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STATISTICAL ANALYSIS PLAN

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

Protocol Number:	ALN-CC5-005
Protocol Version and Date:	Original protocol: 10 September 2018 Amendment 1: 26 November 2018 Amendment 2: 30 August 2019 Amendment 3: 27 April 2020 Amendment 4: 19 January 2021
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Phase:	Phase 2
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APPROVAL SIGNATURE PAGE

Statistical Analysis Plan

A Phase 2, Randomized, Double-blind,

Placebo-controlled Study of Cemdisiran in Adult

Patients with IgA Nephropathy

Protocol Number: ALN-CC5-005

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin converting enzyme inhibitor
ADA	Anti-drug Antibody
AE	Adverse Event
AECI	Adverse Event of Clinical Interest
ANCOVA	Analysis of covariance
ARB	angiotensin II receptor blocker
C5	Complement component 5
C5a	Complement component 5a
CAP	Complement Alternative Pathway
CCP	Complement Classical Pathway
CI	Confidence interval
CIC	Circulating immune complexes
CMH	Cochran Mantel Haenszel
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DB	Double blinded
DMC	Data Monitoring Committee
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
GM	Geometric mean
HLT	High level term
IgAN	Immunoglobulin A nephropathy
IRS	Interactive Response System
ISR	Injection site reactions
ITT	Intent-to-Treat Analysis Set
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
MAC	Membrane attack complex

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PK	Pharmacokinetic(s)
PD	Pharmacodynamic
PT	Preferred Term
RAS	Renin-angiotensin system
RBC	Red blood cell
RNAi	RNA interference
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	System Organ Class
TEAEs	Treatment emergent adverse events
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UP	Urine Protein
UPCR	Urine protein:creatinine ratio
WHO-DRL	WHO Drug Dictionary

1. INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis and can progress to renal failure.

The clinical presentation of IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis. The therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. No disease-specific therapies are currently available, and an unmet need persists for disease-modifying interventions.

Cemdisiran is an investigational RNA interference (RNAi) therapeutic designed to suppress liver production of complement component 5(C5) mRNA that is covalently linked to a triantennary N-acetylgalactosamine (Tri-GalNAc)

ligand, resulting in inhibition of terminal complement pathway activity and prevention of membrane attack complex (MAC) formation and C5a release. This inhibition would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN, resulting in reduced renal injury. 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.

Study ALN-CC5-005 is a Phase 2 study to evaluate the efficacy and safety of cemdisiran in the treatment of patients with IgAN. This statistical analysis plan (SAP) has been developed based on the Protocol Amendment 4 dated 19 January 2021. Any change to the data analysis methods described in the protocol, as well as the justification for the change, will be described in the SAP (Section 8).

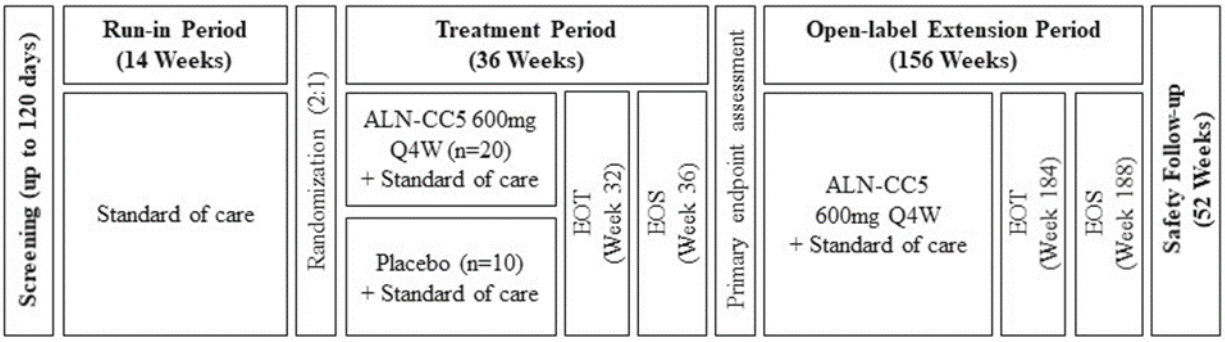
2. STUDY OVERVIEW

2.1. Study Design

This study is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). Eligible patients will begin a 14-week observational run-in period during which treatment with the standard of care is expected to remain unchanged. At the end of run-in period, patients whose average urine protein (UP) of two valid urine collections is at or higher than 1g/24-h are eligible for randomization into the 36-week double blind (DB) period. Approximately 30 patients are planned to be randomized in a 2:1 ratio, 20 in the cemdisiran arm and 10 in the placebo arm in the DB period, which is followed by a 156-week open-label extension (OLE) period to further evaluate the long-term safety and efficacy. All patients will be followed for safety for 52 weeks after the end of study visit.

The independent Data Monitoring Committee (DMC) will have access to subject level treatment assignments and perform periodic reviews of unblinded data throughout. Details are provided in the DMC Charter of the study.

Figure 1 Study Design



2.2. Randomization Methodology

At the end of run-in period, patients will be randomized 2:1 to the cemdisiran or placebo arms upon confirmation of eligibility using the Interactive Response System (IRS), followed by vaccination against meningococcal infections. Randomization will be carried out by the permuted block randomization stratified by baseline urine proteinuria levels (≥1g/24h and <2g/24h versus ≥2g/24h).

2.3. Blinding and Unblinding

Treatment assignments will be maintained by the IRS. Any unplanned unblinding to investigators or patients occurring during the 36-weeks DB placebo-controlled treatment period will be documented and reported in the Clinical Study Report (CSR).

During the DB treatment period, all subjects will be randomly assigned to cemdisiran or placebo. All site personnel and patients will be blinded to study drug during the DB period. Sponsor personnel will not be blinded to study treatment. Details regarding the blinding aspects during the study are outlined in a Randomization and Blinding Plan for ALN-CC5-005.

2.4. Study Procedures

The schedules of assessments are described in study protocol Table 1 for the DB period and study protocol Table 2 for the OLE period.

3. OBJECTIVE AND ENDPOINTS

The study objectives and endpoints based on the study protocol are presented Table 1 below.

Table 1 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-hour) at Week 32 • Percent of patients with >50% reduction in 24-hour proteinuria at Week 32 • Change from baseline in UPCR as measured in 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 • To evaluate the pharmacodynamic (PD) effect of cemdisiran, 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 (Urine Protein [UP] <0.3 g/24-hour) at Week 32 • Change from baseline in 24-hour albuminuria at Week 32

Objectives	Endpoints
• 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)

4. PATIENT POPULATION

4.1. Population Definitions

The following patient populations will be used for analyses:

- Modified Intent-to-Treat Analysis Set (mITT): All patients who receive any amount of study drug and have baseline and at least one post-baseline 24-hour urine protein creatinine ratio assessment. Patients will be grouped by assigned treatments (i.e., as randomized).

- Safety Analysis Set: All patients who receive any amount of study drug. Patients will be analyzed according to the treatment actually received.
- PK Analysis Set: All patients who receive a full dose of study drug and have at least 1 PK concentration measurement.
- PD Analysis Set: All patients who receive a full dose of study drug and who have at least one post-dose blood sample for the determination of plasma C5 level.
- All Cemdisiran Treated Set: All patients who receive at least one dose of cemdisiran, including patients who take cemdisiran during the DB period and patients who first take placebo during the DB period and switch to cemdisiran during the OLE period.

The primary population used to evaluate efficacy will be the mITT Population unless stated otherwise. 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. The All Cemdisiran Treated Set will be used to summarize long-term efficacy and safety of cemdisiran.

4.2. Protocol Deviations

Protocol deviations will be classified into major or minor deviations by medical review. A major deviation is defined as a deviation that may significantly impact the completeness, accuracy and/or reliability of the trial data; that may significantly affect a patient's rights, safety and well-being (ICH.E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry. 2013). Major protocol deviations will be reviewed and approved by Alnylam prior to the interim database lock for the primary analysis of the DB treatment period. All protocol deviations will be presented in a listing. The Sponsor or designee will be responsible for producing the final protocol deviations file. This file will include at a minimum each protocol deviation and whether or not this deviation is classified as a major protocol deviation. This file will be finalized prior to the primary treatment phase database lock. Protocol deviations will be summarized in the CSR.

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

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 urine protein/creatinine ratio [UPCR(mg/mg)] as measured in 24-hour urine 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 NEFIGAN study,[Fellstrom 2017] 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.

5.2. General Methods

Categorical variables will be summarized by frequency and percentage in each category. Continuous variables will be summarized by the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, maximum and geometric mean (GM) when appropriate. For log-transformed data, coefficient of variation (CV) and geometric mean (GM) will also be presented. CV is calculated as $\sqrt{\exp(\text{variance of log transformed data}) - 1} \times 100\%$.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Median, mean, standard deviation and standard error will be presented to the level of precision collected in database plus one additional decimal.

Day 1 will be defined as the day of the first dose of study drug (cemdisiran or placebo). Study Day is relative to first dosing date of study drug for all patients.

- If the assessment date is after the date of first study drug dose, then the study day will be calculated as:

  Study Day = Date of assessment – date of first dose of study drug + 1

- If assessment date is before the date of the first dose of study drug, then study day will be calculated as:

  Study Day = Date of assessment – date of first dose of study drug

For patients who were randomized to placebo and switched to cemdisiran in OLE period, an additional study day will be defined which reflects the study days relative to the first dose of cemdisiran.

For laboratory parameters, any assessments recorded as lower than the lower limit of quantification (LLOQ) will be replaced by the respective LLOQ value. Any assessment recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the respective ULOQ value. For assessments with repeated collections at a given study visit (e.g. ECG parameters) the mean will be used as the value at the visit for all parameters.

For all analysis sets except for the All Cemdisiran Treated Set, summaries will be presented by treatment arm (cemdisiran and placebo). For the All Cemdisiran Treated Set, summaries will be presented by the following treatment sequence groups:

- Cemdisiran / Cemdisiran: all patients who received cemdisiran during the DB period, including patients who continued to receive cemdisiran during the OLE period and patients who discontinued treatment during the DB period
- Placebo / Cemdisiran: all patients who received placebo during the DB period and switched to cemdisiran in the OLE period
- All Cemdisiran: all patients who received at least one dose of cemdisiran during either the DB or OLE period

5.3. Baseline Definitions

Baseline value for 24-hour UP, UPCR, and UACR will be calculated as the average of two valid (as per section 6.4.1.1 of the protocol) collections at week -2 visit (i.e., the last measurement prior to the first dose of study drug). Baseline values for vital signs will be defined as the assessments at week -2 visit because of the required vaccination when applicable. The baseline value for an ECG variable (heart rate, PR interval, QRS interval, QT interval or QT_c interval) will be the average of last triple assessments prior to the first dose of study drug (Day 1). For other parameters, baseline is defined as the last non-missing value prior to the first dose date/time of the study drug, unless otherwise specified.

For the All Cemdisiran Treated Set, baseline for patients randomized to cemdisiran in DB period is as defined above. For patients who switched from placebo in the DB period and received at least one dose of cemdisiran in the OLE period, baseline for all parameters will be redefined as the last non-missing assessments prior to the first dose of cemdisiran, except for assessments based on 24-hour urine collections where the average of the two valid collections at week 32 visit will be the baseline value and for ECG variables where the average of the last triplet assessments prior to the first dose of study drug in OLE period will be the baseline.

5.4. Randomization Stratification Factors

The randomization will be stratified based on the baseline 24-hour UP (≥ 1g/24-hour and <2g/24-hour versus ≥2g/24-hour). The mean of two valid 24-hour urine protein assessments at week -2 visit will be used to determine the stratification. The stratification factor will be recorded in both the IRS and the clinical database.

5.5. Multiple Comparisons/Multiplicity

All comparisons will be descriptive in nature and no multiplicity adjustment will be made.

5.6. Missing Data

Missing values will not be imputed, unless otherwise specified.

Patients who discontinue the study prior to Week 36 visit will be encouraged to remain on study and complete their remaining clinical visits (excluding PK assessments) through the visit at Week 36. All data collected regardless of whether it was collected before or after treatment discontinuation will be used for analysis. However, it is possible that data will remain missing.

In case of missing date or partial date of adverse event (AE) onset, an AE will be considered treatment-emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to first dose of study drug.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug in this study; medications will be classified as prior or both prior and concomitant depending on the medication stop dates. If any medications have a completely missing stop date, then the medication will be assumed as ongoing.

5.7. Visit Windows

For table and figure summaries of the DB period, all data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report forms (eCRF) even if the assessment is outside of window.

For table and figure summaries during cemdisiran treatment period, the data collected at study visits during the OLE period will be re-mapped for the patients randomized to placebo in the DB period to reflect the visit relative to the first dose of cemdisiran. Unless otherwise specified, data collected at an unscheduled visit will be included in by patient listings and/or spaghetti plot figures, but no assignment of the scheduled visit will be made for the purposes of summary tabulations. However, unscheduled study visits will be used in categorical shift tables (e.g. shift from baseline to worst post-baseline value).

5.8. Analysis Cutoff and Database Lock

As this study will be ongoing when the database lock for the primary analysis is performed, the study database will have an interim database lock (i.e. data in EDC will be frozen and external data such as laboratory data will be QA'd and cleaned), when the last patient completes Week 36 assessments. The study will then be unblinded and all data entered as of the date cutoff for the primary interim database lock will be included in the primary analysis. Additional details regarding the database lock are located in the study Data Management Plan.

After the study is completed, i.e., all patients complete the OLE period and the safety follow-up visits, a final database lock will occur, and all data collected will be summarized in the final CSR.

5.9. Interim Analyses

No formal interim analysis is planned for this study. Informal data looks prior to the primary interim analysis are planned for the monitoring of the study by DMC and the sponsor.

5.10. Primary and Final Analyses

The study includes a 36-week DB period, a 156-week OLE period, and a 52-week safety follow up period. The primary analysis is to evaluate the efficacy and safety of cemdisiran compared to placebo during the DB period.

For the primary analysis, tables and figures will be presented by treatment arm (cemdisiran, placebo). Selected outputs will also be summarized by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran and all cemdisiran treated). When assessments or AE onset dates are exactly the first dose date in the OLE period with time missing, the records will be included in the OLE period. Per-patient listings will include all data collected during the entire study. The listings will be sorted by randomized arm. Within patient, there will be a variable to indicate the period of the data collection.

Final analysis evaluating the long-term efficacy and safety of cemdisiran will be described for the All Cemdisiran Treated Set. Summary tables and figures will be presented by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran and all cemdisiran treated).

