ±14	D861±14	D952 ±14
	collected predose; see Section 6.5.																	
C5 Levels Blood Sample	On dosing days samples will be collected predose; see Section 6.5.	X	X		X		X		X		X		X	X	X	X	X	X
eGFR Calculation	See Section 6.4.3.	X	X		X		X		X		X		X	X	X	X	X	X
Urine Sample for Urinalysis	See Section 6.4.1.1.	X	X		X		X		X		X		X	X	X	X	X	X
Spot Urine for Albumin, Protein and Creatinine	See Section 6.4.1.2.	X	X		X		X		X		X		X	X	X	X	X	X
Antidrug Antibodies	Antidrug antibodies samples will be collected predose; see Section 6.7.5.1.				X						X			X				
Exploratory Blood Sample	See Section 6.4.4.		X		X		X		X		X		X	X				
Exploratory Urine Sample	See Section 6.4.4.		X		X		X		X		X		X	X				
Optional home visit	Will be arranged for cemdisiran administration in between 8-weekly study site visits at Weeks 44, 52, 60, 68 76, 97 and 123 during			X		X		X		X		X			X		X	

Study Visit (Day/Week)		**Open-Label Extension Period (52 weeks)**													**Safety Follow up**			
		Week 36	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80 (EOT)**	**Week 84 (EOS)**	**Week 97**	**Week 110**	**Week 123**	**Week 136**
	Notes	**D252 ±7**	**D280 ±7**	**D308 ±7**	**D336 ±7**	**D364 ±7**	**D392 ±7**	**D420 ±7**	**D448 ±7**	**D476 ±7**	**D504 ±7**	**D532 ±7**	**D560 ±7**	**D588 ±7**	**D679 ±14**	**D770 ±14**	**D861±14**	**D952 ±14**
	the extension phases, unless patients are required to visit the study center as judged necessary by the Investigator.																	
Adverse Events	See Section 6.7.6.2.	X																
Concomitant Medications	See Section 5.3.	X																
Antibiotics Compliance (if applicable)	See Section 5.5.3.	X																
IgAN standard of Care Compliance		X																

Table 3: Pharmacokinetic Time Points

Phase	Study Day	Protocol Time Relative to Dosing (hh:mm)[a]	PK Blood	Pooled Urine[b]
Treatment phase	Day 1	Predose (within 60 mins)	X	
		00:00 (dose)		X
		01:00 (±5 mins)	X	
		02:00 (±15 mins)	X	
		04:00 (±15 mins)	X	
		06:00 (±15 mins)	X	
		08:00 (±30 mins)	X	X
		12:00 (±30 mins)		
		24:00 (±120 mins)	X	X

Abbreviations: hh=hours; mm=minutes; mins=minutes; PK=pharmacokinetics.

[a] The actual time of blood sample collection must be recorded.
[b] The pooled urine 8-12 hours and 12-24 hours can be collected as outpatient.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 17
LIST OF TABLES 20
LIST OF FIGURES 21
1. INTRODUCTION 24
1.1. Disease Overview 24
1.2. Cemdisiran 25
1.3. Study Design Rationale 27
1.4. Dose Rationale 28
1.5. Benefit-Risk Assessment 29
2. OBJECTIVES AND ENDPOINTS 30
3. INVESTIGATIONAL PLAN 32
3.1. Summary of Study Design 32
3.2. Duration of Treatment 33
3.3. Duration of Study 33
3.3.1. Definition of End of Study for an Individual Patient 33
3.4. Number of Planned Patients 33
3.5. Method of Assigning Patients to Treatment Groups 33
3.6. Blinding 34
3.6.1. Emergency Unblinding 34
3.7. Data Monitoring Committee 34
4. SELECTION AND WITHDRAWAL OF PATIENTS 35
4.1. Inclusion Criteria 35
4.2. Exclusion Criteria 35
4.3. Removal from Therapy or Assessment 37
4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments 37
4.3.2. Stopping a Patient's Study Participation 38
4.3.2.1. Patient or Legal Guardian Stops Participation in the Study 38
4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data 39
4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study 39
4.3.2.4. Recording Reason for Stopping a Patient's Study Participation 39

4.3.3. Lost to Follow-Up....39
4.3.4. Replacement of Study Patients....40
5. TREATMENTS AND OTHER REQUIREMENTS....41
5.1. Treatments Administered....41
5.2. Study Drug....41
5.2.1. Description....41
5.2.2. Dose and Administration....41
5.2.3. Dose Modifications....41
5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing....42
5.2.4. Preparation, Handling, and Storage....43
5.2.5. Packaging and Labeling....44
5.2.6. Accountability....44
5.3. Concomitant Medications and Procedures....44
5.3.1. Prohibited Concomitant Medications....44
5.3.2. Study-specific Vaccinations....45
5.4. Treatment Compliance....46
5.5. Other Requirements....46
5.5.1. Contraception....46
5.5.2. Alcohol Restrictions....47
5.5.3. Antibiotic Compliance....47
6. STUDY ASSESSMENTS....48
6.1. Screening Assessments....48
6.1.1. Rescreening....48
6.1.2. Retesting....48
6.2. Run-in Period....48
6.3. Baseline Assessments (Treatment Period)....49
6.4. Efficacy Assessments....49
6.4.1. Proteinuria....49
6.4.1.1. 24-Hour Urine Collection....49
6.4.1.2. Spot Urine Collection....50
6.4.2. Hematuria....50
6.4.3. Changes in Renal Function....51
6.4.4. Markers of Complement Activation, Inflammation and Renal Injury....51

6.5. Pharmacodynamic Assessments 51
6.6. Pharmacokinetic Assessments 51
6.7. Safety Assessments 52
6.7.1. Vital Signs 52
6.7.2. Weight and Height 52
6.7.3. Physical Examination 52
6.7.4. Electrocardiogram 53
6.7.5. Clinical Laboratory Assessments 53
6.7.5.1. Immunogenicity 55
6.7.5.2. Pregnancy Testing 55
6.7.5.3. Additional Liver Function Assessments 55
6.7.6. Adverse Events 56
6.7.6.1. Definitions 56
6.7.6.2. Eliciting and Recording Adverse Events 58
6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee 59
6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee 59
6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities 60
6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee 60
6.7.6.7. Pregnancy Reporting 60
6.7.6.8. Overdose Reporting 60
6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository 61
7. STATISTICS 62
7.1. Determination of Sample Size 62
7.2. Statistical Methodology 62
7.2.1. Populations to be Analyzed 62
7.2.2. Examination of Subgroups 62
7.2.3. Handling of Missing Data 63
7.2.4. Baseline Evaluations 63
7.2.5. Efficacy Analyses 63
7.2.5.1. Primary Endpoint 63
7.2.5.2. Secondary Efficacy Endpoints 63
7.2.5.3. Exploratory Endpoints 63

7.2.6. Pharmacodynamic Analysis....64
7.2.7. Pharmacokinetic Analysis....64
7.2.8. Safety Analyses....64
7.2.9. Immunogenicity Analyses....65
7.2.10. Biomarker Analyses....65
7.2.11. Interim Analysis....65
7.2.12. Optional Additional Research....65
8. STUDY ADMINISTRATION....66
8.1. Ethical and Regulatory Considerations....66
8.1.1. Informed Consent....66
8.1.2. Ethical Review....66
8.1.3. Serious Breach of Protocol....67
8.1.4. Study Documentation, Confidentiality, and Records Retention....67
8.1.5. End of Study....67
8.1.6. Termination of the Clinical Study or Site Closure....67
8.2. Data Quality Control and Quality Assurance....68
8.2.1. Data Handling....68
8.2.2. Study Monitoring....68
8.2.3. Audits and Inspections....68
8.3. Publication Policy....68
9. LIST OF REFERENCES....70
10. APPENDICES....72

LIST OF TABLES

Table 1: Schedule of Assessments Run-in and Treatment Periods (Screening through Week 32 Assessments)....10
Table 2: Schedule of Assessments Open-Label Extension Period and Safety Follow up....13
Table 3: Pharmacokinetic Time Points....16
Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified....43
Table 5: Clinical Laboratory Assessments....53

