STATISTICAL ANALYSIS PLAN (FINAL)
Statistical Analysis Plan: 2.0
Protocol Number: APL2-C3G-310

STATISTICAL ANALYSIS PLAN

Pegcetacoplan (APL-2)
PHASE 3

A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis

PROTOCOL IDENTIFIER: VALIANT

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REVISION HISTORY

Version	Issue date	Summary of changes
1.0	07 September 2023	Original
2.0	27 June 2024	• Revised the order of key secondary efficacy endpoints; change from baseline in eGFR is now the last key secondary endpoint. • Removed exploratory endpoint evaluating normalization of hematuria. • Removed exploratory endpoint of evaluation of changes in drusen at 26 weeks. • Updated strategies for addressing ICEs. • Removed mITT set from statistical analysis sets. • Provided further details on the analysis of C3c staining endpoint. • Provided further details on the analysis of time-to-event endpoints. • Provided further details on the analyses of FACIT-Fatigue score, EQ-5D-5L score, and WPAI score endpoints. • Provided further details on immunogenicity analysis. • Provided further details on the analysis of baseline disease characteristics. • Updated strategies for addressing missing data in PP analysis. • Clarified more details on the covariance structures for the MMRM models. • Provided further details on the analysis window mapping for roll-over participants. • For endpoints of C3c histologic activity score, FACIT-Fatigue score, and KDQOL score, clarified in the null/alternative hypothesis that the change from baseline is being modeled instead of the value at week 26. • Clarified for the key secondary endpoints of activity score and C3c staining reduction, modeling will only be based on adult participants. • Updated analysis for the exploratory endpoint of annual rate of change from up to 3 years prior to screening in eGFR. • Updated analysis for the exploratory endpoint of glomerular macrophage count. • Updated analysis for the exploratory endpoint of PGIC score. • Provided more details on the activity score endpoint regarding the primary, secondary, and adjudication reports. • Updated to assign different randomization seeds for different endpoints. • Updated safety analysis to add summary tables for AESIs and exposure-adjusted AEs. • Added new subgroup “baseline immunosuppressants use” in all subgroup analyses, the new subgroup has also been added in primary analysis modeling • Added clarification languages.

APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	Adverse event of special interest
AH50	50% alternative hemolytic complement pathway activity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	autoregressive
ARH	heterogeneous autoregressive
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BLQ	below limit of quantification
BMI	body mass index
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CH50	50% classical hemolytic complement pathway activity
CI	confidence interval
CKD-EPI	Chronic Kidney Disease–Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CS	compound symmetry
CV	coefficient of variation
DBP	diastolic blood pressure
DDD	dense deposit disease
DMC	data monitoring committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	5-Level EuroQol-5 Dimension
FACIT	Functional Assessment of Chronic Illness Therapy
FMU	first-morning spot urine
GGT	gamma-glutamyltransferase

Term	Definition
IC-MPGN	immune-complex membranoproliferative glomerulonephritis
ICE	intercurrent event
INR	international normalized ratio
ITT	intention-to-treat
KDQOL	kidney disease quality of life
LLN	lower limit of normal
LLOQ	lower limit of quantification
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
MNAR	missing not at random
OLP	open-label period
PCS	potentially clinically significant
PD	pharmacodynamic
PEG	polyethylene glycol
PGIC	patient global impression of change
PK	pharmacokinetic
PP	per-protocol
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RCP	randomized controlled period
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
TBL	total bilirubin

Term	Definition
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
uPCR	urine protein-to-creatinine ratio
WBC	white blood cell
WHO	World Health Organization
WPAI	work productivity and activity impairment

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic/pharmacodynamic/immunogenicity data as described in the study protocol Amendment 4 dated 25 April 2024. Specifications for tables, figures, and listings are contained in a separate document.