For patients who received placebo in the DB period and switched to cemdisiran in the OLE period, the intra-patient comparison of the two treatment periods will be conducted for 24-hour UP, 24-hour UPCR, spot UPCR and eGFR in the final analysis. The time period during which patients receiving cemdisiran (i.e. on or after the first date/time of cemdisiran) is referred as "during cemdisiran treatment".

The detailed definitions for different study periods are as the following:

- **DB Period**

It is defined as the time between the first dose of study drug and Week 36/end of study (EOS) visit. For patients who do not have the Week 36/EOS visit, it is the time between the first dose of study drug and the targeted Week 36/EOS visit (Day 252).

- **OLE Period**

The start date of the OLE period is defined as the first dose of cemdisiran of the OLE period (i.e., week 36 visit) and ends at week 188/EOS visit.

- **Safety Follow-up Period**

The 52-week safety follow-up period starts at week 36/EOS visit (for patients not continuing into the OLE) or week 188/EOS visit.

6. STUDY ANALYSES

6.1. Patient Disposition

Number and percentage of patients in the following categories will be summarized by treatment arm (or by treatment sequence) and overall, as appropriate:

- Screen failures (overall only)
- Enrolled for Run-in Period (signed informed consent and met eligibility criteria; overall only) and those failed during Run-in period
- Randomized
- Treated
- Modified Intent-to-Treat Analysis Set (mITT)
- Safety Analysis Set
- PK Analysis Set
- PD Analysis Set
- All Cemdisiran Treated Set (by treatment sequence)
- Entered the OLE period.

In addition, summaries of the number and percentage of patients who discontinued treatment, withdrew from study, and primary reasons for either discontinuation of treatment and/or withdrawal from study will be presented. The number and percentage of patients in each level of

randomization stratification factor, baseline 24-hour UP (>=1g/24-hours and <2 g/24-hours vs. ≥2 g/24-hours), recorded in IRS and the clinical database will be summarized by randomized treatment arm and overall. The numbers of subjects screened will be summarized by country and site.

Data listings of those patients who withdrew study and/or discontinued treatment including the associated reasons will also be presented. A separate listing of screening failure patients with the associated reason for screen failures will be generated.

6.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for mITT and Safety Analysis Sets (if different).

Descriptive statistics of demographic characteristics including but not limited to: age (years), age category (<65 years vs. ≥ 65 years), sex, race, ethnicity, height, weight, and body mass index (BMI) and country.

Baseline disease characteristics including but not limited to: the 24-hour UP, the 24-hour UP category ((≥ 1g/24-hour and < 2g/24-hour vs. ≥ 2g/24-hour), UPCR as measured in 24-hour urine and in spot urine, eGFR (mL/min/1.73m^2), eGFR category (30-44, 45-59, 60-89, ≥90) (mL/min/1.73m^2), eGFR category (30-59, ≥60) (mL/min/1.73m^2), blood pressure (SBP and DBP), age at diagnosis, time from diagnosis to randomization, MEST-C score, IgA, IgG, IgM, C3, C1q, C4d, and C5b-9.

6.3. Medical History, Prior and Concomitant Medications

Medical history, prior and concomitant medications will be summarized for the Safety Analysis Set.

The medical history data will be coded with the Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or higher). The number and percent of subjects by System Organ Class (SOC), high level term (HLT) and Preferred Term (PT) will be summarized by treatment group and overall. Prior and concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary (September 2018 or later).

Prior medications are defined as medications that were taken prior to the first dose of study drug (cemdisiran or placebo). Concomitant medications are defined as medications which were taken prior to and were ongoing while on study drug or medication(s) taken on or after the first dose date of the study drug.

Tabular summary of the number and percentage of subjects taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term. Listing will be provided for medical history, prior and concomitant medications.

6.4. Drug Exposure

The following variables are summarized using Safety Analysis Set but not limited to; the total number of doses received and missed per patient, mean number of dosing per patient, duration of drug exposure (weeks), and cumulative drug exposure time (person years).

Drug exposure (days) will be defined as [Exposure time= (date of last exposure – date of first dose +1)] where date of last exposure will represent either the date of the last administered dose +28, analysis cut-off date or end of study date, whichever is earliest. The exposure during the DB period will be right censored; that is, the date of the last exposure will not be later than the first date of dosing in the OLE period. Dose interruptions and compliance are not taken into account.

Drug exposure for the all cemdisiran treated set will be summarized in a similar way as in the DB period.

7. STATISTICAL ANALYSIS

7.1. Primary Endpoint

The primary endpoint of the study is the percent change from baseline in urine protein/creatinine ratio [UPCR] as measured in 24-hour urine at Week 32. The analysis will be conducted using the modified ITT analysis set.

Valid 24-hour urine protein values collected during the DB period will be included in the primary analysis (1 valid assessment at week 16 visit and the mean of two valid assessments at baseline and week 32 visit). All 24-hour urine samples need to meet the validity criteria below (Section 6.4.1.1 of the protocol). The 24-hour UPCR at baseline or Week 32 is the average of two valid collections.

A 24-hour urine collection will be considered valid if the following criteria are met:

- 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 resulting 24-hour UPCR at each visit will be log transformed for analyses.[Fellstrom 2017; Li 2006] 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 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. Unstructured working correlation will be used to model the within-patient errors. If the fit of covariance structure fails to converge, independent correlation structure will be used. At each visit, least square (LS) means ($\hat{\mu}_j$) with corresponding standard errors (SEM) and 90% CI will be displayed by treatment arm. The primary comparison is the LS mean treatment difference (cemdisiran – placebo) in percent change of 24-hour UPCR at week 32 visit from baseline. This LS mean difference will be presented along with corresponding standard errors (SEMs), 90% CIs and p-value from the model.

The following results will also be presented:

- Placebo-adjusted geometric mean percent change at week 32 visit:

$$\frac{\mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{cemdisiran}} - \mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{placebo}}}{\mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{placebo}}} * 100$$

$= [\exp(\delta) - 1] * 100$, where δ is the LS mean treatment difference between the two arms from the MMRM model in log-scale above.

- The 90% CI for the placebo-adjusted geometric mean percent change:

$$[(\exp(lower\ bound\ for\ \delta) - 1) * 100,\ \ (\exp(upper\ bound\ for\ \delta) - 1) * 100]$$

In addition, the geometric mean for the ratio to baseline at week 32 visit in 24-hour UPCR and 90% confidence intervals for each treatment group will be presented using respective LS means ($\hat{\mu}_j$) and corresponding 90% confidence intervals (j=0 if placebo and j=1 if cemdisiran):

$$exp(\hat{\mu}_j) \text{ and } \left[\exp(lower\ bound\ for\ \mu_j), \exp(upper\ bound\ for\ \mu_j)\right]$$

Descriptive statistics will also be generated for 24-hour UPCR (in original scale and log scale) by treatment arm at each scheduled visit during DB and OLE and plotted. Model adjusted geometric mean (with 90% CI) figures of the ratio to baseline by treatment arm will be plotted as well as individual spaghetti plots.

The 24-hour UPCR data will also be summarized descriptively to evaluate the long-term efficacy of cemdisiran using the All Cemdisiran Treated Analysis Set.

7.1.1. Sensitivity Analyses

The first sensitivity analysis will be conducted to evaluate the robustness of the primary model using normality of log-transformed 24-hour UPCR data assumption. A stratified rank ANCOVA analysis [LaVange and Koch 2006] will be conducted without using the normality assumption of log-transformed 24-hour UPCR data. The following steps will be performed:

1. Standardized ranks within each stratification stratum will be derived across the two treatment groups for the baseline and the change from baseline at Week 32 in 24-hour UPCR
2. The linear regression model will be fitted separately for each stratum where the standardized rank of the change from baseline at Week 32 in 24-hour UPCR is the outcome variable, the standardized rank of the baseline is the only covariate
3. The stratified mean score test will be performed to compare the two treatment groups using the values of the residuals from the above model as scores and stratification factor as the stratum
4. Cochran–Mantel–Haenszel (CMH) p-value is obtained

The second sensitivity analysis is to assess the impact of missing data and the robustness of the primary analysis. The analysis will use the same MMRM model on the imputed data, of which the missing 24-hour UPCR value will be imputed with the spot UPCR [Ginsberg 1983; Viswanathan and Upadhyay 2011] assessed closest to the date of missing value, when available. Depending on the extent of missing values this sensitivity analysis might not be needed.

7.1.2. Subgroup Analyses

Subgroup analyses will be conducted to assess the treatment effect during the DB period for the primary endpoint within the following subgroups: race (Asian vs. non-Asian), gender (Male vs. Female), age (< Median vs. ≥ Median), baseline eGFR (< 60 ml/min/1.73m^2 vs. ≥ 60 ml/min/1.73m^2), and baseline 24-hour UP (>=1g/24-hour and < 2g/24-hour vs. ≥ 2g/24-hour). Other subgroups may be examined, if deemed appropriate.

The subgroup analysis will be performed for the primary endpoint using the mITT analysis set. A forest plot will be generated to illustrate the estimated treatment effect along with the associated 90% confidence interval. The subgroup analyses may be performed for secondary endpoints if appropriate.

7.2. Secondary Endpoints

For secondary endpoints assessed in DB period, the analysis will compare randomized arms (cemdisiran vs. placebo) using the mITT analysis set.

The secondary endpoints which are assessed beyond Week 36 will be summarized to describe the long-term efficacy of cemdisiran using the All Cemdisiran Treated Analysis Set by treatment sequence, i.e., cemdisiran/cemdisiran, placebo/cemdisiran, and All Cemdisiran.

The planned analyses of the secondary endpoints are summarized in Table 2.

Table 2 Summary of Analyses for the Secondary Efficacy Endpoints

Endpoint	Statistical Method	Notes
Percent of patients with partial clinical remission (urine protein [UP] <1.0g/24-hour) at Week 32	Treatment comparison will be conducted using Cochran-Mantel-Haenszel test stratified by baseline 24-hour UP (≥ 1g/24-hour and <2 g/24-hour vs. ≥2 g/24-hour). The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Wilson score method with continuity correction will be presented.	
Percent of patients with >50% reduction in 24-hour proteinuria at Week 32		

Endpoint	Statistical Method	Notes
Percent change from baseline in 24-hour proteinuria (g/24-hour) at Week 32	Treatment comparison and estimates will be conducted by a similar MMRM model used for the analysis of primary endpoint. Descriptive statistics will also be generated by treatment arm at each scheduled visit. Geometric Mean (with 90% CI) figures of the ratio to baseline by treatment arm will be plotted as well as individual spaghetti plots.	
Change from baseline in UPCR as measured in a spot urine at Week 32	The change from baseline in log-transformed spot UPCR by visit through Week 36 will be analyzed via a MMRM model. The model includes log-transformed baseline spot UPCR, treatment, visit, and the interaction of treatment and visit. Robust errors [White 1980] will be used to model the within-patient errors. Descriptive statistics will also be generated by treatment arm at each scheduled visit. Geometric Mean (with 90% CI) figures of the ratio to baseline by treatment arm will be plotted as well as individual spaghetti plots.	Scheduled assessments are outlined in the Table 1 (Schedule of Assessments) of the protocol.
Change from baseline in hematuria at Week 32	Shift tables for both assessment methods (microscopic examination and urine dipstick) will be presented	Results using microscopy and dipstick are both in range categories.

7.3. Exploratory Analyses

Exploratory endpoints will be summarized descriptively by treatment arms during the DB period using mITT Analysis set.

For the slope of eGFR computed for the entire study period, it will also be analyzed by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran) using the All Cemdisiran Treated Analysis Set. However, the other exploratory endpoints may be analyzed over the entire study if deemed appropriate. Table 3 summarizes the planned analyses for exploratory endpoints.

Table 3 Summary of Analyses for Exploratory Endpoints

Exploratory Endpoint	Statistical Method	Notes
Change from baseline in estimated glomerular filtration rate (eGFR)[1] at Week 32	Descriptive statistics of eGFR will be presented by visit and treatment arm. Individual patient data will be presented in spaghetti plots. Shift tables of eGFR categories from baseline to post-baseline visits and an overall worst post-baseline will also be presented.	
The slope of eGFR computed for the first 36 weeks using all assessments during the period	The random coefficient model for eGFR will include baseline eGFR, treatment, time (in year), and the interaction of treatment and time as fixed effects and intercept and time as random effects.	The first study drug dosing will be defined as the time reference point t=0 In addition, the slope of eGFR for each subject will be estimated.
The slope of eGFR computed for the entire cemdisiran treatment period including patients who started on placebo in the DB period then switched to cemdisiran in the OLE period, and those started on cemdisiran in the DB period.	The random coefficient model for eGFR will include baseline eGFR, treatment sequence, time (in year), and the interaction of treatment sequence and time as fixed effects and intercept and time as random effects.	This endpoint will be analyzed only at the final analysis using Cemdisiran Treated Analysis set. The first administration of cemdisiran will be defined as the time reference point t=0.
The slope of eGFR during placebo period comparing the slope during OLE for patients who crossed over from placebo to cemdisiran.	The random coefficient model with piecewise regression will include baseline eGFR, time during the placebo treatment and time during the cemdisiran treatment as fixed effects and intercept and times as random effects.	This endpoint will be analyzed only at the final analysis using placebo/cemdisiran treatment sequence group.
Change from baseline in creatinine clearance at Week 32	Descriptive statistics will be presented by visit and treatment arm.	See section 6.4.3 in the protocol for creatine clearance

Exploratory Endpoint	Statistical Method	Notes
Percent of patients in full clinical remission (Urine Protein [UP]<0.3 g/24-hour) at Week 32	The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Newcombe method based the Wilson score with continuity correction will be presented.	
Change from baseline in 24-hour albuminuria at Week 32	Descriptive statistics will be presented by visit and treatment arm.	
Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32	Descriptive statistics will be presented by visit and treatment arm.	
Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study	The levels of the biomarkers and their changes and percentage changes from baseline will be summarized descriptively by visit and treatment arm or treatment sequence	

[1] eGFR will be based on CKD-EPI: $eGFR = 141 * \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} * \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} * 0.993^{Age} * 1.018[if\ female] * 1.159[if\ black]$. Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1, age is calculated at visit: age at consent + (visit date-consent date)/365.25 and rounded to integer.

7.4. Pharmacodynamic Analyses

PD endpoints will be summarized by treatment arm at the primary analysis using the PD analysis set and at the final analysis by treatment sequence using All Cemdisiran Treated Analysis Set. Analyses of PD endpoints are summarized in Table 4 below.

Table 4 Summary of Analyses for Pharmacodynamic Variables

Endpoint	Statistical Method	Notes
Change from baseline in C5 level over the course of the study	Absolute change and percentage change from baseline in C5 will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	
Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study	The levels of CAP and CCP and the changes and percentage changes from baseline will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	The biomarkers of complement activation include but not limited to C5a, sC5b9 in plasma, and sC5b9 in urine.