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases 56

LIST OF FIGURES

Figure 1: Study Design.....9

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADA	Antidrug antibodies
ACE	Angiotensin-converting enzyme
AE	Adverse event
AECI	Adverse event of clinical interest
aHUS	Atypical hemolytic uremic syndrome
ALN-CC5	Cemdisiran
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Aspartate transaminase
AUC	Area under the concentration curve
BMI	Body mass index
C3	Complement component 3
C3a	Activated complement 3
C5	Complement component 5
C5a	Activated complement component 5
CAP	Complement alternative pathway
CCP	Complement classical pathway
CFH	Complement factor H
CI	Confidence interval
CL/F	Clearance
Cmax	Maximum concentration
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay

Abbreviation	Definition
EOS	End of study
EOT	End of treatment
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hpf	High powered field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgAN	IgA Nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reaction
IV	Intravenous
LFT	Liver function test
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
mRNA	Messenger RNA
NHP	Nonhuman primates
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria

Abbreviation	Definition
RAS	Renin-angiotensin system
RBC	Red blood cell
RNAi	RNA interference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
siRNA	Small interfering RNA
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal half-life
Tmax	Time to maximum concentration
TMF	Trial Master File
UP	Urine protein
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein:creatinine ratio
V/F	Volume of distribution

1. INTRODUCTION

1.1. Disease Overview

Globally, immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis that can progress to renal failure.[1, 2] While the exact pathogenesis of IgAN is incompletely understood, biochemical, genetic, and clinical data suggest IgAN is an autoimmune disease that may originate from overproduction of aberrantly glycosylated IgA1 and the development of glycan-specific IgA and immunoglobulin G (IgG) autoantibodies that recognize the under-galactosylated IgA1 molecule. Both the alternative and lectin complement pathways may be activated, leading to generation of the anaphylatoxins activated complement component 3 (C3a) and activated complement component 5 (C5a) and the membrane attack complex (MAC) C5b-9, with subsequent promotion of inflammatory mediators.[3] Emerging data indicate that mesangial-derived mediators that are released following deposition of IgA1 may lead to podocyte and tubulointerstitial injury.

Given that a biopsy specimen is required to diagnose IgAN, the clinical threshold for performing a biopsy will have a major impact on the prevalence of IgAN. Persistent microscopic hematuria alone and/or mild proteinuria alone are not commonly used as a per cause indication for biopsy in the United States. Thus, the prevalence of IgAN is modest in the United States (10 to 20% of primary glomerulonephritis), higher in some European countries (20 to 30%), and highest in developed countries in Asia (40 to 50%).[4] This considerable geographical variability can be explained by several factors including the variation in access to primary care enabling early diagnosis and the differences in policies for performing renal biopsies as well as for early referrals. For example, in some countries, urine screening tests are conducted in schools or for military service or ahead of employment, explaining the apparent high incidence.[2, 5] Ethnic differences can also contribute to the varying prevalence of IgAN. Genome-wide association studies have identified candidate genes as well as risk-associated and protective alleles, with the highest number of risk alleles present in individuals of East Asian origin and the lowest number in those from Africa.[6] These genes are involved in antigen presentation, mucosal defense system and notably the alternative complement pathway (complement factor H [CFH]/CFHR locus).[6] Finally, patients may present at any age with IgAN but there is a peak incidence in the second and third decades of life. Most cases of IgAN occur in sporadic (90 to 95%) rather than in familial patterns (5 to 10%).[1]

Routine screening for IgAN is not feasible given that no specific diagnostic laboratory tests are available. The first indication for making a diagnosis comes after careful microscopic examination of a urine sample. The presence of red blood cell (RBC) casts and dysmorphic RBCs indicates glomerular bleeding. Varying degrees of proteinuria are present in patients with IgAN. Proteinuria can be quantified with a timed urine collection or a spot urine protein to creatinine ratio (UPCR) measurement. Hence, IgAN can only be diagnosed definitely upon renal biopsy and study of kidney tissue using immunofluorescence. The pathology of IgAN is characterized by deposition of pathogenic polymeric IgA1 immune complexes and C3 in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. A consensus on the pathologic classification of IgAN has been developed by the International IgA Nephropathy Network in collaboration with the Renal Pathology Society (Oxford classification).[1, 7, 8]

The clinical presentation of patients with IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis which is often associated with severe hypertension, but between these extremes, most patients with IgAN pursue a chronic indolent course.[1] Some patients present with more severe proteinuria, hypertension and renal progression over time, typically reaching end-stage renal disease (ESRD) over a span of 20 years. Thus, the severity of proteinuria upon presentation has significant prognostic implications. More importantly, the change in proteinuria over time is being regarded as the current best prognostic indicator: those who had heavy time averaged proteinuria and achieved a partial remission of <1 g/24-hours had a similar course to those who had <1 g/24-hours throughout and fared far better than those who never achieved partial remission.[9] These observations support the notion that every effort should be made to reduce proteinuria in IgAN. In addition to the degree of proteinuria, baseline renal function and the degree of histological injury are of prognostic value. For example, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at the time of renal biopsy have worse outcomes than those with normal eGFR (90 to 120 mL/min/1.73 m^2). The rate of glomerular filtration rate (GFR) decline also correlates with glomerulosclerosis and tubular atrophy or interstitial fibrosis on biopsy as outlined by Oxford-MEST-C classification. Spontaneous full recovery in IgAN is rare in adults, especially if associated with significant proteinuria (>0.5 g/24-hour).[10]

Patients with minor urine abnormalities, normal blood pressure, and normal GFR usually do well and require only monitoring. For other patients, the therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. Thus, no disease-specific therapies are currently available, and an unmet need persists for novel interventions, particularly in patients who are at risk of progressive disease that can result in end-stage renal failure. The optimal role of immunosuppressive therapy is uncertain. The available studies are not conclusive since most are relatively small and have limited follow-up.[1] STOP-IgAN, a German trial, randomly assigned adults with an eGFR of >30 mL/min/1.73 m^2 and persistent proteinuria of >0.75 g/24-hour despite 6 months of supportive care with RAS inhibitors to receive supportive care alone or supportive care plus immunosuppression (prednisone alone for those with initial GFR >60 mL/min and prednisone combined with cyclophosphamide then azathioprine with initial GFR 30-59 mL/min). This strategy did not significantly improve the renal outcome and was associated with increased adverse effects at 36 months.[11] The TESTING trial demonstrated some GFR effect of steroids in Chinese patients, but had to be stopped due to large number of serious adverse events (SAEs) in the steroid arm.[12] The 2012 KDIGO guidelines recommend corticosteroids, albeit at very low level of evidence. Thus, steroids may be tried in some cases as rescue therapy if proteinuria markedly increases or GFR rapidly falls. Further studies to address the role of steroids in IgAN are currently under way. Finally, Rituximab seems to be ineffective in the treatment of patients with progressive IgAN.[13]

1.2. Cemdisiran

Alnylam Pharmaceuticals, Inc. is developing cemdisiran (ALN-CC5), a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of atypical hemolytic uremic syndrome (aHUS) and IgAN. Cemdisiran comprises a

small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand.

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19-25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA.[14] Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [15], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo in animal models (including in rodents and nonhuman primates [NHP]) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations.[15, 16] Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a GalNAc carbohydrate ligand.[17] Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

Cemdisiran (containing siRNA drug substance, ALN-62643, targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via subcutaneous (SC) injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the cemdisiran siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of MAC formation and C5a release. This in turn would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN resulting in renal function improvement.[3] Both lectin and alternative pathways of complement have been implicated in IgAN pathology. Cemdisiran-mediated silencing of C5 will inhibit MAC formation and C5a release regardless of the activating pathway and may be a superior approach in IgAN where the contribution of different pathways may be heterogenous between patients.[18]

The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic abnormalities in subjects with known genetic C5 deficiencies.[19] Subjects with known C5 deficiencies are generally healthy apart from an increased susceptibility to Neisserial infections. In addition, safety data on the treatment of healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria (PNH) with cemdisiran in Study ALN-CC5-001 indicate that cemdisiran is generally well-tolerated; the maximum tolerated dose was 900 mg. There were no serious adverse events (SAEs) or discontinuations due to adverse events (AEs) during this study, and most AEs were mild or moderate in severity.