The current SAP describes analysis of the randomized controlled period (RCP, up to week 26). Analysis on the interim data post-week 26 at the time of the datacut, referred to as the open-label period (OLP) reporting, will be provided in an SAP addendum.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to assess the efficacy of twice-weekly subcutaneous (SC) doses of pegcetacoplan compared with that of placebo in patients with primary C3 glomerulopathy (C3G) or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) on the basis of a reduction in proteinuria.

2.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the effect of pegcetacoplan on estimated glomerular filtration rate (eGFR)
- To assess the effect of pegcetacoplan on additional C3G/IC-MPGN disease-related parameters
- To evaluate the safety of pegcetacoplan over 52 weeks of treatment

2.1.3. Exploratory Objectives

The exploratory objectives are to characterize the additional clinical, laboratory, and histologic findings of C3G/IC-MPGN in response to pegcetacoplan.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the log-transformed ratio of urine protein-to-creatinine ratio (uPCR) at week 26 compared to baseline.

2.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are (to be evaluated at week 26):

- The proportion of participants who meet the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.)
- The proportion of participants with a reduction of at least 50% from baseline in uPCR
- For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score
- The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline
- Change from baseline in eGFR

2.2.3. Additional Secondary Efficacy Endpoints

The additional secondary endpoints are (to be evaluated at week 26):

- The proportion of participants achieving proteinuria <1 g/day
- For participants with serum albumin levels below the lower limit of normal (LLN) at baseline, the proportion of participants with normalization of serum albumin levels
- For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN
- The change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score
- The change from baseline in Kidney Disease Quality of Life (KDQOL) score

2.2.4. Exploratory Efficacy Endpoints

The primary, key secondary, and additional secondary efficacy endpoints will also be evaluated at week 52 as exploratory efficacy endpoints.

In addition, the following exploratory efficacy endpoints will be evaluated:

- The change from baseline in uPCR using the 24-hour urine collections at week 24 and week 48
- The annual rate of change from up to 3 years prior to screening in eGFR at week 26 and week 52
- The proportion of participants with reductions from baseline in proteinuria of at least 30% at week 26 and week 52
- The proportion of participants with normalization of proteinuria at week 26 and week 52
- The time to 50% reduction in uPCR with a stable or improved eGFR
- The time to normalization for the following parameters for participants in whom the parameter is abnormal at baseline:
  - serum C3
  - uPCR
  - serum albumin
  - blood pressure
- The change from baseline in glomerular macrophage count, as determined by CD68 staining at week 26 and week 52
- The change from baseline in Patient Global Impression of Change (PGIC) score at week 26 and week 52
- The change from baseline in 5-Level EuroQol-5 Dimension (EQ-5D-5L) score at week 26 and week 52

- The change from baseline in Work Productivity and Activity Impairment (WPAI) score at week 26 and week 52
- Change in drusen from baseline at week 52:
  - change in maximum drusen size
  - change in number of intermediate or large drusen

2.2.5. Safety Endpoints

The safety endpoints are as follows:

- The incidence and severity of treatment-emergent adverse events (TEAEs)
- The change from baseline in:
  - vital signs measurements
  - clinical laboratory tests
  - Electrocardiogram (ECG) results
- The number and incidence of rejection episodes (posttransplant participants only)
- The number and incidence of graft loss (posttransplant participants only)
- The incidence of death, stratified by transplant history

2.2.6. Pharmacokinetic Endpoint

The pharmacokinetic (PK) endpoint is pegcetacoplan serum concentrations over time.

2.2.7. Pharmacodynamics Endpoints

The pharmacodynamic (PD) endpoints are:

- Changes from baseline in complement levels at week 26 and week 52:
  - CH50 (50% classical hemolytic complement pathway activity)
  - AH50 (50% alternative hemolytic complement pathway activity)
  - sC5b-9

Additional complement components may be measured, as noted in Protocol Table 4 and Protocol Section 11.1.11, and evaluated as exploratory endpoints.