7.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed for cemdisiran and active metabolite, AS(N-2)3'-ALN-CC5 and AS(N-3)3'-ALN-CC5 cemdisiran, using noncompartmental methods. PK analyses will be performed at the final analysis based on the Pharmacokinetic Analysis Set. Summaries will be provided for each scheduled time point. PK data will be included in by-patient data listings. The following PK parameters will be estimated for each subject, as appropriate and if data permits: area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{½\beta}$), apparent clearance (CL/F), apparent volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe). Additional PK parameters may be calculated, if deemed necessary. The PK parameters will be summarized using descriptive statistics.

Pharmacokinetic analyses will be conducted using noncompartmental methods. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

7.6. Safety Analyses

Primary safety analyses will compare cemdisiran versus placebo during the DB period using the Safety Analysis Set. Long-term safety analyses of cemdisiran will be summarized by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran, all cemdisiran treated arm) using the all Cemdisiran Treated Analysis set.

The primary safety parameter is the frequency of treatment emergent adverse events (TEAEs). A TEAE is defined as an AE that occurred or worsened on or after the first dose of study drug through 28 days after the last dose of study drug. In addition, an AE that occurs after the 28 days from the last dose but is considered to be related to study drug, is considered to be a TEAE. Other safety parameters include vital signs, ECGs, clinical laboratory assessments, and physical exams. Adverse events that are non-treatment emergent (e.g., during safety follow up period) will be summarized and listed separately.

7.6.1. Adverse Events

All TEAEs hereafter will be referred to as AEs in this document. No statistical tests will be performed to compare AE rates between treatment groups. Adverse events will be coded using MedDRA version 21.1 or higher and displayed in tables using SOC and PT.

An overview table of AEs will be tabulated. The overview table will include the number and percentage of patients in following categories such as, but not limited to:

- At least 1 AE
- At least 1 study drug related AE
- At least 1 severe AE
- At least 1 study drug related severe AE
- At least 1 Serious Adverse Event (SAE)
- At least 1 study drug related SAE
- At least 1 AE leading to treatment discontinuation
- At least 1 study drug related AE leading to treatment discontinuation
- At least 1 AE leading to study withdrawal
- At least 1 study drug related AE leading to study withdrawal
- Death

Tabulations by SOC and PT displaying the number of patients (percentage) and total events will be produced for the following tables:

- All AEs
- Severe AEs
- AEs by Maximum Severity
- AE related to treatment
- AEs related to treatment by Maximum Severity
- All SAEs
- SAEs related to treatment
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AEs leading to study withdrawal

Tabulations by PT in decreasing order in frequency within the cemdisiran arm will be generated for the following tables:

- All AEs
- All SAEs

- AEs related to treatment
- SAEs related to treatment

In summaries by SOC and PT, AEs will be sorted alphabetically by SOC then by PT.

There will also be an overall AE table generated displaying rates of adverse events adjusted for exposure-time during the respective period. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence or most related.

Separate listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug, withdrawal of study drug, and/or dose interruption. By-subject AE listings will be provided.

7.6.2. Adverse Event of Clinical Interest (AECI)

Additional summaries of safety areas of interest based on Standardized MedDRA Queries (SMQs) and other groupings of AEs may be summarized such as, but not limited to the following:

- Injection Site Reactions [ISRs]: AEs mapping to the High-Level Term (HLT) = "Injection Site Reactions" using MedDRA dictionary will be included in the summary.

  Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. A table will also be generated to display the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose in summary), total number of doses with ISRs, and the signs and symptoms reported due to ISRs. If there are multiple ISRs that occur in between two consecutive injections, then these events will be considered as 1 ISR and considered related to the earlier injection.

- Hepatic AEs, including AEs of LFT abnormalities: These AEs are mapped to the SMQ Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms).

  Frequency (percentages) of drug-related hepatic disorders will be summarized by SOC, HLT and PT. A separate listing will be generated of all patients reporting these events.

7.6.3. Laboratory Data

Clinical laboratory parameters will be expressed in Standard International (SI) units. Summaries will only include data from central laboratory. For any local collections of LFTs, these will be included in a separate data listing. Key laboratory parameters will be graded according to NCI CTCAE v5.0.

Summaries for each lab parameter (hematology, chemistry, liver function tests, coagulation and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics

at each scheduled visit. Descriptive statistics include actual value, change from baseline and percent change from baseline at each scheduled visit.

Shift tables will be generated to summarize shifts from baseline categories to the worst post-baseline categories with directionality specified for any labs which could be reported in either direction (e.g. above the upper limit of normal [ULN] or below ULN).

Clinical laboratory tests with normal ranges will be classified as Low, Normal, and High. For these tests, abnormal values will be flagged in the listings with H when the value is higher than the upper limit of the reference ranges and with L when the value is lower than the lower limit of the reference ranges.

For hematology and chemistry labs, summary tables of potentially clinically significant abnormalities will also be provided.

All laboratory data will be presented in data listings. Separate listings will be included for those laboratory data collected from local labs such as LFTs. Out of range laboratory results will be identified in listings.

7.6.4. Liver Function Analysis

A listing will be generated for all patients with abnormal liver function tests as defined by ALT>3xULN, AST>3xULN and total bilirubin >2x ULN at any visit.

A tabular summary for LFTs will be generated to summarize the number and associated percentage of patient in each of the categories at any post-baseline visit:

- ALT>1 & ≤3, ALT>3 & ≤5, ALT>5 & ≤10, ALT>10 & ≤20, ALT>20xULN
- AST>1 & ≤3, AST>3&≤5, AST>5& ≤10, AST>10 & ≤20, AST>20xULN
- ALT or AST>1 & ≤3, ALT or AST>3 & ≤5, ALT or AST>5 & ≤10, ALT or AST>10 & ≤20, AST or ALT>20xULN
- WNL, ALP>1.5xULN
- Total Bilirubin>1.5& ≤2, Total Bilirubin>2&≤3, Total Bilirubin>3& ≤5 and Total Bilirubin>5

eDISH plots of peak total bilirubin at any time versus peak ALT or AST at any time will also be presented. For selected labs (e.g. ALT/ULN and AST/ULN), a table and figure of the values across the entire study (DB+OLE) will be generated by treatment sequence arms.

7.6.5. Vital Signs

Descriptive statistics for each vital sign (e.g. systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, weight, body mass index) will be summarized at scheduled visits. Summaries will include actual values and changes from baseline.

Vital sign measurements will be presented for each patient in a data listing, with abnormal vital signs flagged.

7.6.6. Electrocardiogram

For electrocardiogram (ECG) parameters, these will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each timepoint will be summarized. For assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis

ECG findings will include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTc).

Corrected QT interval, if not collected, will be calculated using Fridericia's correction formula.

Fridericia's cube-root corrected QT: QTcF (ms) = QT (ms) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$.

Baseline, post baseline maximum QTcF and post baseline maximum change from baseline in QTcF during the study will be summarized with descriptive statistics. The incidence of notable ECG changes from baseline in maximum absolute QT_cF, intervals (<=450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF, maximum changes from baseline (<=30 ms, > 30 -60 ms and > 60 ms) over all post-treatment evaluations will be summarized. A listing of all ECG data will be provided.

7.6.7. Physical Examination Findings

Physical examinations will be conducted throughout the study. If any abnormalities are observed during these physical exams, then this will be recorded on the adverse event form.

A separate listing per patient will be generated to display the date and time of the physical exam.

7.7. Anti-Drug Antibody

Patients with treatment-induced ADA will be placed in the treatment emergent ADA positive group for the calculation of ADA incidence. Treatment induced ADA is defined as ADA developed de novo (seroconversion) after drug administration (i.e., formation of ADA at any time after the initial drug administration in patients without pre-existing ADA)

The number and associated percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized by treatment group. A listing of patients with positive ADA assay results and corresponding titers will be provided along with the ADA results. Circulating Immune Complexes (CIC) and anti-GdIgA1 antibody will be summarized descriptively by visit as appropriate and the corresponding listing will be provided.

7.8. COVID-19 Pandemic Impact Analyses

Additional data were collected to characterize the impact of the COVID-19 pandemic on study conduct as shown in Appendix 10.1.

7.8.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 as assessed in the COVID-19 Data Collection Instrument will be included in patient disposition summaries.

Impact on study participation due to COVID-19 pandemic, including visit(s) missed, delayed, partially completed, completed, location changes (telehealth, local labs, other sites), study drug dosing missed or delayed will be summarized overall on the patient level, and overall and by visit on the event level. Visit and dosing delays can be defined by time windows specified by the protocol before the pandemic and the relaxed windows in responding to the pandemic in Amendment 4 (dated 19 January, 2021).

7.8.2. Impact on Efficacy

A summary of missing data for primary and secondary efficacy endpoints due to COVID-19 pandemic will be provided. Specifically, the number and percent of patients in each treatment arm with missing data in 24h UPCR/24h UP, spot UPCR, and hematuria by microscopic examination and urine dipstick at each scheduled assessment visit will be presented. Missing efficacy data due to Covid-19 could be identified by if the visit associated with the assessment is missed (Appendix 10.1).

For primary and secondary efficacy endpoints, the number and percentage of patients with out-of-window visits based on the original protocol at each scheduled visit will be summarized.

7.8.3. Impact on Adverse Events

The number and percent of patients with AEs mapped to COVID-19 custom query by HLT and PT will be presented for overall and by treatment.

7.8.4. Other Impacts

Protocol deviation due to the COVID-19 pandemic will be summarized and will be indicated in the listing of protocol deviation. AEs, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic. For patients reporting an AE mapped to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings.

8. CHANGES TO PLANNED ANALYSES

Change from SAP Amendment 1.0	Detailed Description/Rationale
5.8 Analysis Cutoff and Database Lock	Removed wording of Week 36 primary CSR as there will be no CSR for the Week 36 primary analysis.
6.4 Drug Exposure	Summary for the All Cemdisiran Treated Set added.
7.1 Primary Endpoint	Plots for summary of 24-hour UPCR in original and log scale added. Summary for long term efficacy using the all cemdisiran treated set added.
7.1.2 Subgroup Analysis	Added Race (Asian vs. non-Asian) to the list of subgroups.

Change from SAP Amendment 1.0	**Detailed Description/Rationale**
7.2 Secondary Endpoints	Summary tables and plots added for endpoints: 1.Percent change from baseline in 24-hour proteinuria (g/24-hour) at Week 32 2. Change from baseline in UPCR as measured in a spot urine at Week 32
7.3 Exploratory Analyses	Individual spaghetti plot added for endpoint: Change from baseline in estimated glomerular filtration rate (eGFR)[1] at Week 32
7.5 Pharmacokinetic Analyses	Added language to move PK analysis to the final analysis.
Various editorial changes	To add clarity

9. REFERENCES

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10. APPENDIX

10.1. COVID-19 Data Collection Instrument

Was the patient's participation in the study impacted by the COVID-19 global pandemic (e.g. missed, delayed or partially completed visit, missed/delayed study drug dose, visit location change such as phone visit, etc.)?

If yes, please provide details of study assessments/procedures (by visit) that were impacted:

Visit completion status

- Completed
- Partially completed
- Delayed
- Missed

Visit location changes (check all that apply)

- Telehealth, phone or home visit
- Local labs used to assess safety
- Visit occurred at different site
- Other, specify: _____
- Not applicable

Study drug dosing changes

- Missed dose
- Delayed dose
- No change

Signature Page for VV-CLIN-006399 v1.0
ALN-CC5-005 SAP Amend2

Task: Approval Verdict: Approve	[redacted]T+0000
Task: Approval Verdict: Approve	[redacted]T+0000
Task: Approval Verdict: Approve	[redacted]12:40 GMT+0000

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ALN-CC5-005 SAP Amend2

STATISTICAL ANALYSIS PLAN

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

Protocol Number:	ALN-CC5-005
Protocol Version and Date:	Original protocol: 10 September 2018 Amendment 1: 26 November 2018 Amendment 2: 30 August 2019 Amendment 3: 27 April 2020 Amendment 4: 19 January 2021
Investigational Drug:	ALN-CC5 (Cemdisiran)
Phase:	Phase 2
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 Tel: [redacted] Fax: [redacted]
Sponsor Representative:	[redacted]
Analysis Plan Version and Date:	Original version 1.0: 28 February, 2020 Amendment 1: 29 April 2021

Confidentiality Statement

APPROVAL SIGNATURE PAGE

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

Protocol Number: **ALN-CC5-005**

Analysis Plan Version and Date: Amendment 1: 29 April 2021

This document has been approved and signed electronically on the final page by the following:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin converting enzyme inhibitor
ADA	Anti-drug Antibody
AE	Adverse Event
AECI	Adverse Event of Clinical Interest
ANCOVA	Analysis of covariance
ARB	angiotensin II receptor blocker
C5	Complement component 5
C5a	Complement component 5a
CAP	Complement Alternative Pathway
CCP	Complement Classical Pathway
CI	Confidence interval
CIC	Circulating immune complexes
CMH	Cochran Mantel Haenszel
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DB	Double blinded
DMC	Data Monitoring Committee
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
GM	Geometric mean
HLT	High level term
IgAN	Immunoglobulin A nephropathy
IRS	Interactive Response System
ISR	Injection site reactions
ITT	Intent-to-Treat Analysis Set
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PK	Pharmacokinetic(s)
PD	Pharmacodynamic
PT	Preferred Term
RAS	Renin-angiotensin system
RBC	Red blood cell
RNAi	RNA interference
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	System Organ Class
TEAEs	Treatment emergent adverse events
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

Abbreviation	Definition
UP	Urine Protein
UPCR	Urine protein:creatinine ratio
WHO-DRL	WHO Drug Dictionary

1. INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis and can progress to renal failure.

The clinical presentation of IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis. The therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. No disease-specific therapies are currently available, and an unmet need persists for disease-modifying interventions.

Cemdisiran is an investigational RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, resulting in inhibition of terminal complement pathway activity and prevention of membrane attack complex (MAC) formation and C5a release. This inhibition would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN, resulting in reduced renal injury. 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. This approach is particularly appealing in IgAN where the relative contribution of the different complement pathways may vary between patients.

Study ALN-CC5-005 is a Phase 2 study to evaluate the efficacy and safety of cemdisiran in the treatment of patients with IgAN. This statistical analysis plan (SAP) has been developed based on the Protocol Amendment 4 dated 19 January 2021. Any change to the data analysis methods described in the protocol, as well as the justification for the change, will be described in the SAP (Section 8).