A detailed description of the chemistry, pharmacology, nonclinical pharmacokinetics (PK) and toxicology, as well as preliminary efficacy, and safety of cemdisiran is provided in the current edition of the Investigator's Brochure (IB).

1.3. Study Design Rationale

In contrast to the RBC lysis which characterises the pathophysiology of PNH, which requires extremely high level of C5 inhibition for protection, endothelial cells and mesangial cells are the cellular targets of dysregulated complement in aHUS and IgAN, respectively. These cells are nucleated cells which possess complement regulatory proteins as well as the ability to shed membrane associated MAC to defend against MAC-mediated damage, a key step in thrombotic microangiopathy progression in aHUS and renal damage in IgAN. It is therefore hypothesized that a lesser degree of cemdisiran mediated C5 knockdown will be required for disease control in patients with IgAN and aHUS than in patients with PNH.[20, 21] This hypothesis is supported by the observation that aHUS patients who achieve C5 inhibition maintain good disease control despite complement activity levels consistent with higher free C5 levels.[22] Therefore, cemdisiran monotherapy may be a viable treatment option in patients with IgAN at levels of C5 silencing achieved in Study ALN-CC5-001.

This therapeutic hypothesis will be tested in a multicenter, multinational, double-blind, placebo-controlled study to evaluate the effect of multiple doses of cemdisiran given by SC injection in patients with IgAN with persistent proteinuria (>1 g/24-hours) despite the standard of care (angiotensin converting enzyme inhibitors [ACE], angiotensin II receptor blockers [ARB] or direct renin inhibitors) and additional medications if necessary for blood pressure control followed by a treatment extension to evaluate long-term safety and clinical activity. The study population has been selected based on two major factors: 1) the severity of proteinuria upon presentation has significant prognostic implications.[23] IgAN patients with heavy proteinuria >1 g/24-hours have a significantly worse renal outcome than those who have proteinuria <1 g/24-hours.[9] 2) For patients with persistent proteinuria, despite the nonspecific treatment to reduce blood pressure and proteinuria by RAS blockade, no disease-specific therapies are currently available, and an unmet need persists for novel interventions. Since proteinuria can result both from active inflammation as well as irreversible scarring of renal tissue and in lieu of a protocol biopsy, we enrich our patients for presence of potentially reversible disease activity by requiring presence of hematuria and relatively preserved renal function with eGFR >30 mL/min. To ensure the selection of patients who are truly at risk of progression of kidney disease despite standard of care, the first period of the study consists of a run-in period during which patients will not receive study drug (cemdisiran or placebo). The run-in period will be an observational period during which patients' treatment with standard of care, blood pressure, kidney function, degree of hematuria, and proteinuria will be documented. The standard of care is expected to remain unchanged during this run-in period. Only patients whose

- proteinuria level remains above 1 g/24-hours within 2 weeks before the end of the run-in period,
- continue to have hematuria, and meet blood pressure and eGFR criteria

will be eligible to enroll in the 32-week treatment period portion of the study.

Randomization to cemdisiran or placebo will be performed in a 2:1 ratio so that more patients will receive cemdisiran. This will allow a more precise estimation of the effect of cemdisiran with only marginal loss of power. Inclusion of a placebo arm will allow better assessment of safety and interpretation of the efficacy of cemdisiran.

The primary endpoint for the study is percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32. This is justified for a phase 2 study given the slow progression of renal disease and the established role of proteinuria as a marker of disease progression.

1.4. Dose Rationale

In the Phase 1/2 Study (ALN-CC5-001), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). Treatment with cemdisiran was generally well tolerated in both healthy volunteers and patients with PNH. There were no SAEs and no discontinuations due to AEs during this study, including at the highest doses administered. Most AEs observed were mild or moderate in severity.

Dose selection for the current study is based on the expected level of C5 and complement activity inhibition necessary for efficacy in patients with IgAN and the extent to which different doses of cemdisiran can inhibit production of C5. C5 silencing is a novel approach for the treatment of IgAN and little clinical precedent exists for inhibiting the terminal complement pathway in this disease. Since complement regulation is not impaired in IgAN like it is in PNH, and the kidney glomerular cells are nucleated cells, it is expected that the level of silencing needed for efficacy in IgAN is lower than that needed for PNH (see IB Section 2.4). For this proof-of-concept study, a dose was selected that is expected to produce rapid and robust C5 suppression and complement activity inhibition across the patient population, allowing an unambiguous evaluation of whether C5 silencing results in proteinuria improvement in IgAN. In Study ALN-CC5-001, a single dose of 600 mg cemdisiran achieved a C5 level of 12.3±1.47 µg/mL by Day 14 and 2.3±0.76 µg/mL by Day 56, corresponding to 60.9% reduction in complement alternative pathway (CAP) activity and a 69.3% reduction in complement classical pathway (CCP) activity by Day 14 and 90.2% and 91.4% reduction in CAP and CCP activities, respectively, by Day 56. Single and multiple biweekly doses of 600 mg were well-tolerated with an acceptable safety profile in healthy volunteers in Study ALN-CC5-001A. In this initial study, the cemdisiran dose of 600 mg that was safe and well-tolerated was chosen for evaluation. This dose will yield robust C5 silencing and will have maximal opportunity to produce a meaningful clinical effect in patients with IgAN. Since the relationship between C5 levels and complement activity is non-linear, with small C5 fluctuations resulting in a larger increase in complement activity, a monthly dose regimen was selected to maintain a constant level of C5 silencing. Additionally, a more consistent effect of cemdisiran on C5 protein and CCP level is predicted after monthly dosing when compared to quarterly dosing based on a modeling approach.

During the extension treatment phase, patients treated with both cemdisiran and placebo will have the option to receive a 600 mg dose of cemdisiran every four weeks for an additional 52 weeks.

IgAN can result in progressive renal impairment; however, patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2) who may have sustained irreversible damage to the kidney are not eligible for participation in this trial. As the kidney is not the major elimination pathway for

cemdisiran and based on available nonclinical and clinical data obtained with cemdisiran (with 10.6 to 31.6% of the cemdisiran dose recovered in a 24-hour urine collection in the ALN-CC5-001 study), it is expected that moderate renal impairment (eGFR<60 mL/min/1.73 m^2) will not affect the PK of cemdisiran to the extent that a dose adjustment would be required. Therefore, patients with moderate renal impairment are eligible for study enrollment. More information on urine PK can be found in the IB.

1.5. Benefit-Risk Assessment

To date, no medications have been approved specifically for the treatment of IgAN. Therefore, there is a large unmet need for novel interventions, particularly in patients who are at risk of progressive renal disease such as those with persistent proteinuria despite treatment with RAS inhibitors. Available data from studies on the role of immunosuppressive therapy in IgAN are not conclusive as most are relatively small and have limited follow-up.[1] Use of immunosuppressive drugs and high-dose steroids are also associated with increased AEs which is particularly common in patients with lower GFR.[24]

Given the biological target of cemdisiran, the available nonclinical and clinial data, and mode of administration, important potential risks for cemdisiran are infections, liver function test (LFT) abnormalities and injection site reactions (ISRs). Since C5 inhibition is associated with increased susceptibility for Neisserial infections, prior immunization against *N. meningitidis* using meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine are required. Patients will be instructed to contact study site if any early signs of meningococcal infections are experienced. As cemdisiran is targeted for delivery to the liver, patients will be closely monitored for changes in LFTs and patients with a medical history or evidence of chronic liver disease or cirrhosis have been excluded. Criteria for dose withholding, and stopping of cemdisiran are provided in Section 5.2.3.1. Patients will also be monitored for the development of ISRs and rotation of injection site are recommended during the study.
Detailed information about the known and expected benefits and risks of cemdisiran and additional information on the clinical and nonclinical data may be found in the current version of the IB.
An independent data monitoring committee (DMC) will be monitoring the program for safety.