2.2.8. Immunogenicity Endpoint

The immunogenicity endpoint is:

- The incidence of antidrug antibodies (ie, antibodies against the peptide and polyethylene glycol [PEG] domains of pegcetacoplan)

3. STUDY DESIGN

3.1. General Description

This phase 3 randomized, placebo-controlled, double-blinded, multicenter clinical study is designed to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with primary C3G or IC-MPGN. There will be approximately 80 to 100 participants enrolled in this study, at least 78 of whom will have native kidney disease and up to 22 of whom may have posttransplant recurrence of C3G or IC-MPGN. At least 63 participants with C3G in native kidney will be enrolled. The enrollment of participants with C3G or IC-MPGN will be monitored to ensure balance between the groups. At least 10 adolescent participants (aged 12-17 years) will be enrolled; adolescent participants may be either patients with native kidney disease or posttransplant disease recurrence. Participants initially screened as adolescents will follow adolescent procedures and requirements through the duration of their participation in study, even if they pass their 18th birthday while enrolled in the study.

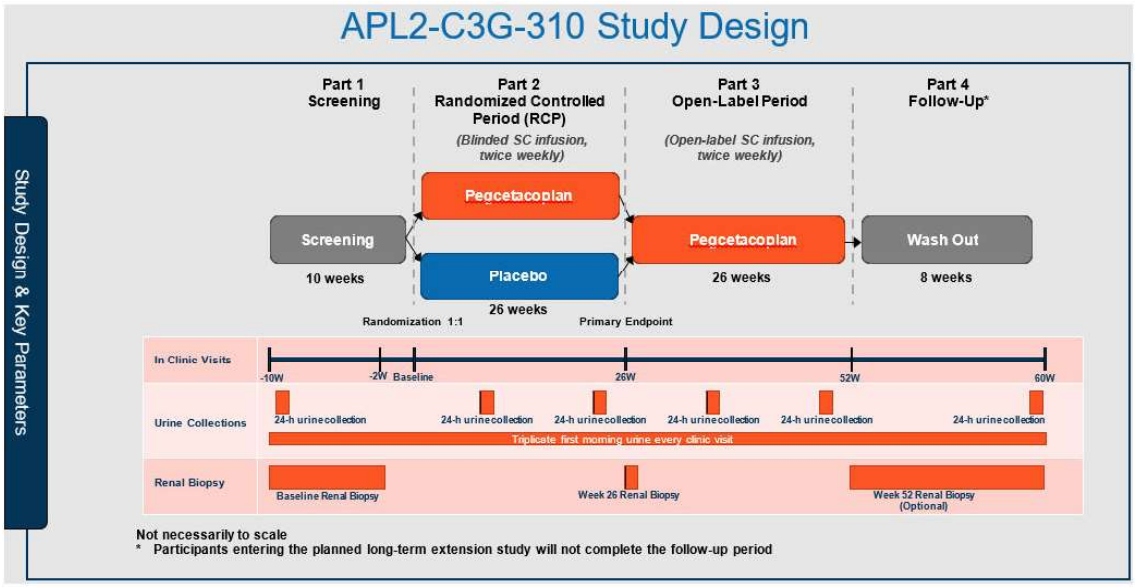
The planned length of participation in the study for each participant is a maximum of approximately 70 weeks. This study will consist of 4 parts:

- Part 1: 10-week screening period
- Part 2: 26-week randomized controlled period (RCP)
- Part 3: 26-week open-label period
- Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study)

Informed consent (and assent, when applicable) will be obtained prior to any study-related procedures being conducted. The screening period will start once informed consent has been obtained.

See Figure 1 for the study schematic, and Section 17.1 for the schedule of activities.

Figure 1: Study Design



Abbreviations: SC = subcutaneous; uPCR = urine protein-to-creatinine ratio; W = week.