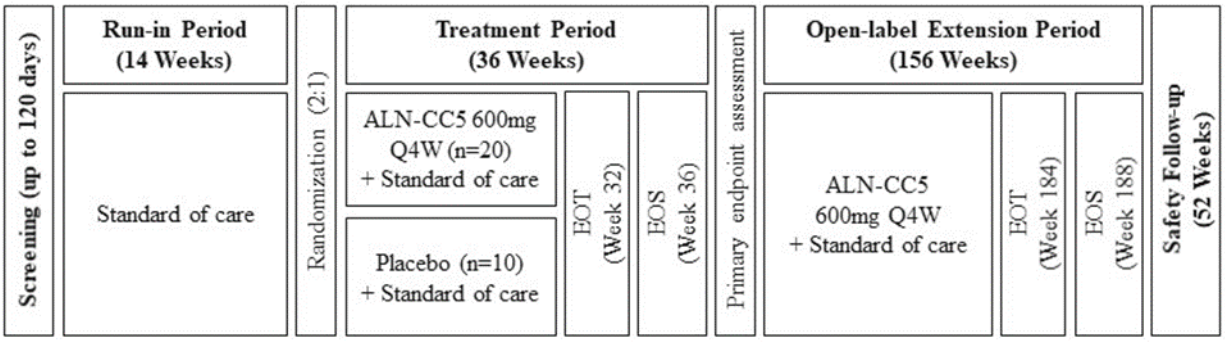
2. STUDY OVERVIEW

2.1. Study Design

This study is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). Eligible patients will begin a 14-week observational run-in period during which treatment with the standard of care is expected to remain unchanged. At the end of run-in period, patients whose average urine protein (UP) of two valid urine collections is at or higher than 1g/24h are eligible for randomization into the 36-week double blind (DB) period. Approximately 30 patients are planned to be randomized in a 2:1 ratio, 20 in the cemdisiran arm and 10 in the placebo arm in the DB period, which is followed by a 156-week open-label extension (OLE) period to further evaluate the long-term safety and efficacy. All patients will be followed for safety for 52 weeks after the end of study visit.

The independent Data Monitoring Committee (DMC) will have access to subject level treatment assignments and perform periodic reviews of unblinded data throughout. Details are provided in the DMC Charter of the study.

Figure 1 Study Design



2.2. Randomization Methodology

At the end of run-in period, patients will be randomized 2:1 to the cemdisiran or placebo arms upon confirmation of eligibility using the Interactive Response System (IRS), followed by vaccination against meningococcal infections. Randomization will be carried out by the permuted block randomization stratified by baseline urine proteinuria levels (≥1g/24h and <2g/24h versus ≥2g/24h).

2.3. Blinding and Unblinding

Treatment assignments will be maintained by the IRS. Any unplanned unblinding to investigators or patients occurring during the 36-weeks DB placebo-controlled treatment period will be documented and reported in the Clinical Study Report (CSR).

During the DB treatment period, all subjects will be randomly assigned to cemdisiran or placebo. All site personnel and patients will be blinded to study drug during the DB period. Sponsor personnel will not be blinded to study treatment. Details regarding the blinding aspects during the study are outlined in a Randomization and Blinding Plan for ALN-CC5-005.

2.4. Study Procedures

The schedules of assessments are described in study protocol Table 1 for the DB period and study protocol Table 2 for the OLE period.

3. OBJECTIVE AND ENDPOINTS

The study objectives and endpoints based on the study protocol are presented Table 1 below.

Table 1 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 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 • To evaluate the pharmacodynamic (PD) effect of cemdisiran, 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 (Urine Protein [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)

4. PATIENT POPULATION

4.1. Population Definitions

The following patient populations will be used for analyses:

- Modified Intent-to-Treat Analysis Set (mITT): All patients who receive any amount of study drug and have baseline and at least one post-baseline 24-hour urine protein creatinine ratio assessment. Patients will be grouped by assigned treatments (i.e., as randomized).
- Safety Analysis Set: All patients who receive any amount of study drug. Patients will be analyzed according to the treatment actually received.

- PK Analysis Set: All patients who receive a full dose of study drug and have at least 1 PK concentration measurement.
- PD Analysis Set: All patients who receive a full dose of study drug and who have at least one post-dose blood sample for the determination of plasma C5 level.
- All Cemdisiran Treated Set: All patients who received at least one dose of cemdisiran, including patients who took cemdisiran during the DB period and patients who first took placebo during the DB period and switched to cemdisiran during the OLE period.

The primary population used to evaluate efficacy will be the mITT Population unless stated otherwise. Safety during the DB period will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively. The All Cemdisiran Treated Set will be used to summarize long-term efficacy and safety of cemdisiran.

4.2. Protocol Deviations

Protocol deviations will be classified into major or minor deviations by medical review. A major deviation is defined as a deviation that may significantly impact the completeness, accuracy and/or reliability of the trial data; that may significantly affect a patient's rights, safety and well-being (ICH.E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry. 2013). Major protocol deviations will be reviewed and approved by Alnylam prior to the interim database lock for the primary analysis of the DB treatment period. All protocol deviations will be presented in a listing. The Sponsor or designee will be responsible for producing the final protocol deviations file. This file will include at a minimum each protocol deviation and whether or not this deviation is classified as a major protocol deviation. This file will be finalized prior to the primary treatment phase database lock. Protocol deviations will be summarized in the CSR.

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

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 urine protein/creatinine ratio [UPCR(mg/mg)] as measured in 24-hour urine 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 NEFIGAN study [Fellstrom 2017], 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.

5.2. General Methods

Categorical variables will be summarized by frequency and percentage in each category. Continuous variables will be summarized by the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum. For log-transformed data, coefficient of variation (CV) and geometric mean (GM) will also be presented. CV is calculated as $\sqrt{\exp(\text{variance of log transformed data}) - 1} \times 100\%$.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Median, mean, standard deviation and standard error will be presented to the level of precision collected in database plus one additional decimal.

Day 1 will be defined as the day of the first dose of study drug (cemdisiran or placebo). Study Day is relative to first dosing date of study drug for all patients.
If the assessment date is after the date of first study drug dose, then the study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug + 1

If assessment date is before the date of the first dose of study drug, then study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug

For patients who were randomized to placebo and switched to cemdisiran in OLE period, an additional study day will be defined which reflects the study days relative to the first dose of cemdisiran.

For laboratory parameters, any assessments recorded as lower than the lower limit of quantification (LLOQ) will be replaced by the respective LLOQ value. Any assessment recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the respective ULOQ value. For assessments with repeated collections at a given study visit (e.g. ECG parameters) the mean will be used as the value at the visit for all parameters.

For all analysis sets except for the All Cemdisiran Treated Set, summaries will be presented by treatment arm (cemdisiran and placebo). For the All Cemdisiran Treated Set, summaries will be presented by the following treatment sequence groups:

- Cemdisiran / Cemdisiran: all patients who received cemdisiran during the DB period, including patients who continued to receive cemdisiran during the OLE period and patients who discontinued treatment during the DB period
- Placebo / Cemdisiran: all patients who received placebo during the DB period and switched to cemdisiran in the OLE period
- All Cemdisiran: all patients who received at least one dose of cemdisiran during either the DB or OLE period

5.3. Baseline Definitions

Baseline value for 24-hour UP, UPCR, and UACR will be calculated as the average of two valid (as per section 6.4.1.1 of the protocol) collections at week -2 visit (i.e., the last measurement

prior to the first dose of study drug). Baseline values for vital signs will be defined as the assessments at week -2 visit because of the required vaccination when applicable. The baseline value for an ECG variable (heart rate, PR interval, QRS interval, QT interval or QT_c interval) will be the average of last triple assessments prior to the first dose of study drug (Day 1). For other parameters, baseline is defined as the last non-missing value prior to the first dose date/time of the study drug, unless otherwise specified.

For the All Cemdisiran Treated Set, baseline for patients randomized to cemdisiran in DB period is as defined above. For patients who switched from placebo in the DB period and received at least one dose of cemdisiran in the OLE period, baseline for all parameters will be redefined as the last non-missing assessments prior to the first dose of cemdisiran, except for assessments based on 24-hour urine collections where the average of the two valid collections at week 32 visit will be the baseline value.

5.4. Randomization Stratification Factors

The randomization will be stratified based on the baseline 24-hour UP (≥ 1g/24h and <2g/24h versus ≥2g/24h). The mean of two valid 24-hour urine protein assessments at week -2 visit will be used as the baseline. The stratification factor will be recorded in both the IRS and the clinical database.

5.5. Multiple Comparisons/Multiplicity

All comparisons will be descriptive in nature and no multiplicity adjustment will be made.

5.6. Missing Data

Missing values will not be imputed, unless otherwise specified.

Patients who discontinue the study prior to Week 36 visit will be encouraged to remain on study and complete their remaining clinical visits (excluding PK assessments) through the visit at Week 36. All data collected regardless of whether it was collected before or after treatment discontinuation will be used for analysis. However, it is possible that data will remain missing.

In case of missing date or partial date of adverse event (AE) onset, an AE will be considered treatment-emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to first dose of study drug.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug in this study; medications will be classified as prior or both prior and concomitant depending on the medication stop dates. If any medications have a completely missing stop date, then the medication will be assumed as ongoing.

5.7. Visit Windows

For table and figure summaries of the DB period, all data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report forms (eCRF) even if the assessment is outside of window.

For table and figure summaries during cemdisiran treatment, the data collected at study visits during the OLE period will be re-mapped for the patients randomized to placebo in the DB period to reflect the visit relative to the first dose of cemdisiran. Unless otherwise specified, data collected at an unscheduled visit will be included in by patient listings and/or spaghetti plot figures, but no assignment of the scheduled visit will be made for the purposes of summary tabulations. However, unscheduled study visits will be used in categorical shift tables (e.g. shift from baseline to worst post-baseline value).

5.8. Analysis Cutoff and Database Lock

As this study will be ongoing when the database lock for the primary analysis is performed, the study database will have an interim database lock (i.e. data in EDC will be frozen and external data such as laboratory data will be QA'd and cleaned), when the last patient completes Week 36 assessments. Additional details regarding the database lock are located in the study Data Management Plan. The study will then be unblinded and all data entered as of the date cutoff for the primary interim database lock will included in the primary analysis for the primary interim CSR.

After the study is completed, i.e., all patients complete the OLE period and the safety follow-up visits, a final database lock will occur and all data collected will be summarized in the final CSR.

5.9. Interim Analyses

No formal interim analysis is planned for this study. Informal data looks prior to the primary interim analysis are planned for the monitoring of the study by DMC and the sponsor.

5.10. Primary and Final Analyses

The study includes a 36-week DB period, a 156-week OLE period, and a 52-week safety follow up period. The primary analysis is to evaluate the efficacy and safety of cemdisiran compared to placebo during the DB period. For the primary analysis, tables and figures will be presented by treatment arm. When assessments or AE onset dates are exactly the first dose date in the OLE period with time missing, the records will be included in the OLE period. Per-patient listings will include all data collected during the entire study. The listings will be sorted by randomized arm. Within patient, there will be a variable to indicate the period of the data collection.

Final analysis evaluating the long-term efficacy and safety of cemdisiran will be described for the All Cemdisiran Treated Set. Summary tables and figures will be presented by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran and all cemdisiran treated).

For patients who received placebo in the DB period and switched to cemdisiran in the OLE period, the intra-patient comparison of the two treatment periods will be conducted for UP, UPCR, and eGFR in the final analysis. The time period during which patients receive cemdisiran (i.e. on or after the first date/time of cemdisiran) is referred as "during cemdisiran treatment".

The detailed definitions for different treatment periods are as the following:

- **DB Period**

It is defined as the time between the first dose of study drug and Week 36/end of study (EOS) visit. For patients who do not have the Week 36/EOS visit, it is the time between the first dose of study drug and the targeted Week 36/EOS visit (Day 252).

- **OLE Period**

The start date of the OLE period is defined as the first dose of cemdisiran of the OLE period (i.e., week 36 visit) and ends at week 188/EOS visit.

- **Safety Follow-up Period**

The 52-week safety follow-up period starts at week 36/EOS visit (for patients not continuing into the OLE) or week 188/EOS visit.

6. STUDY ANALYSES

6.1. Patient Disposition

Number and percentage of patients in the following categories will be summarized by treatment arm (or by treatment sequence) and overall as appropriate:

- Screen failures (overall only)
- Enrolled for Run-in Period (signed informed consent and met eligibility criteria; overall only) and those failed during Run-in period
- Randomized
- Treated
- Modified Intent-to-Treat Analysis Set (mITT)
- Safety Analysis Set
- PK Analysis Set
- PD Analysis Set
- All Cemdisiran Treated Set (by treatment sequence group)
- Entered the OLE period.

In addition, summaries of the number and percentage of patients who discontinued treatment, withdrew from study, and primary reasons for either discontinuation of treatment and/or withdrawal from study will be presented. The number and percentage of patients in each level of randomization stratification factor, baseline 24-hour UP (<2 g/24-hours vs. ≥2 g/24-hours), recorded in IRS and the clinical database will be summarized by randomized treatment arm and overall. The numbers of subjects screened will be summarized by country and site.

Data listings of those patients who withdrew study and/or discontinued treatment including the associated reasons will also be presented. A separate listing of screening failure patients with the associated reason for screen failures will be generated.

6.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for mITT and Safety Analysis Sets (if different).

Descriptive statistics of demographic characteristics including but not limited to: age (years), age category (<65 years vs. ≥ 65 years), sex, race, ethnicity, height, weight, and body mass index (BMI) and country.

Baseline disease characteristics including but not limited to: the 24-hour UP, the 24-hour UP category (< 2g/24-hour vs. ≥ 2g/24-hour), UPCR as measured in 24-hour urine and in spot urine, eGFR (mL/min/1.73m^2), eGFR category (30-44, 45-59, 60-89, ≥90) (mL/min/1.73m^2), blood pressure (SBP and DBP), age at diagnosis, time from diagnosis to randomization, MEST-C score, IgA, IgG, IgM, C3, C1q, C4d, and C5b-9.

6.3. Medical History, Prior and Concomitant Medications

Medical history andprior and concomitant medications will be summarized for the Safety Analysis Set.

The medical history data will be coded with the Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or higher). The number and percent of subjects by System Organ Class (SOC), high level term (HLT) and Preferred Term (PT) will be summarized by treatment group and overall. Prior and concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary (September 2018 or later).

Prior medications are defined as medications that were taken prior to the first dose of study drug (cemdisiran or placebo). Concomitant medications are defined as medications which were taken prior to and were ongoing while on study drug or medication(s) taken on or after the first dose date of the study drug.

Tabular summary of the number and percentage of subjects taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term. Listing will be provided for medical history, prior and concomitant medications.