Cumulatively, clinical data regarding the role of complement pathways in IgAN progression, robust nonclinical and clinical data with cemdisiran (see IB for more information), and prior and ongoing clinical experience with other RNAi therapeutics in humans suggest cemdisiran will have a favorable risk profile in the intended population and supports the initial clinical development of cemdisiran in IgAN. In addition, cemdisiran may address the unmet medical need for the first efficacious and disease-specific treatment for patients with IgAN.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of cemdisiran on proteinuria in adult patients with immunoglobulin A nephropathy (IgAN)	• Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32
Secondary	
• To evaluate the effect of cemdisiran on remission of proteinuria in adult patients with IgAN • To evaluate the effect of cemdisiran on hematuria in adult patients with IgAN • To evaluate the safety and tolerability of cemdisiran	• Percent of patients with partial clinical remission (urine protein [UP] <1.0 g/24-hours) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in urine protein/creatinine ratio (UPCR; in g/g) as measured in 24-hour urine at Week 32 • Change from baseline in UPCR as measured in a spot urine at Week 32 • Change from baseline in hematuria at Week 32 (red blood cells per high powered field [RBC/hpf]) • Frequency of adverse events (AEs)
Exploratory	
• To evaluate the effect of cemdisiran on renal function parameters • To evaluate the pharmacodynamic (PD) effect of cemdisiran in adult patients with IgAN • To characterize the pharmacokinetics (PK) of cemdisiran and relevant metabolites in plasma and urine in adult patients with IgAN • To evaluate the effect of cemdisiran on serum and urine markers of complement activation, renal damage and inflammation • To assess the incidence of antidrug antibodies (ADA)	• Change from baseline in estimated glomerular filtration rate (eGFR) at Week 32 • The slope of eGFR computed for the first 32 weeks using all assessments during the period • The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study. • Change from baseline in creatinine clearance at Week 32 • Percent of patients in full clinical remission (Urine Protein [UP] <0.3 g/24-hours) at Week 32

	• Change from baseline in 24-hour albuminuria at Week 32 • Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32 • Change from baseline in C5 level over the course of the study • Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study • Evaluation of area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal half-life (t1/2), clearance (CL/F), volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae) and percent of dose excreted in the urine (fe) of cemdisiran (25-mer) and 23-mer • Evaluation of AUC, Cmax, Tmax, t1/2, CL/F, V/F, Ae and fe of 22-mer AS(N-1)3' • Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study • Incidence of antidrug antibodies (ADA)

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). The first period of the study is an observational 14-week run-in period during which patients' blood pressure, kidney function, degree of hematuria, and proteinuria will be measured. Patients will not receive study drug (cemdisiran or placebo) during this time. The standard of care is expected to remain unchanged during this run-in period. The second study period is a 32-week treatment period which will evaluate the efficacy and safety of SC cemdisiran compared to SC placebo in combination with standard of care in patients with IgAN and persistent proteinuria. The third period of the study is a 52-week optional open-label extension (OLE) period to further evaluate the long-term safety and clinical activity of cemdisiran. During the OLE, all patients (including those initially on placebo) will be treated with cemdisiran in combination with standard of care.

The study will include Screening of up to 90 days to determine eligibility of patients and to complete disease-related assessments. Patients will provide written informed consent and visit the study center approximately 2 weeks before starting the run-in period to complete the protocol screening assessments. Following successful screening, the 14-week run-in period will commence, during which patients' blood pressure, kidney function, degree of hematuria and proteinuria as well as treatment with standard of care will be documented by the Investigator. The standard of care is expected to remain unchanged during this run-in period. Patients whose proteinuria level remains >1 g/24-hours within 2 weeks of the end of the run-in period, who continue to have hematuria, and who meet blood pressure and eGFR criteria will be eligible to enroll in the 32-week treatment period. Upon confirmation of eligibility followed by vaccination against meningococcal infections, patients will be randomized at a 2:1 ratio to receive 600 mg of cemdisiran or placebo every 4 weeks in combination with standard of care. Thirty patients are planned to be randomized in total, 20 in the cemdisiran arm and 10 in the placebo arm. Patients excluded before randomization will be replaced at Screening.

During the run-in period, patients will visit the study center 14, 8, and 2 weeks prior to randomization (Weeks 0, 6 and 12 of the run-in period). Patients will then return to the study center every 4 weeks after the start of study drug treatment period. The primary endpoint will be assessed at the end of the treatment period at Week 32.

At the end of the treatment period (Week 32), patients in the two treatment arms will enter the optional OLE period where they will receive cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care for 52 weeks. The first study drug administration of the OLE will be administered at Week 32. Patients will return to the study center at Weeks 36, 40, and every 8 weeks thereafter during the OLE. Home visits, where locally feasible, may be arranged for cemdisiran administration in between 8-weekly study center visits (Weeks 44, 52, 60, 68 and 76), unless patients are required to visit the study center as judged necessary by the Investigator, or if home visits cannot be arranged. An end of treatment (EOT) visit will occur at Week 80 and an end of study (EOS) visit will be completed at Week 84. For patients who complete the treatment period only who do not consent to continue to participate in the study in the OLE period, the EOS will be at Week 32.

Patients will return to the clinical study center for safety follow-up visits approximately 13, 26, 39 and 52 weeks after the EOS visit (regardless if EOS visit is at Week 32 or Week 84), unless enrolled in another study with cemdisiran. Home visits, where locally feasible, may be arranged during safety follow-up at visit Weeks 97 (13 weeks after the EOS visit) and 123 (39 weeks after the EOS visit).

Regular reviews of safety and tolerability data will be performed by a DMC throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study.

3.2. Duration of Treatment

Subcutaneous doses of cemdisiran or matching placebo will be administered every 4 weeks over a period of 32 weeks during the treatment period and patients will receive 600 mg SC doses of cemdisiran for 52 weeks in the optional OLE.

3.3. Duration of Study

The maximum estimated total time on study, inclusive of Screening (maximum of 90 days), run-in period (14 weeks), treatment period (32 weeks), optional OLE period (52 weeks) and safety follow-up (52 weeks), is up to approximately 36 months or 3.0 years.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if the patient has completed the EOS (Week 84) visit or the Week 32 assessments for those patients who do not consent to continue to participate in the study in the OLE period. Upon study completion (regardless if EOS visit is at Week 32 or Week 84) patients will enter a safety follow-up period with visits scheduled at intervals of 13 weeks.

For patients withdrawing from the study after receiving one dose of cemdisiran at a minimum, all efforts should be made to conduct the EOS assessments. Patients should then be encouraged to enter the safety follow up period.

3.4. Number of Planned Patients

Thirty patients are planned for randomization in this study.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the cemdisiran or placebo arms. Randomization will be stratified by baseline urine proteinuria levels (≥ 1g/24h and <2g/24h versus >=2g/24h).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the IRS. The Investigator or his/her designee will contact the IRS after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria at screening and prior to randomization.

3.6. Blinding

All site personnel including sponsor delegated clinical research associates and patients will be blinded to study drug treatment during the efficacy period (up to Week 32). Sponsor personnel will not be blinded to study treatment. Cemdisiran and placebo will be packaged identically. The study drug will be administered under the supervision of the Investigator or at the patient's home by a healthcare professional (see Section 5.2.2). Since cemdisiran may be visually distinguishable from placebo, the syringe will be masked by a site pharmacist prior to administration by a healthcare professional. See the Pharmacy Manual for additional details. Further details on blinding and unblinding arrangements will be documented in a separate plan /manual.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before unblinding to discuss the need to unblind the patient but must do so within 1 working day after the unblinding event. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the Trial Master File (TMF).

Further details on blinding and unblinding arrangements will be documented in a separate plan / manual.