6.4. Drug Exposure

The following variables are summarized using Safety Analysis Set but not limited to; the total number of doses received and missed per patient, mean number of dosing per patient, duration of drug exposure (months), and cumulative drug exposure time (person years).

Drug exposure (days) will be defined as [Exposure time= (date of last exposure – date of first dose +1)] where date of last exposure will represent either the date of the last administered dose +28, analysis cut-off date or end of study date, whichever is earliest. The exposure during the DB period will be right censored; that is, the date of the last exposure will not be later than the first date of dosing in the OLE period. Dose interruptions and compliance are not taken into account.

7. STATISTICAL ANALYSIS

7.1. Primary Endpoint

The primary endpoint of the study is the percent change from baseline in urine protein/creatinine ratio [UPCR] as measured in 24-hour urine at Week 32. The analysis will be conducted using the modified ITT analysis set.

Valid 24-hour urine protein values will be included in the primary analysis (1 valid assessment at week 16 visit and the mean of two valid assessments at baseline and week 32 visit). All 24-hour urine samples need to meet the validity criteria below (Section 6.4.1.1 of the protocol). The 24-hour UPCR at baseline or Week 32 is the average of two valid collections.

A 24-hour urine collection will be considered valid if the following criteria are met:

- 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 resulting 24-hour UPCR at each visit will be log transformed for analyses [Fellstrom 2017; Li 2006]. 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 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. Unstructured working correlation will be used to model the within-patient errors. If the fit of covariance structure fails to converge, independent correlation structure will be used. At each visit, least square (LS) means ($\hat{\mu}_j$) with corresponding standard errors (SEM) and 90% CI will be displayed by treatment arm. The primary comparison is the LS mean treatment difference (cemdisiran – placebo) in percent change of 24-hour UPCR at week 32 visit from baseline. This LS mean difference will be presented along with corresponding standard errors (SEMs), 90% CIs and p-value from the model.

The following results will also be presented:

- Placebo-adjusted geometric mean percent change at week 32 visit:

$$\frac{\mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{cemdisiran}} - \mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{placebo}}}{\mathrm{GM}\left(\frac{\text{UPCR at week32}}{\text{UPCR at baseline}}\right)_{\text{placebo}}} * 100$$

$= [\exp(\delta) - 1] * 100$, where δ is the LS mean treatment difference between the two arms from the MMRM model in log-scale above.

- The 90% CI for the placebo-adjusted geometric mean percent change:

$$[(\exp(lower\ bound\ for\ \delta) - 1) * 100,\ \ (\exp(upper\ bound\ for\ \delta) - 1) * 100]$$

In addition, the geometric mean for the ratio from baseline at week 32 visit in 24-hour UPCR and 90% confidence intervals for each treatment group will be presented using respective LS means ($\hat{\mu}_j$) and corresponding 90% confidence intervals (j=0 if placebo and j=1 if cemdisiran):

$$exp(\hat{\mu}_j) \text{ and } \left[\exp(lower\ bound\ for\ \mu_j), \exp(upper\ bound\ for\ \mu_j) \right]$$

Descriptive statistics will also be generated by treatment arm at each scheduled visit. Geometric Mean (with 90% CI) figures of the ratio to baseline by treatment arm will be plotted as well as individual spaghetti plots.

7.1.1. Sensitivity Analyses

The first sensitivity analysis will be conducted to evaluate the robustness of the primary model using normality of log-transformed UPCR data assumption. A stratified rank ANCOVA analysis [LaVange and Koch 2006] will be conducted without using the normality assumption of log-transformed UPCR data. The following steps will be performed:

1. Standardized ranks within each stratification stratum will be derived across the two treatment groups for the baseline and the change from baseline at Week 32 in 24-hour UPCR
2. The linear regression model will be fitted separately for each stratum where the standardized rank of the change from baseline at Week 32 in 24-hour UPCR is the outcome variable, the standardized rank of the baseline is the only covariate
3. The stratified mean score test will be performed to compare the two treatment groups using the values of the residuals from the above model as scores and stratification factor as the stratum
4. Cochran–Mantel–Haenszel (CMH) *p* value is obtained

The second sensitivity analysis is to assess the impact of missing data and the robustness of the primary analysis. The analysis will use the same MMRM model on the imputed data, of which the missing 24-hour UPCR value will be imputed with the spot UPCR [Ginsberg 1983; Viswanathan and Upadhyay 2011] assessed closest to the date of missing value, when available. Depending on the extend of missing values this sensitivity analysis might not be needed.

7.1.2. Subgroup Analyses

Subgroup analyses will be conducted to assess the treatment effect during the DB period for the primary endpoint within the following subgroups: gender (Male vs. Female), age (< Median vs. ≥ Median), baseline eGFR (< 60 vs. ≥ 60), and baseline 24-hour UP (< 2g/24-hour vs. ≥ 2g/24-hour). Other subgroups may be examined, if deemed appropriate.

The subgroup analysis will be performed for the primary endpoint using the mITT analysis set. A forest plot will be generated to illustrate the estimated treatment effect along with the associated 90% confidence interval. The subgroup analyses may be performed for secondary endpoints if appropriate.

7.2. Secondary Endpoints

For secondary endpoints assessed in DB period, the analysis will compare randomized arms (cemdisiran vs. placebo) using the mITT analysis set.

The secondary endpoints which are assessed beyond Week 36 will be summarized to describe the long-term efficacy of cemdisiran using the All Cemdisiran Treated Analysis Set by treatment sequence, i.e., cemdisiran/cemdisiran, placebo/cemdisiran, and All Cemdisiran.

The planned analyses of the secondary endpoints are summarized in Table 2.

Table 2 Summary of Analyses for the Secondary Efficacy Endpoints

Endpoint	Statistical Method	Notes
Percent of patients with partial clinical remission (urine protein [UP] <1.0g/24-hours) at Week 32	Treatment comparison will be conducted using Cochran-Mantel-Haenszel test stratified by baseline 24-hour UP (<2 g/24-hours vs. ≥2 g/24-hours). The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Wilson score method with continuity correction will be presented.	
Percent of patients with >50% reduction in 24-hour proteinuria at Week 32		
Percent change from baseline in 24-hour proteinuria (g/24-hours) at Week 32	Treatment comparison and estimates will be conducted by a similar MMRM model used for the analysis of primary endpoint.	
Change from baseline in UPCR as measured in a spot urine at Week 32	The change from baseline in log-transformed spot UPCR by visit through Week 36 will analyzed via a MMRM model. The model includes log-transformed baseline spot UPCR, treatment, visit, and the interaction of treatment and visit. Robust errors [White 1980] will be used to model the within-patient errors.	Scheduled assessments are outlined in the Table 1 (Schedule of Assessments) of the protocol.
Change from baseline in hematuria at Week 32	Shift tables for both assessment methods (microscopic examination and urine dipstick) will be presented	Results using microscopy and dipstick are both in range categories.

7.3. Exploratory Analyses

Exploratory endpoints will be summarized descriptively by treatment arms during the DB period using mITT Analysis set.

For the slope of eGFR computed for the entire study period, it will also be analyzed by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran) using the All Cemdisiran Treated Analysis Set. However, the other exploratory endpoints may be analyzed over the entire study if deemed appropriate. Table 3 summarizes the planned analyses for exploratory endpoints.

Table 3 Summary of Analyses for Exploratory Endpoints

Exploratory Endpoint	Statistical Method	Notes
Change from baseline in estimated glomerular filtration rate (eGFR)[1] at Week 32	Descriptive statistics of eGFR will be presented by visit and treatment arm. Shift tables of eGFR categories from baseline to post-baseline visits and an overall worst post-baseline will also be presented.	
The slope of eGFR computed for the first 36 weeks using all assessments during the period	The random coefficient model for eGFR will include baseline eGFR, treatment, time, and the interaction of treatment and time as fixed effects and intercept and time as random effects.	The first study drug dosing will be defined as the time reference point t=0 In addition, the slope of eGFR for each subject will be estimated.
The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study	The random coefficient model for eGFR will include baseline eGFR, treatment sequence, time, and the interaction of treatment sequence and time as fixed effects and intercept and time as random effects.	This endpoint will be analyzed only at the final analysis using Cemdisiran Treated Analysis set. The first administration of cemedisiran will be defined as the time reference point t=0.
The slope of eGFR during placebo period comparing the slope during OLE for patients who crossed over from placebo to cemdisiran.	The random coefficient model with piecewise regression will include baseline eGFR, time during the placebo treatment and time during the cemdisiran treatment as fixed effects and intercept and times as random effects.	This endpoint will be analyzed only at the final analysis using placebo/cemdisiran treatment sequence group.
Change from baseline in creatinine clearance at Week 32	Descriptive statistics will be presented by visit and treatment arm.	See section 6.4.3 in the protocol for creatine clearance

Exploratory Endpoint	Statistical Method	Notes
Percent of patients in full clinical remission (Urine Protein [UP]<0.3 g/24-hours) at Week 32	The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Newcombe method based the Wilson score with continuity correction will be presented.	
Change from baseline in 24-hour albuminuria at Week 32	Descriptive statistics will be presented by visit and treatment arm.	
Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32	Descriptive statistics will be presented by visit and treatment arm.	
Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study	The levels of the biomarkers and their changes and percentage changes from baseline will be summarized descriptively by visit and treatment arm or treatment sequence	

[1] eGFR will be based on CKD-EPI: $eGFR = 141 * \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} * \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} * 0.993^{Age} * 1.018[if\ female] * 1.159[if\ black]$. Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1, age is calculated at visit: age at consent + (visit date-consent date)/365.25 and rounded to integer.

7.4. Pharmacodynamic Analyses

PD endpoints will be summarized by treatment arm at the primary analysis using mITT analysis set and at the final analysis by treatment sequence using All Cemdisiran Treated Analysis Set. Analyses of PD endpoints are summarized in Table 4 below.

Table 4 Summary of Analyses for Pharmacodynamic Variables

Endpoint	Statistical Method	Notes
Change from baseline in C5 level over the course of the study	The levels of C5, absolute change and percentage change from baseline in C5 will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	
Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study	The levels of CAP and CCP and the changes and percentage changes from baseline will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	The biomarkers of complement activation include but not limited to C5a, sC5b9 in plasma, and sC5b9 in urine.

7.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed for cemdisiran and active metabolite, AS(N-2)3'-ALN-CC5 and AS(N-3)3'-ALN-CC5 cemdisiran, using noncompartmental methods. PK analyses will be based on the Pharmacokinetic Analysis Set. Summaries will be provided for each scheduled time point. PK data will be included in by-patient data listings. The following PK parameters will be estimated for each subject, as appropriate and if data permits: area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{½}\beta$), apparent clearance (CL/F), apparent volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe). Additional PK parameters may be calculated, if deemed necessary. The PK parameters will be summarized using descriptive statistics.

Pharmacokinetic analyses will be conducted using noncompartmental methods. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

7.6. Safety Analyses

Primary safety analyses will compare cemdisiran versus placebo during the DB period using the Safety Analysis Set. Long-term safety analyses of cemdisiran will be summarized by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran, all cemdisiran treated arm) using the all Cemdisiran Treated Analysis set.

The primary safety parameter is the frequency of treatment emergent adverse events (TEAEs). A TEAE is defined as an AE that occurred or worsened on or after the first dose of study drug through 28 days after the last dose of study drug. In addition, an AE that occurs after the 28 days from the last dose but is considered to be related to study drug, is considered to be a TEAE. Other safety parameters include vital signs, ECGs, clinical laboratory assessments, and physical exams. Adverse events that are non-treatment emergent (e.g., during safety follow up period) will be summarized and listed separately.

7.6.1. Adverse Events

All TEAEs hereafter will be referred to as AEs in this document. No statistical tests will be performed to compare AE rates between treatment groups. Adverse events will be coded using MedDRA version 21.1 or higher and displayed in tables using SOC and PT.

An overview table of AEs will be tabulated. The overview table will include the number and percentage of patients in following categories such as, but not limited to:

- At least 1 AE
- At least 1 study drug related AE
- At least 1 severe AE
- At least 1 study drug related severe AE
- At least 1 Serious Adverse Event (SAE)
- At least 1 study drug related SAE
- At least 1 AE leading to treatment discontinuation
- At least 1 study drug related AE leading to treatment discontinuation
- At least 1 AE leading to study withdrawal
- At least 1 study drug related AE leading to study withdrawal
- Death

Tabulations by SOC and PT displaying the number of patients (percentage) and total events will be produced for the following tables:

- All AEs
- Severe AEs
- AEs by Maximum Severity
- AE related to treatment
- AEs related to treatment by Maximum Severity
- All SAEs
- SAEs related to treatment
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AEs leading to study withdrawal

Tabulations by PT in decreasing order in frequency within the cemdisiran arm will be generated for the following tables:

- All AEs
- All SAEs

- AEs related to treatment
- SAEs related to treatment

In summaries by SOC and PT, AEs will be sorted alphabetically by SOC then by PT.

There will also be an All AE table generated displaying rates of adverse events adjusted for exposure-time during the respective period. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence or most related.

Separate listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug, withdrawal of study drug, and/or dose interruption. By-subject AE listings will be provided.

7.6.2. Adverse Event of Clinical Interest (AECI)

Additional summaries of safety areas of interest based on Standardized MedDRA Queries (SMQs) and other groupings of AEs may be summarized such as, but not limited to the following:

- Injection Site Reactions [ISRs]: AEs mapping to the High-Level Term (HLT) = "Injection Site Reactions" using MedDRA dictionary will be included in the summary.

  Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. A table will also be generated to display the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose in summary), total number of doses with ISRs, and the signs and symptoms reported due to ISRs. If there are multiple ISRs that occur in between two consecutive injections, then these events will be considered as 1 ISR and considered related to the earlier injection.

- Hepatic AEs, including AEs of LFT abnormalities: These AEs are mapped to the SMQ Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms).

  Frequency (percentages) of drug-related hepatic disorders will be summarized by SOC, HLT and PT. A separate listing will be generated of all patients reporting these events.

7.6.3. Laboratory Data

Clinical laboratory parameters will be expressed in Standard International (SI) units. Summaries will only include data from central laboratory. For any local collections of LFTs, these will be included in a separate data listing. Key laboratory parameters will be graded according to NCI CTCAE v5.0.

Summaries for each lab parameter (hematology, chemistry, liver function tests, coagulation and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics

at each scheduled visit. Descriptive statistics include actual value, change from baseline and percent change from baseline at each scheduled visit.

Shift tables will be generated to summarize shifts from baseline categories to the worst post-baseline categories with directionality specified for any labs which could be reported in either direction (e.g. above the upper limit of normal [ULN] or below ULN).