3.7. Data Monitoring Committee

An independent DMC will perform regular reviews of safety and tolerability data throughout the study with the primary purpose of protecting the safety of participating patients and the integrity of the study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. The DMC will perform periodic reviews of data during the clinical trial, and on an ad hoc basis review of emergent safety data. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age and Sex

1. Male or female ≥18 years and ≤65 years of age at the time of informed consent

Patient and Disease Characteristics

2. Clinical diagnosis of primary IgAN as demonstrated by historical biopsy collected within 60 months of screening
3. Treated for IgAN with stable, optimal pharmacological therapy. In general, stable and optimal treatment will include maximum allowed or tolerated ACE inhibitor or an ARB or a direct renin-inhibitor for at least 3 months prior to start of run-in period
4. Urine protein ≥1g/24-hour at screening and mean urine protein ≥1g/24-hour from two valid 24-hour urine collections at the end of the run-in period, prior to randomization
5. Hematuria ≥10 RBCs per high powered field (RBC/hpf) at screening and at the end of the run-in period, prior to randomization (local result accepted for assessment of eligibility at the end of the run-in period)
6. Females of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception 14 days before first dose, throughout study participation, and for 90 days after last dose administration
7. Previously vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine or willingness to receive these vaccinations as well as prophylactic antibiotic treatment if required

Informed Consent

8. Patient is willing and able to provide written informed consent and to comply with the study requirements

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Concomitant significant renal disease other than IgAN
2. A diagnosis of rapidly progressive glomerulonephritis as measured by eGFR loss >30% over the duration of the run-in phase
3. Secondary etiologies of IgAN (eg, inflammatory bowel disease, celiac disease)
4. Diagnosis of Henoch-Schonlein Purpura (IgA Vasculitis)

5. eGFR <30 mL/min/1.73 m^2 2 weeks prior to randomization (local results will be used for assessment of eligibility)

Laboratory Assessments

6. Has any of the following laboratory parameter assessments:
   a. Alanine transaminase (ALT) >1.5×upper limit of normal (ULN), International Normalized Ratio (INR) >2 (or >3.5 if on anticoagulants), or total bilirubin >1.5×ULN (unless bilirubin elevation is due to Gilbert's syndrome)
7. Clinical laboratory test results considered clinically relevant and unacceptable in the opinion of the Investigator
8. Known human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection or hepatitis B virus (HBV) infection

Prior/Concomitant Therapy

9. Treatment with systemic steroids at dosages exceeding 20 mg prednisone-equivalent for more than 7 days or other immunosuppressant agents in the 12 months prior to randomization
10. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment

Medical Conditions

11. Malignancy (except for non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate cancer) within the last 5 years
12. Active psychiatric disorder, including, but not limited to schizophrenia, bipolar disorder, or severe depression despite current pharmacological intervention
13. Known medical history or evidence of chronic liver disease or cirrhosis
14. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation
15. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc
16. History of intolerance to SC injection(s) or significant abdominal scarring that could potentially hinder study drug administration or evaluation of local tolerability
17. Known contraindication to meningococcal vaccines (group ACWY conjugate and group B vaccines) required for this study. Refer to the most recent local product information for each vaccine for the current list of contraindications
18. Unable to take antibiotics for meninigococcal prophylaxis
19. Sustained blood pressure >140/90 mmHg as defined by 2 or more readings during the run-in period, measured in supine position after 10 minutes of rest
20. Receipt of an organ transplant (including hematologic transplant)

21. History of meningococcal infection within 12 months before Screening
22. Patients with systemic bacterial or fungal infections, as demonstrated by a positive culture result, that require systemic treatment with antibiotics or antifungals
    a. Patients receiving empiric or prophylactic antibiotics are not excluded

Alcohol Use

23. Patients who consume more than 14 units of alcohol a week (unit 1 glass of wine [125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL])

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-adverse event)
- Or, study is terminated by the Sponsor

The Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.7.5.2 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments through the Week 80/EOT visit and safety follow-up so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedule of Assessments (Table 2), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and adverse events, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.7.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 32-week treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Week 32 assessments) will be encouraged to remain on the study and complete assessments through Week 32; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks after their last dose of study drug (see Table 2).

Patients who discontinue study drug during the OLE period will be asked to return for their next scheduled visit to complete EOS/EOT assessments; they will also be asked to complete safety follow-up visits 13, 26, 39 and 52 weeks after their last dose of study drug (see Table 2).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient/legal guardian considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments through the Week 32 visit, including entering the 52-week safety follow-up. If a patient/legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 32-week treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the Week 32 visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an adverse event (AE), including serious adverse events (SAEs), the event should be followed as described in Section 6.7.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes to continue in the study, 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 or legal guardian (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 or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study during the 32-week treatment period or the OLE will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of cemdisiran and placebo is provided in the Pharmacy Manual.

5.2.1. Description

Cemdisiran will be supplied as a sterile solution for SC injection that contains 200 mg/mL cemdisiran sodium (equivalent to 189 mg/mL of cemdisiran), formulated in water for injection (WFI) for SC administration. See the Pharmacy Manual for further details of solution concentration and fill volume.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to cemdisiran.

5.2.2. Dose and Administration

Patients will be administered cemdisiran (600 mg) or placebo (at the same volume as the active drug) as an SC injection once every 4 weeks in combination with standard of care in the 32-week treatment phase. During the 52-week OLE phase, patients will be administered cemdisiran at a dose of 600 mg every 4 weeks in combination with standard of care.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. At-home dosing may be administered by a healthcare professional. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained, if permitted. Detailed instructions for study drug administration are found in the Pharmacy Manual.

To maintain the blind during the treatment period, the syringes are to be masked prior to study drug withdrawal. A full description of the blinding procedure is included in the Pharmacy Manual.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.3.1. LFT Criteria for Withholding, Monitoring and Stopping Cemdisiran Dosing

1. LFT results (Table 5) from the previous visit should be reviewed prior to dosing. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.
2. For any ALT or AST elevation >3×ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 4.
3. For any ALT or AST elevation >3×ULN:
   a. Confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
   b. Perform assessments per Table 4 and Table 6.
   c. If an alternative cause is found, provide appropriate care.
4. For any ALT or AST elevation >3×ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2×ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3×ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2×ULN or INR ≥1.5, see Table 4

Table 4: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least every two weeks: LFT and coagulation per Table 6
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold cemdisiran dosing until recovery to ≤1.5×ULN; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 6 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 5
	• Monitor at least weekly: LFT and coagulation per Table 6 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5×ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of cemdisiran doses, according to procedures detailed in the Pharmacy Manual. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements.

Cemdisiran (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of a 0.5-mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

The standard of care treatment should be held stable throughout the run-in and treatment periods. Use of concomitant medications and procedures will be recorded on the patient's eCRF as specified in the Schedule of Assessments (see Table 1 and Table 2). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded on the eCRF.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

For other permitted concomitant medications administered SC, do not administer in same injection site area as the study drug/placebo, for 7 days after the last dose of either study drug or placebo.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.3.1. Prohibited Concomitant Medications

The following concomitant medications are prohibited during the study:

- Systemic steroids (short-term steroid course for <7 days for common conditions not related to IgAN (i.e. asthma, gout) is permitted)
- Immunosuppressive agents
- Fish oil supplements
- Hydroxychloroquine

5.3.2. Study-specific Vaccinations

All patients taking part in this study must be vaccinated against meningitis types A, C, W135, Y and B, upon determination of eligibility at the end of run-in period as per the schedule of assessments. Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions. On days of vaccination, urinary samples should be collected prior to administration of vaccines.

Patients will be immunized against *Neisseria meningitidis* according to the following specifications:

- Patients who have previously completed the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) at least 14 days but no more than 3 years from randomization can start study assessments after confirming eligibility. Documented vaccine history must be available to, and verified by, study site staff at the time of Screening.
- Patients who were previously vaccinated with polysaccharide type vaccines within 3 years of study entry will be revaccinated using conjugate vaccines if found eligible at the end of the run-in period. Patients who complete the vaccination series after starting cemdisiran will receive prophylactic antibiotics according to local standard of care for at least 2 weeks after completing the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) or longer, if required by local standard of care.
- Patients who either completed the recommended series of meningococcal vaccines less than 14 days from initiation of treatment with cemdisiran or those who have an incomplete meningococcal vaccination series will receive prophylactic antibiotic treatment according to local standard of care for at least 2 weeks after completing the recommended series of meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) or longer, if required by local standard of care.
- Patients who have not been previously vaccinated against *Neisseria meningitidis,* those without documentation of vaccination history, or those vaccinated more than 3 years from study randomization will commence the vaccination series with the recommended meningococcal vaccines (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) per the schedule of assessments if determined to be eligible for the study at the end of the run-in period. Patients who complete the vaccine series after receiving cemdisiran will receive prophylactic antibiotics according to the local standard of care for at least 2 weeks after completing

the recommended series of meningococcal vaccinations or longer, if required by local standard of care.

5.4. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

Females of child-bearing potential must be willing to use acceptable methods of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration.

Birth control methods which are considered acceptable include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral, implantable, injectable, or transdermal hormonal methods of contraception. Females of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- If hormonal methods of contraception are medically contraindicated due to their underlying disease, a double-barrier method (combination of male condom with cap, diaphragm, or sponge, in conjunction with spermicide) is also considered an acceptable method of contraception.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study) and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study.

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. Antibiotic Compliance

Patients who require prophylactic antibiotics following study specific vaccinations (see Section 5.3.1) per local standard of care will undergo antibiotic compliance checks. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments. Antibiotic dose adjustments will be permitted in the case of renal impairment. All dose adjustments must comply with the manufacturer's instructions.

6. STUDY ASSESSMENTS

The Schedule of Assessments is provided in Table 1 and Table 2.

6.1. Screening Assessments

An ICF approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian) before the Screening procedures are initiated. All patients (or their legal guardians) will be given a copy of the signed and dated ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor; see Section 6.1.1.

Patient demographic data and medical history/disease history will be obtained. In particular, the MEST-C score and degree of IgG, IgA, IgM, C3, C1q, C4d and C5b-9 stains will be obtained from pathology reports, if available, and documented. Any changes to medical history occurring between the Screening assessment and Day 1 will be updated prior to study drug administration. Additional screening assessments include a full physical examination (with emphasis on presence/degree of edema), collection of vital signs, height, weight and body mass index (BMI), 12-lead electrocardiogram (ECG), clinical laboratory assessments, pregnancy, 24-hours urine proteinuria assessment (from a single valid collection; see Section 6.4.1.1), eGFR, and urinalysis.

6.1.1. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) will be allowed to return for rescreening (once only). A patient will be re-consented, if rescreening occurs outside of the 90-day screening window. In this case, all screening procedures must be repeated.

6.1.2. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The investigator's rationale is to be documented. Laboratory values can be retested once during Screening as long as the patient can be evaluated for eligibility and randomized within the allowed Screening period.

6.2. Run-in Period

During the 14-week run-in period, the following will be performed at time points specified in the Schedule of Assessments (Table 1): vital signs, clinical laboratory assessments, pregnancy test, 24-hour urine proteinuria assessment (from 2 single valid collections; see Section 6.4.1.1), urinalysis for hematuria, spot urine for proteinuria, and eGFR. Clinical laboratory tests will be performed centrally; however, hematuria and eGFR will also be assessed locally at the end of the run-in period to facilitate assessment of patient eligibility and administer vaccination on the same day. During this period, patients will begin the recommended meningitis vaccination regimen if eligible for the study. Vaccines should be administered only if patient eligibility for randomization is confirmed and after urine collections are completed.

6.3. Baseline Assessments (Treatment Period)

Prior to dosing on Day 1, patients will be reassessed for eligibility and blood and urine samples for clinical laboratory assessments and exploratory analyses collected, including blood samples for complement activity tests (CAP/CCP), C5 analysis, PK and ADA.

In addition, prior to administration of study drug, the following assessments will be performed: full physical examination, body weight and height, vital signs, ECG, urine pregnancy test, eGFR assessment, and urinalysis.

Collection of blood and urine samples for PK analysis on Day 1 will be performed as outlined in Table 3.

6.4. Efficacy Assessments

6.4.1. Proteinuria

Primary efficacy will be assessed by determining the percent change from baseline in 24 hour proteinuria (g/24-hour) after 32 weeks of treatment. 24 hour urine samples for determination of proteinuria will be collected throughout the study as outlined in the Schedules of Assessments and will be analyzed by a central laboratory.

6.4.1.1. 24-Hour Urine Collection

Patients will be required to provide two separate valid 24-hour urine collections 2 weeks prior to randomization (to assess eligibility after the run-in period), at Week 32 (to assess the primary endpoint) and at Week 84/EOS visit. Patients will also be asked to provide a single valid 24-hour urine sample for other 24-hour urinary assessments outlined in the Schedule of Assessments. Rigorous exercise and significant change in diet (in particular salt intake) should be avoided within 48 hours of collection of 24-hour urine samples whenever possible.The two valid 24-hour urine samples may be collected within 2 weeks before assessment is due while the one valid 24-hour urine sample may be collected within one week before the assessment takes place. If any of the collections do not meet validity criteria outlined below, then repeat collections must be scheduled within the time frames outlined above to assure the minimum number of valid collections required for each of the study time points. The duration of collection and volume of urine in the collection will be recorded in the eCRF. In addition to protein, albumin, sodium and creatinine will also be quantified in each of the 24-hour urine samples. Both protein/creatinine (UPCR) as well as albumin/creatinine ratios (UACR) will also be calculated in an aliquot of the 24-hour urine collection.

Completeness of the 24-hour urine collection can be estimated from rate of creatinine excretion. Normal values of creatinine excretion vary with age and body weight. An aliquot of the 24-hour urine collection will be used to determine urinary creatinine content to determine if the 24-hour urine collections need to be repeated. Hence, a 24-hour urine collection will only be considered valid if all the following criteria are met, otherwise a repeat urine collection will be required:

- The collection is between 22-26 hours in duration between the initial discarded void and the last void or attempt to void.

- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection diary.
- The 24-hour creatinine content is within 25% of expected range as estimated by the following formula: [(140-age) x weight]/5000, where weight is in kilograms. This result is multiplied by 0.85 in women.[25]
- In case of need of two valid samples, the maximum variation in total 24-hour urine creatinine between the two urine collections must be <25%.

Primary efficacy will be evaluated by comparing the percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32 in patients treated with cemdisiran versus those treated with placebo.

Secondary and exploratory efficacy assessments include comparisons of the proportion of patients with partial or complete clinical remission, respectively, as measured by the amount of urine protein (UP) in a 24-hour urine sample. Partial clinical remission is defined as having UP <1 g/24-hours and complete clinical remission is defined as UP <0.3 g/24-hours. Each will be assessed at Week 32.

Additional secondary endpoints that will be evaluated using 24-hour samples include the change from baseline in the UP/creatinine ratio (UPCR) and the change from baseline in the UP/albumin ratio (UACR) at Week 32.

6.4.1.2. Spot Urine Collection

Urinary protein, albumin and creatinine levels from spot urine collections prior to dosing will also be measured to assess the effect of cemdisiran on urinary protein/creatinine (UPCR) and albumin/creatinine (UACR) as outlined in the Schedule of Assessments.

The change from baseline in UPCR at Week 32 will be evaluated in spot urine samples. Spot urine samples will be collected at the time points outlined in the Schedule of Assessments (Table 1).

6.4.2. Hematuria

Hematuria from spot urine collections will also be evaluated to assess the effect of cemdisiran on disease course in patients with IgAN. The degree of hematuria will be assessed by examination of the spun urine sediment by microscopy (RBC/hpf). Single void collections for random urine sample for hematuria evaluation should be collected as a first morning void when possible. If the investigator determines that the hematuria is transient due to menses in women or exercise, the sample may need to be repeated.
Random spot urine samples for hematuria measurement will be collected throughout the study as outlined in the Schedule of Assessments and will be analyzed by a central laboratory. On dosing days, samples should be collected prior to cemdisiran administration, if applicable.