Clinical laboratory tests with normal ranges will be classified as Low, Normal, and High. For these tests, abnormal values will be flagged in the listings with H when the value is higher than the upper limit of the reference ranges and with L when the value is lower than the lower limit of the reference ranges.

For hematology and chemistry labs, summary tables of potentially clinically significant abnormalities will also be provided.

All laboratory data will be presented in data listings. Separate listings will be included for those laboratory data collected from local labs such as LFTs. Out of range laboratory results will be identified in listings.

7.6.4. Liver Function Analysis

A listing will be generated for all patients with abnormal liver function tests as defined by ALT>3xULN, AST>3xULN and total bilirubin >2x ULN at any visit.

A tabular summary for LFTs will be generated to summarize the number and associated percentage of patient in each of the categories at any post-baseline visit:

- ALT>1 & ≤3, ALT>3 & ≤5, ALT>5 & ≤10, ALT>10 & ≤20, ALT>20xULN
- AST>1 & ≤3, AST>3&≤5, AST>5& ≤10, AST>10 & ≤20, AST>20xULN
- ALT or AST>1 & ≤3, ALT or AST>3 & ≤5, ALT or AST>5 & ≤10, ALT or AST>10 & ≤20, AST or ALT>20xULN
- WNL, ALP>1.5xULN
- Total Bilirubin>1.5& ≤2, Total Bilirubin>2&≤3, Total Bilirubin>3& ≤5 and Total Bilirubin>5

eDISH plots of peak total bilirubin at any time versus peak ALT or AST at any time will also be presented. For selected labs (e.g. ALT/ULN and AST/ULN), a table and figure of the values across the entire study (DB+OLE) will be generated by treatment sequence arms.

7.6.5. Vital Signs

Descriptive statistics for each vital sign (e.g. systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, weight, body mass index) will be summarized at scheduled visits. Summaries will include actual values and changes from baseline.

Vital sign measurements will be presented for each patient in a data listing, with abnormal vital signs flagged.

7.6.6. Electrocardiogram

For electrocardiogram (ECG) parameters, these will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each timepoint will be summarized. For assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis

ECG findings will include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTc).

Corrected QT interval, if not collected, will be calculated using Fridericia's correction formula.

Fridericia's cube-root corrected QT: QTcF (ms) = QT (ms) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$.

Baseline, post baseline maximum QTcF and post baseline maximum change from baseline in QTcF during the study will be summarized with descriptive statistics. The incidence of notable ECG changes from baseline in maximum absolute QT_cF, intervals (<=450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF, maximum changes from baseline (<=30 ms, > 30 -60 ms and > 60 ms) over all post-treatment evaluations will be summarized. A listing of all ECG data will be provided.

7.6.7. Physical Examination Findings

Physical examinations will be conducted throughout the study. If any abnormalities are observed during these physical exams, then this will be recorded on the adverse event form.

A separate listing per patient will be generated to display the date and time of the physical exam.

7.7. Anti-Drug Antibody

The number and associated percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized by treatment group. A listing of patients with positive ADA assay results and corresponding titers will be provided as well as a listing of all ADA results. Circulating Immune Complexes (CIC) and anti-GdIgA1 antibody will be summarized descriptively by visit and listing will be provided.

7.8. COVID-19 Pandemic Impact Analyses

Additional data were collected to characterize the impact of the COVID-19 pandemic on study conduct as shown in Appendix 10.1.

7.8.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 as assessed in the COVID-19 Data Collection Instrument will be included in patient disposition summaries. Impact on study participation due to COVID-19 pandemic, including visit(s) missed, delayed, partially completed, completed, location changes (telehealth, local labs, other sites), study drug dosing missed or delayed will be summarized overall on the patient level, and overall and by visit on the event level. Visit and dosing delays can be defined by time windows specified by the

protocol before the pandemic and the relaxed windows in responding to the pandemic in Amendment 4 (dated 19 January, 2021).

7.8.2. Impact on Efficacy

A summary of missing data for primary and secondary efficacy endpoints due to COVID-19 pandemic will be provided. Specifically, the number and percent of patients in each treatment arm with missing data in 24h UPCR/24h UP, spot UPCR, and hematuria by microscopic examination and urine dipstick at each scheduled assessment visit will be presented. Missing efficacy data due to Covid-19 could be identified by if the visit associated with the assessment is missed (Appendix 10.1).

For primary and secondary efficacy endpoints, the number and percentage of patients with out-of-window visits based on the original protocol at each scheduled visit will be summarized.

7.8.3. Impact on Adverse Events

The number and percent of patients with AEs mapped to COVID-19 custom query by HLT and PT will be presented for overall and by treatment.

7.8.4. Other Impacts

Protocol deviation due to the COVID-19 pandemic will be summarized and will be indicated in the listing of protocol deviation. AEs, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic. For patients reporting an AE mapped to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings.

8. CHANGES TO PLANNED ANALYSES

Change from SAP V1.0	**Detailed Description/Rationale**
Change the primary and secondary endpoints	Per protocol amendment 3
The working correlation structure in the MMRM model for the analysis of the primary endpoint is changed to unstructured	Since there are only two post baseline assessments, the unstructured working correlation will provide robust estimates by REML.
Section 7.8 and Appendix 10 are added	To address COVID-19 pandemic impact
Various editorial changes	To improve clarity

9. REFERENCES

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10. APPENDIX

10.1. COVID-19 Data Collection Instrument

Was the patient's participation in the study impacted by the COVID-19 global pandemic (e.g. missed, delayed or partially completed visit, missed/delayed study drug dose, visit location change such as phone visit, etc.)?

If yes, please provide details of study assessments/procedures (by visit) that were impacted:

Visit completion status
- o Completed
- o Partially completed
- o Delayed
- o Missed

Visit location changes (check all that apply)
- o Telehealth, phone or home visit
- o Local labs used to assess safety
- o Visit occurred at different site
- o Other, specify: _____
- o Not applicable

Study drug dosing changes
- o Missed dose
- o Delayed dose
- o No change

Signature Page for VV-CLIN-005525 v1.0
ALN-CC5-005 SAP Amend1

Task: Approval Verdict: Approve	[redacted]T+0000
Task: Approval Verdict: Approve	[redacted]T+0000
Task: Approval Verdict: Approve	[redacted]02:50 GMT+0000

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ALN-CC5-005 SAP Amend1

STATISTICAL ANALYSIS PLAN

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

Protocol Number:	ALN-CC5-005
Protocol Version and Date:	Amendment 2: 30 August 2019 Amendment 1: 26 November 2018 Original protocol: 10 September 2018
Investigational Drug:	ALN-CC5 (Cemdisiran)
Phase:	Phase 2
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 Tel: [redacted] Fax:
Sponsor Representative:	[redacted]
Analysis Plan Version and Date:	Original version 1.0: 28 February 2020

Confidentiality Statement

APPROVAL SIGNATURE PAGE

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

Protocol Number: **ALN-CC5-005**

Analysis Plan Version and Date: Version 1.0: 28 February 2020

This document has been approved and signed electronically on the final page by the following:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin converting enzyme inhibitor
ADA	Anti-drug Antibody
AE	Adverse Event
AECI	Adverse Event of Clinical Interest
ANCOVA	Analysis of covariance
ARB	angiotensin II receptor blocker
C5	Complement component 5
C5a	Complement component 5a
CAP	Complement Alternative Pathway
CCP	Complement Classical Pathway
CI	Confidence interval
CIC	Circulating immune complexes
CMH	Cochran Mantel Haenszel
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DB	Double blinded
DMC	Data Monitoring Committee
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
GM	Geometric mean
HLT	High level term
IgAN	Immunoglobulin A nephropathy
IRS	Interactive Response System
ISR	Injection site reactions
ITT	Intent-to-Treat Analysis Set
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PK	Pharmacokinetic(s)
PD	Pharmacodynamic
PT	Preferred Term
RAS	Renin-angiotensin system
RBC	Red blood cell
RNAi	RNA interference
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SOC	System Organ Class
TEAEs	Treatment emergent adverse events
UACR	Urine albumin:creatinine ratio
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

Abbreviation	Definition
UP	Urine Protein
UPCR	Urine protein:creatinine ratio
WHO-DRL	WHO Drug Dictionary

1. INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis and can progress to renal failure.

The clinical presentation of IgAN is highly variable, ranging from asymptomatic microscopic hematuria to a rapidly progressive form of glomerulonephritis. The therapeutic options are limited and include nonspecific treatment to reduce blood pressure and proteinuria by renin-angiotensin system (RAS) blockade. No disease-specific therapies are currently available, and an unmet need persists for disease-modifying interventions.

Cemdisiran is a investigational RNAi therapeutic designed to suppress liver production of C5 protein, resulting in inhibition of terminal complement pathway activity and prevention of membrane attack complex (MAC) formation and C5a release. This inhibition would be expected to reduce mesangial cell proliferation and tissue injury in patients with IgAN, resulting in reduced renal injury. 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. This approach is particularly appealing in IgAN where the relative contribution of the different complement pathways may vary between patients.

Study ALN-CC5-005 is a Phase 2 study to evaluate the efficacy and safety of cemdisiran in the treatment of patients with IgAN. This statistical analysis plan (SAP) has been developed based on the Protocol Amendment 2 dated 30 August 2019. Any change to the data analysis methods described in the protocol, as well as the justification for the change, will be described in the SAP (Section 8).

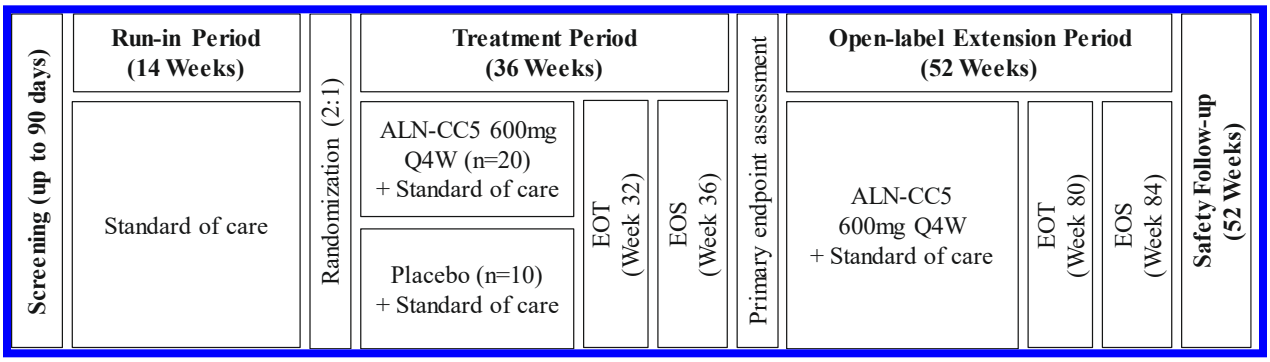
2. STUDY OVERVIEW

2.1. Study Design

This study is a multicenter, double-blind, placebo-controlled study comprised of three periods (Figure 1). Eligible patients will begin a 14-week observational run-in period during which treatment with the standard of care is expected to remain unchanged. At the end of run-in period, patients whose average urine protein (UP) of two valid urine collections is at or higher than 1g/24h are eligible for randomization into the 36-week double blind (DB) period. Approximately 30 patients are planned to be randomized in a 2:1 ratio, 20 in the cemdisiran arm and 10 in the placebo arm in the DB period, which is followed by a 52-week open-label extension (OLE) period to further evaluate the long-term safety and efficacy. All patients will be followed for safety for 52 weeks after the end of study visit.

The independent Data Monitoring Committee (DMC) will have access to subject level treatment assignments and perform periodic reviews of unblinded data throughout. Details are provided in the DMC Charter of the study.

Figure 1 Study Design



2.2. Randomization Methodology

At the end of run-in period, patients will be randomized 2:1 to the cemdisiran or placebo arms upon confirmation of eligibility followed by vaccination against meningococcal infections using the Interactive Response System (IRS). Randomization will be carried out by the permuted block randomization stratified by baseline urine proteinuria levels (≥ 1g/24h and <2g/24h versus ≥2g/24h).

2.3. Blinding and Unblinding

Treatment assignments will be maintained by the interactive response system (IRS). Any unplanned unblinding to investigators or patients occurring during the 36-weeks DB placebo-controlled treatment period will be documented and reported in the CSR.

During the DB treatment period, all subjects will be randomly assigned to cemdisiran or placebo. All site personnel and patients will be blinded to study drug during the DB period. Sponsor personnel will not be blinded to study treatment. Details regarding the blinding aspects during the study are outlined in a Randomization and Blinding Plan for ALN-CC5-005.

2.4. Study Procedures

The schedules of assessments are described in Table 1 for the DB period and Table 2 for the OLE period in the study protocol.

3. OBJECTIVE AND ENDPOINTS

The study objectives and endpoints based on the study protocol are presented Table 1 below.

Table 1 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 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)

4. PATIENT POPULATION

4.1. Population Definitions

The following patient populations will be used for analyses:

- Modified Intent-to-Treat Analysis Set (mITT): All patients who receive any amount of study drug and have baseline and at least one post-baseline 24-hour urine protein assessment. Patients will be grouped by assigned treatments (i.e., as randomized).
- Safety Analysis Set: All patients who receive any amount of study drug. Patients will be analyzed according to the treatment actually received.

- PK Analysis Set: All patients who receive any amount of study drug and have at least 1 PK concentration measurement.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least one post-dose blood sample for the determination of plasma C5 level.
- All Cemdisiran Treated Set: All patients who received at least one dose of cemdisiran, including patients who took cemdisiran during the DB period and patients who first took placebo during the DB period and switched to cemdisiran during the OLE period.

The primary population used to evaluate efficacy will be the mITT Population unless stated otherwise. Safety during the DB period will be analyzed using the Safety Analysis Set. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively. The All Cemdisiran Treated Set will be used to summarize long-term efficacy and safety of cemdisiran.

4.2. Protocol Deviations

Protocol deviations will be classified into major or minor deviations by medical review. A major deviation is defined as a deviation that may significantly impact the completeness, accuracy and/or reliability of the trial data; that may significantly affect a patient's rights, safety and well-being (ICH.E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry. 2013). Major protocol deviations will be reviewed and approved by Alnylam prior to the interim database lock for the primary analysis of the DB treatment period. All protocol deviations will be presented in a listing. The Sponsor or designee will be responsible for producing the final protocol deviations file. This file will include at a minimum each protocol deviation and whether or not this deviation is classified as a major protocol deviation. This file will be finalized prior to the primary treatment phase database lock. Protocol deviations will be summarized in the clinical study report.

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

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

Quantitatively, we assume that mean percent change from baseline in proteinuria is similar to that in urine protein and urine protein creatinine ratio. Specifically, based on NEFIGAN study [Fellstrom 2017], we assume that in the placebo arm the geometric mean ratio of proteinuria 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.

5.2. General Methods

Categorical variables will be summarized by frequency and percentage in each category. Continuous variables will be summarized by the number of patients, mean, median, standard deviation (SD), interquartile range (Q1, Q3), minimum, and maximum. For log-transformed data, coefficient of variation (CV) and geometric mean (GM) will also be presented. CV is calculated as $\sqrt{\exp(\text{variance of log transformed data}) - 1} \times 100\%$.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Median, mean, standard deviation and standard error will be presented to the level of precision collected in database plus one additional decimal.

Day 1 will be defined as the day of the first dose of study drug (cemdisiran or placebo). Study Day is relative to first dosing date of study drug for all patients.
If the assessment date is after the date of first study drug dose, then the study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug + 1

If assessment date is before the date of the first dose of study drug, then study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug

For patients who were randomized to placebo and switched to cemdisiran in OLE period, an additional study day will be defined which reflect the study days relative to the first dose of cemdisiran.

For laboratory parameters, any assessments recorded as lower than the lower limit of quantification (LLOQ) will be replaced by the respective LLOQ value. Any assessment recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the respective ULOQ value. For assessments with repeated collections at a given study visit (e.g. ECG parameters) the mean will be used as the value at the visit for all parameters.

For all analysis sets except for the All Cemdisiran Treated Set, summaries will be presented by treatment arm (cemdisiran and placebo). For the All Cemdisiran Treated Set, summaries will be presented by the following treatment sequence groups:

- Cemdisiran / Cemdisiran: all patients who received cemdisiran during the DB period, including patients who continued to receive cemdisiran during the OLE period and patients who discontinued treatment during the DB period
- Placebo / Cemdisiran: all patients who received placebo during the DB period and switched to cemdisiran in the OLE period
- All Cemdisiran: all patients who received at least one dose of cemdisiran during either the DB or OLE period

5.3. Baseline Definitions

Baseline value for 24-hour UP, UPCR, and UACR will be calculated as the average of two valid (as per section 6.4.1.1 of the protocol) collections at week -2 visit (i.e., the last measurement prior to the first dose of study drug). Baseline values for vital signs will be defined as the assessments at week -2 visit because of the required vaccination when applicable. The baseline value for an ECG variable (heart rate, PR interval, QRS interval, QT interval or QT_c interval) will be the average of triple assessments on or prior to the first dose of study drug (Day 1). For other parameters, baseline is defined as the last non-missing value prior to the first dose date/time of the study drug, unless otherwise specified.

For the All Cemdisiran Treated Set, baseline for patients randomized to cemdisiran in DB period is as defined above. For patients who switched from placebo in DB period to cemdisiran who take at least one dose of cemdisiran in the OLE period, baseline for all parameters will be redefined as the last non-missing assessments prior to the first dose of cemdisiran except for assessments based on 24-hour urine collections where the average of the two valid collections at week 32 visit will be the baseline value.

5.4. Randomization Stratification Factors

The randomization will be stratified based on the baseline 24-hour UP (≥ 1g/24h and <2g/24h versus ≥2g/24h). The mean of two valid 24-hour urine protein assessments at week -2 visit will be used as the baseline. The stratification factor will be recorded in both the IRS (Interactive Response System) and the clinical database.

5.5. Multiple Comparisons/Multiplicity

All comparisons will be descriptive in nature and no multiplicity adjustment will be made.

5.6. Missing Data

Missing values will not be imputed, unless otherwise specified.

Patients who discontinue the study prior to week 36 visit will be encouraged to remain on study and complete their remaining clinical visits (excluding PK assessments) through the visit at week 36. All data collected regardless of whether it was collected before or after treatment discontinuation will be used for analysis. However, it is possible that data will remain missing.

In case of missing date or partial date of AE onset, an AE will be considered treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to first dose of study drug.

For medications with partial start or stop dates: the first day/ month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug in this study; medications will be classified as prior or both prior and concomitant depending on the medication stop dates. If any medications have a completely missing stop date, then the medication will be assumed as ongoing.

5.7. Visit Windows

For table and figure summaries of the DB period, all data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report forms (eCRF) even if the assessment is outside of window.

For table and figure summaries of the during cemdisiran treatment, the data collected at study visits during the OLE period will be re-mapped for the patients randomized to placebo to reflect the visit relative to the first dose of cemdisiran. Unless otherwise specified, data collected at an unscheduled visit will be included in by patient listings and/or spaghetti plot figures, but no assignment of the scheduled visit will be made for the purposes of summary tabulations. However, unscheduled study visits will be used in categorical shift tables (e.g. shift from baseline to worst post-baseline value).

5.8. Analysis Cutoff and Database Lock

As this study will be ongoing when the database lock for the primary analysis is performed, the study database will have an interim database lock (i.e. data in EDC will be frozen and external data such as laboratory data will be QA'd and cleaned), when the last patient completes Week 36 assessments. Additional details regarding the database lock are located in the study Data Management Plan. The study will then be unblinded and all data entered as of the date cutoff for the primary interim database lock will included in the summary of the primary interim CSR.

After the study is completed, i.e., all patients complete the OLE period and the safety follow-up visits, a final database lock will occur and all data collected will be summarized in the final CSR.

5.9. Interim Analyses

No formal interim analysis is planned for this study.

5.10. Primary and Final Analyses

The study includes a 36-week DB period, a 52-week OLE period, and a 52-week safety follow up period. The primary analysis is to evaluate the efficacy and safety of cemdisiran compared to placebo during the DB period. For the primary analysis, tables and figures will be presented by treatment arm. When assessments or AE onset dates are exactly the first dose date in the OLE period with time missing, the records will be included in the OLE period. Per-patient listings will include all data collected during the entire study. The listings will be sorted by randomized arm. Within patient, there will be a variable to indicate the period of the data collection.

Final analysis evaluating the long-term efficacy and safety of cemdisiran will be described for the All Cemdisiran Treated Set. Summary tables and figures will be presented by treatment sequence (cemdisiran /cemdisiran, placebo/ cemdisiran and all cemdisiran treated).

For patients who received placebo in the DB period and switch to cemdisiran in the OLE period, the intra-patient comparison of the two treatment periods will be conducted for UP, UPCR, and eGFR in the final analysis. The time period during which patients receive cemdisiran (i.e. on or after the first date/time of cemdisiran) is referred as "during cemdisiran treatment".

The detailed definitions for different treatment periods are as the following.

- **DB Period**

It is defined as the time between the first dose of study drug and week 36/end of study (EOS) visit. For patients who do not have the week 36/EOS visit, it is the time between the first dose of study drug and the targeted week 36/EOS visit (Day 252).

- **OLE Period**

The start date of the OLE period is defined as the first dose of cemdisiran of the OLE period (i.e., week 36 visit) and ends at week 84/EOS visit.

- **Safety Follow-up Period**

The 52-week safety follow-up period starts at week 36/EOS visit (for patients not continuing into the OLE) or week 84/EOS visit.

6. STUDY ANALYSES

6.1. Patient Disposition

Number and percentage of patients in the following categories will be summarized by treatment arm (or by treatment sequence) and overall as appropriate:

- Screen failures (overall only)
- Enrolled for Run-in Period (signed informed consent and met eligibility criteria; overall only) and those failed during Run-in period
- Randomized
- Treated
- Modified Intent-to-Treat Analysis Set (mITT)
- Safety Analysis Set
- PK Analysis Set
- PD Analysis Set
- All Cemdisiran Treated Set (by treatment sequence group)
- Entered the OLE period.

In addition, summaries of the number and percentage of patients who discontinued treatment, withdrew from study, and primary reasons for either discontinuation of treatment and/or withdrawal from study will be presented. The number and percentage of patients in each level of randomization stratification factor, baseline 24-hour UP (<2 g/24-hours vs. ≥2 g/24-hours), recorded in IRS and the clinical database will be summarized by randomized treatment arm and overall. The numbers of subjects screened will be summarized by country and site.

Data listings of those patients who withdrew study and/or discontinued treatment including the associated reasons will also be presented. A separate listing of screening failure patients with the associated reason for screen failures will be generated.

6.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall for mITT and Safety Analysis Sets (if different).

Descriptive statistics of demographic characteristics including but not limited to: age (years), age category (<65 years vs. ≥ 65 years), sex, race, ethnicity, height, weight, and body mass index (BMI) and country.

Baseline disease characteristics including but not limited to: the 24-hour urine protein, the 24-hour urine protein category (< 2g/24-hour vs. ≥ 2g/24-hour), UPCR as measured in 24-hour urine and in spot urine, eGFR, eGFR category 30-44, 45-59, 60-89, ≥90), blood pressure (SBP and DBP), age at diagnosis, time from diagnosis to randomization, MEST-C score, IgA, IgG, IgM, C3, C1q, C4d, and C5b-9.

6.3. Medical History, Prior and Concomitant Medications

Medical History, prior and concomitant medications will be summarized for the Safety Analysis Set.

The medical history data will be coded with the Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or higher). The number and percent of subjects by System Organ Class (SOC), high level term (HLT) and Preferred Term (PT) will be summarized by treatment group and overall. Prior and concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary (September 2018 or later).

Prior medications are defined as medications that were taken prior to the first dose of treatment (cemdisiran or placebo). Concomitant medications are defined as medications which were taken prior to and were ongoing while on study drug or medication(s) taken on or after the first dose date of the study drug.

Tabular summary of the number and percentage of subjects taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term. Listing will be provided for medical history, prior and concomitant medications.

6.4. Drug Exposure

The following variables are summarized using Safety Analysis Set but not limited to; the total number of doses received per patient, mean number of dosing per patient, duration of drug exposure (months), cumulative drug exposure time (person years)

Definition of drug exposure (days) will be defined as [Exposure time= (date of last exposure – date of first dose +1)] where date of last exposure will represent either the date of the last administered dose +28, analysis cut-off date or end of study date, whichever is earliest. The exposure during the DB period will be right censored; that is, the date of the last exposure will not be later than the first date of dosing in the OLE period. Dose interruptions and compliance are not taken into account.

7. STATISTICAL ANALYSIS

7.1. Primary Endpoint

The primary endpoint of the study is the percent change from baseline in 24-hour urine protein (UP) at Week 32. The analysis will be conducted using the modified ITT analysis set.

Valid 24-hour urine protein values will be included in the primary analysis (1 valid assessment at week 16 visit and the mean of two valid assessments at baseline and week 32 visit). All 24-hour urine samples need to meet the validity criteria below (Section 6.4.1.1 of the protocol). The 24-hour UP at baseline or Week 32 is the average of two valid collections.

A 24-hour urine collection will be considered valid if the following criteria are met:

- 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 age in years and weight is in kilograms. This result is multiplied by 0.85 in women.
- 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%.

The resulting 24-hour UP at each visit will be log transformed for analyses [Fellstrom 2017; Li 2006]. 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 urine protein in log-scale at 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 urine protein in log-scale (continuous), and patient as a random effect. Robust errors [White 1980] will be used to model the within-patient errors. If the fit of covariance structure with the robust errors fails to converge, a compound symmetric correlation structure will be used. At each visit, least square (LS) means ($\hat{\mu}_j$) with corresponding standard errors (SEM) and 90% CI will be displayed by treatment arm. The primary comparison is the LS mean treatment difference (cemdisiran – placebo) in percent change of 24-hour urine protein at week 32 visit from baseline. This LS mean difference will be presented along with corresponding standard errors (SEMs), 90% CIs and p-value from the model.

The following results will also be presented:

- Placebo-adjusted geometric mean percent change at week 32 visit:

$$\frac{\mathrm{GM}\left(\frac{\text{UP at week32}}{\text{UP at baseline}}\right)_{\text{cemdisiran}} - \mathrm{GM}\left(\frac{\text{UP at week32}}{\text{UP at baseline}}\right)_{\text{placebo}}}{\mathrm{GM}\left(\frac{\text{UP at week32}}{\text{UP at baseline}}\right)_{\text{placebo}}} * 100$$

$= [\exp(\delta) - 1] * 100$ where δ is the LS mean treatment difference between the two arms from the MMRM model above.

- The 90% CI for the placebo-adjusted geometric mean percent change:

$$[(\exp(lower\ bound\ for\ \delta) - 1) * 100,\ \ (\exp(upper\ bound\ for\ \delta) - 1) * 100]$$

In addition, the geometric mean for the ratio from baseline at week 32 visit in 24-hour UP and 90% confidence intervals for each treatment group will be presented using respective LS means ($\hat{\mu}_j$) and corresponding 90% confidence intervals (j=0 if placebo and j=1 if cemdisiran):

$$exp(\hat{\mu}_j) \text{ and } [\exp(lower\ bound\ for\ \mu_j), \exp(upper\ bound\ for\ \mu_j)]$$

Descriptive statistics will also be generated by treatment arm at each scheduled visit. Geometric Mean (+/- SEM) figures of the ratio to baseline by treatment arm will be plotted as well as individual spaghetti plots.

7.1.1. Sensitivity Analyses

The first sensitivity analysis will be conducted to evaluate the robustness of the primary model using normality of log-transformed UP data assumption. A stratified rank ANCOVA analysis [LaVange and Koch 2006] will be conducted without using the normality assumption of log-transformed UP data. The following steps will be performed:

1. Standardized ranks within each stratification stratum will be derived across the two treatment groups for the baseline and the change from baseline at Week 32 in 24-hour UP
2. The linear regression model will be fitted separately for each stratum where the standardized rank of the change from baseline at Week 32 in 24-hour UP is the outcome variable, the standardized rank of the baseline is the only covariate
3. The stratified mean score test will be performed to compare the two treatment groups using the values of the residuals from the above model as scores and stratification factor as the stratum
4. Cochran–Mantel–Haenszel (CMH) p value is obtained

The second sensitivity analysis is to assess the impact of missing data and the robustness of the primary analysis. The analysis will use the same MMRM model on the imputed data, of which the missing 24-hour UP value will be imputed with the spot urine creatinine ratio [Ginsberg 1983; Viswanathan and Upadhyay 2011] assessed closest to the date of missing value, when available.

7.1.2. Subgroup Analyses

Subgroup analyses will be conducted to assess the treatment effect during the DB period for the primary endpoint within the following subgroups: Gender (Male vs. Female), Age (< Median vs. ≥ Median), eGFR (< 60 vs. ≥ 60), and 24-hour UP (< 2g/24-hour vs. ≥ 2g/24-hour). Other subgroups may be examined, if deemed appropriate.

The subgroup analysis will be performed for the primary endpoint using the mITT analysis set. A forest plot will be generated to illustrate the estimated treatment effect along with the associated

90% confidence interval. The subgroup analyses may be performed for secondary endpoints if appropriate.