To allow evaluation of eligibility on the same day at the end of the run in period, 2 weeks prior to randomization, the single void can be split in two containers, one evaluated by local lab and another by central lab. The local hematuria evaluation will be utilized to determine eligibility for study.

6.4.3. Changes in Renal Function

Changes in renal function will be monitored using measurements of serum creatinine and eGFR (mL/min/1.73m^2) as outlined in the Schedule of Assessments. The calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for all patients. For assessment of eligibility at the last visit of run-in period, 2 weeks prior to randomization, local lab can be utilized. This will allow evaluation for eligibility on the same day. A sample will also be sent to central lab.
Renal function will also be estimated as creatinine clearance based on the 24-hour urine collection. The creatinine clearance is a widely used test to estimate the GFR using the following formula:
GFR = [UCr x V] / SCr
SCr is the serum creatinine concentration and the value assessed closest to collection of 24-hour urine collection will be utilized for purpose of above calculation. UCr is the urine creatinine concentration and V is the urine flow rate or volume.
Blood and urine samples for renal function assessments will be collected prior to administration of cemdisiran on dosing days, if applicable.

The change from baseline in eGFR will be measured throughout the course of the study. In addition, the slope of eGFR will be computed for the first 32 weeks and the entire study period (including the OLE).

6.4.4. Markers of Complement Activation, Inflammation and Renal Injury

Samples for measurement of markers of complement activation, inflammation and renal injury will be collected at the time points outlined in the Schedule of Assessments (Table 1) and analyzed by central laboratories. On dosing days, blood samples will be collected predose.

6.5. Pharmacodynamic Assessments

Blood samples for PD analysis will be collected at the time points outlined in the Schedule of Assessments (Table 1). Samples will be collected prior to administration of cemdisiran on dosing days.

Analysis of PD will include the impact of cemdisiran administration on plasma C5 protein levels (assessed by a mass spectrometry-based method) and serum complement activity (assessed by CAP enzyme linked immunosorbent assay [ELISA] and CCP ELISA). Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in the Laboratory Manual.

6.6. Pharmacokinetic Assessments

Blood samples and urine samples will be collected for assessment of cemdisiran PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed schedule of time points for the collection of blood samples and urine samples for PK analysis is in Table 3.

The concentration of cemdisiran will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of the frequency of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and ECG findings and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.7.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the seated or supine position, after the patient has rested comfortably for 10 minutes. On Day 1, vital signs will be collected at predose and 4 hours postdose. On all other dosing days, vital signs will be collected predose.

Blood pressure should be taken using the same arm throughout the study. Body temperature in degrees Celsius will be obtained via oral method. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.7.2. Weight and Height

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1 and Table 2; height at Screening only and dosing weight during the clinical study center visits) and will be recorded in the eCRF.

6.7.3. Physical Examination

Full and directed physical examinations will be conducted according to the Schedule of Assessments (Table 1 and Table 2); if a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. On Day 1, routine physical examination will be performed at predose and 4 hours postdose. On all other dosing days, the routine physical examination will be performed predose.

Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Directed physical examinations will include examination of the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF.

6.7.4. Electrocardiogram

Twelve-lead ECGs reporting rhythm, ventricular rate, RR interval, PR interval, QRS duration, and QT interval and Fridericia corrected QT interval will be obtained, as specified in the Schedule of Assessments (Table 1 and Table 2). Patients should be supine for at least 5 minutes before each ECG is obtained. A single 12-lead ECG will be performed at Screening. At all other time points, 12-lead ECGs will be performed in triplicate, with readings approximately 1 minute apart. 12-lead ECGs will be performed at predose; 60 minutes postdose; and 4 hours postdose in relation to the Day 1 and Week 32 cemdisiran doses.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice.

6.7.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. However, to assess patient eligibility at the end of the run-in period, hematuria and eGFR will also be assessed locally. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 5 and include: hematology, serum chemistry and urinalysis parameters. Parameters will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 5 which are performed at the clinic should also be sent in parallel to the central laboratory. In the case of discrepant local and central laboratory results on samples drawn on the same day, central laboratory results will be relied upon for clinical and dosing decisions.

Clinical laboratory assessments may be collected at the clinical study center or at home by a trained healthcare professional.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Table 5: Clinical Laboratory Assessments

Hematology
Complete blood count with differential

Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the CKD-EPI formula)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
GGT	
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy
Protein	
Coagulation	
Prothrombin time	International Normalized Ratio
Partial Thromboplastin Time	
Immunogenicity (see Section 6.7.5.1)	
Antidrug antibodies	
Hepatic Tests (Screening Only)	
Hepatitis C, including: HCV RNA PCR – qualitative and quantitative assays	Hepatitis B, including: HBs Ag, HBc antibody IgM and IgG
Pregnancy Testing (Females of Child-bearing Potential Only) (see Section 6.7.5.2)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBsAg=hepatitis B virus surface

antigen; HBc=hepatitis B virus core; HCV=hepatitis C virus; IgG= IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid.

6.7.5.1. Immunogenicity

Blood samples will be collected to evaluate ADA. Blood samples for antidrug antibody testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1 and Table 2). A blood sample to evaluate antidrug antibodies will be collected at the Early Termination visit, if applicable.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.7.5.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed thereafter per the Schedule of Assessments and any time pregnancy is suspected. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.7.6.7 for follow-up instructions).

6.7.5.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any liver function test (LFT) abnormalities. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 5, and other assessments or evaluations per Investigator discretion, as appropriate.

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2a	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

[a] HIV testing will not be performed where prohibited by local regulations.

6.7.6. Adverse Events

6.7.6.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

Based on the biological target and the available nonclinical and clinical data, AEs of Clinical Interest (AECI) for this study are:

- Severe infections as judged by the investigator
- ALT or AST >3×ULN
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of cemdisiran.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site (eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site) is not considered an ISR.

For information on recording and reporting of AECIs, see Section 6.7.6.2 and Section 6.7.6.3 , respectively.

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?"

6.7.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording all SAEs and only AEs related to study procedures that are observed or reported by the patient during the run-in period (before the administration of the first dose of study drug) regardless of their relationship to study drug through the end of study. Events occurring after signing of the ICF and before study drug administration will be

captured as medical history (see Section 6.1). All AEs will be collected starting after administration of the first dose through the end of the safety follow-up period. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.7.6.1), the Sponsor or its designee should complete the supplemental AEs of Clinical Interest eCRF. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.7.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AECIs (Section 6.7.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.7.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.7.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Investigator Site File.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.7.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.7.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.7.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 90 days following the last dose of study drug, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.7.6.4.

6.7.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. The investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.8. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect.

More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with IgAN, as well as their responses to treatment.

To permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of cemdisiran, a set of biological specimens will be collected at the intervals indicated in the Schedule of Assessments (Table 1 and Table 2).

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and patient consent, the samples will be collected as part of this study. Examples of potential exploratory investigations would include DNA, RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

Thirty patients are planned to be randomized 2:1 (cemdisiran:placebo) in this study. This is based on the assumption that, in the placebo arm, the estimated geometric mean ratio of proteinuria at Week 32 to baseline is 0.88 (log standard deviation [SD] 0.597), corresponding to a 12% reduction. A sample size of 27 with 2:1 randomization (cemdisiran:placebo) will provide a width of 0.80 for the 90% confidence interval (CI) for treatment effect size estimate (cemdisiran placebo) in log scale. This corresponds to a 90% CI of (15%, 62%) for the treatment difference in the percentage scale if the true Week 32 reduction is 50% for the cemdisiran arm. To account for potential dropouts, 30 patients are planned to be randomized.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The following populations will be analyzed:

- Modified Intent-to-treat (mITT): All patients who receive any amount of study drug and have at least one post baseline assessment in proteinuria. Patients will be grouped by assigned treatments (ie, as randomized).
- Safety Analysis Set: All patients who received any amount of study drug. Patients who received any amount of cemdisiran will be included in the cemdisiran arm and will be grouped by treatment received.
- PK Analysis Set: All patients who receive any amount of study drug and have at least one postdose blood or urine sample for PK concentration.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one postdose blood sample for the determination of plasma C5 level.