7.2. Secondary Endpoints

For secondary endpoints assessed in DB period, the analysis will compare randomized arms (cemdisiran vs. placebo) using the mITT analysis set.

The secondary endpoints which are assessed beyond Week 36 will be summarized to describe the long-term efficacy of cemdisiran using the All Cemdisiran Treated Analysis Set by treatment sequence, i.e., cemdisiran /cemdisiran, placebo/ cemdisiran, and overall.

The planned analyses of the secondary endpoints are summarized in Table 2.

Table 2 Summary of Analyses for the Secondary Efficacy Endpoints

Endpoint	Statistical Method	Notes
Percent of patients with partial clinical remission (urine protein [UP] <1.0g/24-hours) at Week 32	Treatment comparison will be conducted using Cochran-Mantel-Haenszel test stratified by baseline 24-hour UP (<2 g/24-hours vs. ≥2 g/24-hours). The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Wilson score method with continuity correction will be presented.	
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	MMRM of change from baseline in log-transformed UPCR. Model includes log-transformed baseline and treatment, visit, and the interaction of treatment and visit.	
Change from baseline in UPCR as measured in a spot urine at Week 32	The MMRM of change from baseline in log-transformed spot UPCR. The model includes log-transformed baseline spot UPCR, treatment, visit, and the interaction of treatment and visit.	Scheduled assessments are outlined in the Table 1 (Schedule of Assessments) of the protocol. Proper adjustment to the analysis method may be needed when data become available.
Change from baseline in hematuria at Week 32 (RBC/hpf)	Descriptive statistics will be presented by visit and treatment arm.	

7.3. Exploratory Analyses

Exploratory endpoints will be summarized descriptively by treatment arms during the DB period using mITT Analysis set.

For the slope of eGFR computed for the entire study period, it will also be analyzed by treatment sequence (cemdisiran/cemdisiran, placebo/cemdisiran) using the All Cemdisiran Treated Analysis Set. However, the other exploratory endpoints may be analyzed over the entire study if deemed appropriate. Table 3 summarizes the planned analyses for exploratory endpoints.

Table 3 Summary of Analyses for Exploratory Endpoints

Exploratory Endpoint	Statistical Method	Notes
Change from baseline in estimated glomerular filtration rate (eGFR)[1] at Week 32	Descriptive statistics of eGFR will be presented by visit and treatment arm. Shift tables of eGFR categories from baseline to post-baseline visits and an overall worst post-baseline will also be presented.	
The slope of eGFR computed for the first 32 weeks using all assessments during the period	The random coefficient model for eGFR will include baseline eGFR, treatment, time, and the interaction of treatment and time as fixed effects and intercept and time as random effects.	The first study drug dosing will be defined as the time reference point t=0 In addition, the slope of eGFR for each subject will be estimated.
The slope of eGFR computed for the entire study period including the open label extension using all assessments during the study	The random coefficient model for eGFR will include baseline eGFR, treatment sequence, time, and the interaction of treatment sequence and time as fixed effects and intercept and time as random effects.	This endpoint will be analyzed only at the final analysis using Cemdisiran Treated Analysis set. The first administration of cemedisiran will be defined as the time reference point t=0.
The slope of eGFR during placebo period comparing the slope during OLE for patients who crossed over from placebo to cemdisiran.	The random coefficient model with piecewise regression will include baseline eGFR, time during the placebo treatment and time during the cemdisiran treatment as fixed effects and intercept and times as random effects.	This endpoint will be analyzed only at the final analysis using placebo/cemdisiran treatment sequence group.
Change from baseline in creatinine clearance at Week 32	Descriptive statistics will be presented by visit and treatment arm.	See section 6.4.3 in the protocol for creatine clearance

Exploratory Endpoint	Statistical Method	Notes
Percent of patients in full clinical remission (Urine Protein [UP]<0.3 g/24-hours) at Week 32	The number and percentage of patients who are responders at Week 32 are summarized by treatment arm. The difference in percentages of responders and corresponding 90% CI based on the Newcombe method based the Wilson score with continuity correction will be presented.	
Change from baseline in 24-hour albuminuria at Week 32	Descriptive statistics will be presented by visit and treatment arm.	
Change from baseline in the urine albumin/creatinine ratio (UACR) as measured in 24-hour urine at Week 32	Descriptive statistics will be presented by visit and treatment arm.	

[1] eGFR will be based on CKD-EPI: $eGFR = 141 * \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} * \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} * 0.993^{Age} * 1.018[if\ female] * 1.159[if\ black]$. Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

7.4. Pharmacodynamic Analyses

PD endpoints will be summarized by treatment arm at the primary analysis using mITT analysis set and at the final analysis by treatment sequence using All Cemdisiran Treated Analysis Set. Analyses of PD endpoints are summarized in Table 4 below.

Table 4 Summary of Analyses for Pharmacodynamic Variables

Endpoint	Statistical Method	Notes
Change from baseline in C5 level over the course of the study	The levels of C5, absolute change and percentage change from baseline in C5 will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	
Change from baseline in complement activity (Complement Alternative Pathway [CAP] and Complement Classical Pathway [CCP]) over the course of the study	The levels of CAP and CCP and the changes and percentage changes from baseline will be summarized descriptively and plotted over time by treatment arm or treatment sequence.	The biomarkers of complement activation include but not limited to C5a, sC5b9 in plasma, and sC5b9 in urine.

Endpoint	Statistical Method	Notes
Change from baseline in levels of renal damage, complement activation and inflammation markers over the course of the study	The levels of the biomarkers and their changes and percentage changes from baseline will be summarized descriptively by visit and treatment arm or treatment sequence	

7.5. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed for cemdisiran and active metabolite, AS(N-2)3'-ALN-CC5 and AS(N-3)3'-ALN-CC5 cemdisiran, using noncompartmental methods. PK analyses will be based on the Pharmacokinetic Analysis Set. Summaries will be provided for each scheduled time point. PK data will be included in by-patient data listings. The following PK parameters will be estimated for each subject, as appropriate and if data permits: area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{½\beta}$), apparent clearance (CL/F), apparent volume of distribution (V/F), cumulative amount excreted unchanged in urine (Ae), and percent of dose excreted (fe). Additional PK parameters may be calculated, if deemed necessary. The PK parameters will be summarized using descriptive statistics.

Pharmacokinetic analyses will be conducted using noncompartmental methods. PK parameters will be calculated using a validated version of Phoenix® WinNonlin. Population PK analysis is planned for all patients in the study and will be described in a separate population PK analysis plan.

7.6. Safety Analyses

Primary safety analyses will compare cemdisiran versus placebo during the DB period using the Safety Analysis Set. Long-term safety analyses of cemdisiran will be summarized by treatment sequence (cemdisiran / cemdisiran, placebo/ cemdisiran, all cemdisiran treated arm) using the all Cemdisiran Treated Analysis set.

The primary safety parameter is the treatment emergent adverse events (TEAEs). A TEAE is defined as an AE that occurred or worsened on or after the first dose of study drug through 28 days after the last dose of study drug. In addition, an AE occurs after the 28 days from the last dose but it is considered to be related to study drug, then it is considered to be TEAE. Other safety parameters also include vital signs, ECGs, clinical laboratory assessments, and physical exams. Adverse events of non-treatment emergent (e.g., during safety follow up period) will be summarized and listed separately.

7.6.1. Adverse Events

All TEAEs hereafter will be referred to as AEs in this document. No statistical tests will be performed to compare Adverse Event (AE) rates between treatment groups. Adverse events will be coded using MedDRA version 21.1 or higher and displayed in tables using SOC and PT.

An overview table of AEs will be tabulated. The overview table will include the number and percentage of patients in following categories such as, but not limited to:

- At least 1 AE
- At least 1 study drug related AE
- At least 1 severe AE
- At least 1 study drug related severe AE
- At least 1 Serious Adverse Event (SAE)
- At least 1 study drug related SAE
- At least 1 AE leading to treatment discontinuation
- At least 1 study drug related AE leading to treatment discontinuation
- At least 1 AE leading to study withdrawal
- At least 1 study drug related AE leading to study withdrawal
- Death

Tabulations by System Organ Class (SOC) and Preferred Term (PT) displaying the number of patients (percentage) and total events will be produced for the following tables:

- All AEs
- Severe AEs
- AEs by Maximum Severity
- AE related to treatment
- AEs related to treatment by Maximum Severity
- All SAEs
- SAEs related to treatment
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AEs leading to study withdrawal

Tabulations by PT in decreasing order in frequency within the cemdisiran arm will be generated for the following tables:

- All AEs
- All SAEs
- AEs related to treatment
- SAEs related to treatment

In summaries by SOC and PT, AEs will be sorted alphabetically by SOC then by PT.

There will also be an All AE table generated displaying rates of adverse events adjusted for exposure-time during the respective period. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence or most related.

Separate listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug, withdrawal of study drug and/or dose interruption. By-subject AE listings will be provided.

7.6.2. Adverse Event of Clinical Interest (AECI)

Additional summaries of safety areas of interest based on Standardized MedDRA Queries (SMQs) and other groupings of adverse events may be summarized such as, but not limited to the following:

Injection Site Reactions [ISRs]: AEs mapping to the High-Level Term (HLT) = "Injection Site Reactions" using MedDRA dictionary will be included in the summary.

Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs. A table will also be generated to display the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose in summary), total number of doses with ISRs, and the signs and symptoms reported due to ISRs. If there are multiple ISRs that occur in between two consecutive injections, then these events will be considered as 1 ISR and considered related to the earlier injection.

Hepatic AEs, including AEs of LFT abnormalities: These AEs are mapped to the SMQ Drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms).

Frequency (percentages) of drug-related hepatic disorders will be summarized by SOC, HLT and PT. A separate listing will be generated of all patients reporting these events.

7.6.3. Laboratory Data

Clinical laboratory parameters will be expressed in Standard International (SI) units. Summaries will only include data from central laboratory. For any local collections of LFTs, these will be included in a separate data listing. Key laboratory parameters will be graded according to NCI CTCAE v5.0.

Summaries for each lab parameter (hematology, chemistry, liver function tests, coagulation and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics at each scheduled visit. Descriptive statistics include actual value, change from baseline and percent change from baseline at each scheduled visit.

Shift tables will be generated to summarize shifts from baseline categories to the worst post-baseline categories with directionality specified for any labs which could be reported in either direction (e.g. above ULN or below ULN).

Clinical laboratory tests with normal ranges will be classified as Low, Normal, and High. For these tests, abnormal values will be flagged in the listings with H when the value is higher than the upper limit of the reference ranges and with L when the value is lower than the lower limit of the reference ranges.

For hematology and chemistry labs, summary tables of potentially clinically significant abnormalities will also be provided.

All laboratory data will be presented in data listings. Separate listings will be included for those laboratory data collected from local labs such as LFTs. Out of range laboratory results will be identified in listings.

7.6.4. Liver Function Analysis

A listing will be generated for all patients with abnormal liver function tests as defined by ALT>3xULN, AST>3xULN and total bilirubin >2x ULN at any visit.

A tabular summary for LFTs will be generated to summarize the number and associated percentage of patient in each of the categories at any post-baseline visit:

- ALT>1 & ≤3, ALT>3 & ≤5, ALT>5 & ≤10, ALT>10 & ≤20, ALT>20xULN
- AST>1 & ≤3, AST>3&≤5, AST>5& ≤10, AST>10 & ≤20, AST>20xULN
- ALT or AST>1 & ≤3, ALT or AST>3 & ≤5, ALT or AST>5 & ≤10, ALT or AST>10 & ≤20, AST or ALT>20xULN
- WNL, ALP>1.5xULN
- Total Bilirubin>1.5& ≤2, Total Bilirubin>2&≤3, Total Bilirubin>3& ≤5 and Total Bilirubin>5

eDISH plots of peak total bilirubin at any time versus peak ALT or AST at any time will also be presented. For selected labs (e.g. ALT/ULN and AST/ULN), a table and figure of the values across the entire study (DB+OLE) will be generated by treatment sequence arms.

7.6.5. Vital Signs

Descriptive statistics for each vital sign (e.g. systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, weight, body mass index) will be summarized at scheduled visits. Summaries will include actual values and changes from baseline.

Vital sign measurements will be presented for each patient in a data listing, with abnormal vital signs flagged.

7.6.6. Electrocardiogram

For electrocardiogram (ECG) parameters, these will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each timepoint will be summarized. For assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis

ECG findings will include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTc).

Corrected QT interval, if not collected, will be calculated using Fridericia's correction formula.

Fridericia's cube-root corrected QT: QTcF (ms) = QT (ms) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$.

Baseline, post baseline maximum QTcF and post baseline maximum change from baseline in QTcF during the study will be summarized with descriptive statistics. The incidence of notable ECG changes from baseline in maximum absolute QT_cF, intervals (<=450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF, maximum changes from baseline (<=30 ms, > 30 -60 ms and > 60 ms) over all post-treatment evaluations will be summarized. A listing of all ECG data will be provided.

7.6.7. Physical Examination Findings

Physical examinations will be conducted throughout the study. If any abnormalities are observed during these physical exams, then this will be recorded on the adverse event form.

A separate listing per patient will be generated to display the date and time of the physical exam.

7.7. Anti-Drug Antibody

The number and associated percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized by treatment group. A listing of patients with positive ADA assay results will be provided as well as a listing of all ADA results. Circulating Immune Complexes (CIC) and anti-GdIgA1 antibody will be summarized descriptively by visit and listing will be provided.

8. CHANGES TO PLANNED ANALYSES

Key changes to analyses described in the protocol are listed in the table below.

Change from Protocol	Detailed Description/Rationale
The primary analysis - The analysis method is changed to MMRM model, instead of linear model based on Week 32. - Use only the continuous baseline value of 24-hour urine protein as a covariate in the model (removing the randomization stratification factor 24-hour urine protein <2 g/24-hours vs. ≥2 g/24-hours).	To allow use of all the data when modeling the primary endpoint, including patients who may not have Week 32 data. Additionally, since the baseline 24-hour urine protein and the stratification factor are correlated, the primary analysis model, MMRM only includes the continuous baseline 24-hour urine protein.

Change from Protocol	Detailed Description/Rationale
Change to the sensitivity analysis - Remove per-protocol analysis (Protocol Section 7.2.1) - Add an additional analysis (Protocol section 7.2.5.1)	- Per protocol analysis set is not defined for this study - New sensitivity analysis is added to evaluate the sensitivity of the treatment effect by the normality assumption of the log-transformed UP data and missing data
Change to “treatment arm” from “dose level” - Correct the error in “The extent of exposure will be summarized by dose level and overall” (Protocol Section 7.2.8)	There is only 1 dose level and it is corrected to treatment arm

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