The primary population used to evaluate efficacy will be the mITT Population. Sensitivity analyses for efficacy will be performed using the Per Protocol Analysis Set. Safety will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other baseline characteristics, including disease-specific information, will be summarized descriptively by treatment arm and overall for the mITT and Safety Analysis Set.

Baseline value for proteinuria will be calculated as average of two valid 24-hour urine protein levels before randomization.

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint of the study is the percentage reduction from baseline in 24-hour proteinuria at Week 32. The 24-hour urine protein will be log transformed for analyses. The primary analysis will be performed on the change from baseline in log transformed urine protein using a linear model with log transformed baseline urine protein as covariate and treatment and randomization stratification factor as fixed effect. The least square mean difference and its 90% confidence interval will be estimated and then back transformed to original scale. In the end the estimated ratio of percentage reduction in urine protein for cemdisiran to placebo and 90% confidence interval will be presented.

A sensitivity analysis using all urine protein assessments including a single 24-hour assessment will be conducted using mixed-effects model repeated measures (MMRM) method.

7.2.5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include percent of patients with partial clinical remission (UP <1.0 g/24-hours), percent of patients with >50% reduction in 24-hour proteinuria, change from baseline in UPCR as measured in 24-hour urine at Week 32, change from baseline in urine protein/creatinine ratio (UPCR) as measured in a spot urine at Week 32 and change from baseline in hematuria at Week 32.

The percentage of patients with partial clinical remission or with >50% reduction in 24-hour proteinuria for each treatment arm and the difference between treatment arms will be presented together with an approximate 90% confidence interval based on Wilson score method.

Change from baseline in urine protein / creatinine ratio (UPCR) will be analyzed similarly to the analysis of the primary variable as appropriate. UPCR will be log transformed first before analysis.

7.2.5.3. Exploratory Endpoints

Change from baseline in exploratory efficacy variables will be summarized. Percent of patients in full clinical remission and incidence of ADA will be tabulated by treatments. Inferential statistics for exploratory efficacy variables may be presented as needed. Details will be described in the SAP.

The slope of eGFR for the first 32 weeks will be estimated for each subject with the linear regression method using all assessment data during the period.

Descriptive statistics including the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum values will be presented for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables.

7.2.6. Pharmacodynamic Analysis

Assessment of the PD effect of the treatment will be performed descriptively, including plotting graphically levels of serum C5 protein and CAP/CCP over time and relative to baseline levels. Inferential statistics maybe generated as deemed necessary.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. Pharmacokinetic parameters include, but will not be limited to: AUC, C_{max}, T_{max}, T½, CL/F, V/F, cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe) in the urine of cemdisiran (25-mer) and 23-mer.

Other parameters may be calculated, if deemed necessary. Summary statistics and figures will be presented. Inferential statistics may be generated when deemed necessary.

7.2.8. Safety Analyses

The primary parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. The extent of exposure will be summarized by dose level and overall.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Prior and concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary. All SAEs occurring before the first dose of study drug and AEs related to study procedures will be listed. The number and percentage of patients experiencing AEs after the first dose of the study drug or events that worsened in severity after dosing will be summarized. AEs will be presented by maximum severity and relationship to study medication. SAEs and AEs leading to discontinuation of treatment will also be tabulated.

By-subject listings will be provided for deaths, SAEs, and AEs leading to study discontinuation.

Frequency of adverse events of clinical interest will also be summarized and by-subject listings will be provided.

Descriptive statistics will be provided for clinical laboratory data, 12-lead ECG interval data and vital signs data, presented as both actual values and changes from baseline over time. Laboratory shift tables from baseline to worst values will be presented. Baseline will be defined as the last observation on or prior to Study Day 1.

Abnormal physical examination findings and 12-lead ECG data will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

All safety analyses will be conducted using the Safety Analysis Set.

7.2.9. Immunogenicity Analyses

Antidrug antibody results will be summarized descriptively.

7.2.10. Biomarker Analyses

Urine and serum complement activation products, inflammation and renal injury markers will be summarized descriptively.

7.2.11. Interim Analysis

No formal interim analysis is planned.

7.2.12. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the ICF (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's/legal guardian's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient/legal guardian.

8.1.2. Ethical Review

The study protocol, including the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.7.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are randomized under the amended protocol, and patients must be re-consented to the most current version of the ICF.

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor reserves the right to terminate the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, or if there is insufficient adherence to the protocol requirements, the study may be closed at that site. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the

decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee, immediately if contacted by a regulatory agency or an IRB/IEC about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 18 months after completion of the study at all centers. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at

least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

1. Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nature Reviews Disease Primers. 2016;2:16001.

2. Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. Journal of the American Society of Nephrology. 1998;9(5):853-8.

3. Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current understanding of the role of complement in IgA nephropathy. Journal of the American Society of Nephrology. 2015;26(7):1503-12.

4. Woo K-T, Chan C-M, Chin YM, Choong H-L, Tan H-K, Foo M, et al. Global evolutionary trend of the prevalence of primary glomerulonephritis over the past three decades. Nephron Clinical practice. 2010;116(4):c337-c46.

5. Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clinical journal of the American Society of Nephrology. 2007;2(6):1360-6.

6. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nature genetics. 2014;46(11):1187.

7. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney international. 2009;76(5):534-45.

8. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney international. 2009;76(5):546-56.

9. Reich HN, Troyanov S, Scholey JW, Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. Journal of the American Society of Nephrology. 2007;18(12):3177-83.

10. Knoop T, Vikse BE, Mwakimonga A, Leh S, Bjørneklett R. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. Nephrology Dialysis Transplantation. 2017;32(11):1841-50.

11. Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. New England Journal of Medicine. 2015;373(23):2225-36.

12. Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy. Jama. 2017;318(5):432.

13. Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. Journal of the American Society of Nephrology. 2016:ASN. 2016060640.

14. Elbashir SM, Lendeckel W, Tuschl T. RNA interference is mediated by 21-and 22-nucleotide RNAs. Genes & development. 2001;15(2):188-200.

15. Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, et al. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. Nature. 2004;432(7014):173-8.

16. Zimmermann TS, Lee AC, Akinc A, Bramlage B, Bumcrot D, Fedoruk MN, et al. RNAi-mediated gene silencing in non-human primates. Nature. 2006;441(7089):111-4.

17. Ashwell G, Morell AG. The role of surface carbohydrates in the hepatic recognition and transport of circulating glycoproteins. Advances in Enzymology and Related Areas of Molecular Biology, Volume 41. 2006:99-128.

18. Medjeral-Thomas NR, Troldborg A, Constantinou N, Lomax-Browne HJ, Hansen AG, Willicombe M, et al. Progressive IgA Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin Associated Serine Protease-3 (MASP-3) and Increased Glomerular Factor H Related Protein-5 (FHR5) Deposition. Kidney international reports. 2018;3(2):426-38.

19. Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984;63(5):243-73.

20. Rosse WF. Variations in the red cells in paroxysmal nocturnal haemoglobinuria. British journal of haematology. 1973;24(3):327-42.

21. Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochemical Journal. 1989;264(1):1.

22. Cugno M, Gualtierotti R, Possenti I, Testa S, Tel F, Griffini S, et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. Journal of Thrombosis and Haemostasis. 2014;12(9):1440-8.

23. Coppo R, D'amico G. Factors predicting progression of IgA nephropathies. Journal of nephrology. 2005;18(5):503-12.

24. Sarcina C, Tinelli C, Ferrario F, Pani A, De Silvestri A, Scaini P, et al. Changes in proteinuria and side effects of corticosteroids alone or in combination with azathioprine at different stages of IgA nephropathy. Clinical journal of the American Society of Nephrology. 2016;11(6):973-81.

25. Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clinical journal of the American Society of Nephrology. 2011;6(1):184-91.

10. APPENDICES

None.