3.2. Randomization

Participants will be randomized to receive pegcetacoplan or placebo in a ratio of 1:1 via stratified permuted block randomization. The randomization will be performed centrally. To achieve balance between the arms, 2 stratification factors will be applied to the randomization. The first stratification factor examines participants with posttransplant recurrence versus nontransplant participants; at least 78 participants with C3G or IC-MPGN in a native kidney will be enrolled. This is followed by the second stratification factor, which examines participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomization) versus participants without baseline renal biopsies.

3.3. Blinding

This is a double-blinded study during the randomized controlled period. The open-label period is not blinded.

Designated blinded study staff (eg, research coordinators, nurses, technicians administering questionnaires, participants, central pathologists, assigned evaluating physicians, and the sponsor) will be blinded to treatment assignment. Access to unblinded study treatment information will be strictly limited as mandated in the study's Blinding Plan; any individuals who are unblinded are not allowed to discuss treatment and/or participant outcome with blinded study staff, including the evaluating physician. The principal investigator must be blinded to participants' treatment assignment. Although treatment in the open-label period is not blinded, investigators, study site personnel, and participants will remain blinded to the RCP treatment assignment until the blind has been broken.

3.4. Sample Size and Power Considerations

Approximately 80 to 100 participants, including patients with native kidney disease or post-transplant, will be randomized 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm.

Based on preliminary data from Study APL2-201, a reduction of 60% in uPCR in the pegcetacoplan group at week 26 is assumed vs a reduction of 20% in uPCR in the placebo arm, which corresponds to a mean log ratio to baseline of -0.92 vs -0.22 respectively, and a standard deviation of 0.88 (on log-scale). Based on this assumption, a sample size of 70 participants in total provides at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and the impact of coronavirus disease 2019 (COVID-19), it is expected that at least 78 participants with native kidney disease should be enrolled.

A minimum of 63 participants with C3G in native kidneys will be enrolled, which is approximately 80% of the enrolled participants with native kidney disease.

3.5. Analysis Timing and Unblinding

The analysis of data from the RCP of the study will be performed when all participants have completed the RCP or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized, and the week 26 Analysis database locked. At that time, the sponsor analysis team will be unblinded to the treatment code, and the primary analysis will be performed, which will include all efficacy and safety analyses for the RCP.

4. STATISTICAL ANALYSIS SETS

4.1. Screened Set

The screened set includes all participants who provide written informed consent. This set will be used only for the purpose of describing participant disposition.

4.2. Intent-to-Treat Set

The intent-to-treat (ITT) set includes all participants who are randomized. Participants will be analyzed in the treatment arm assigned at randomization.

4.3. Safety Set

The safety set includes all participants who receive at least one dose of pegcetacoplan or placebo. Participants will be analyzed according to the actual treatment received. This population will be used for all safety analyses.

4.4. Per-protocol Set

The per-protocol (PP) set includes all participants in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of participants from the PP set will be made and documented prior to week 26 Analysis database lock.

The review and classification of protocol deviations are described in the study's Protocol Deviation Handling Plan, where the criteria for major and minor deviations are also defined. Deviations that affect exclusion from the PP set are a subset of protocol deviations; major protocol deviations do not necessarily result in exclusion of the participant from the PP set.

4.5. Pharmacokinetic Set

The pharmacokinetic (PK) set includes all participants in the safety set who have at least one quantifiable post-dose concentration of pegcetacoplan (even with values below the limit of quantification [BLQ]).

4.6. Pharmacodynamic Set

The pharmacodynamic (PD) set includes all participants in the safety set who have at least one quantifiable post-dose PD endpoint (eg, C3, CH50, or AH50) evaluated.

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

For summary of analysis sets, the number and percentage of participants screened, who failed screening, and who were included in each of the analysis sets as specified in Section 4 will be summarized and listed using the Screened Set.

For summary of disposition, the number and percentage of participants who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, who withdrew from the study with a primary reason for withdrawal will be summarized and listed using the ITT set.

Participant disposition by region will also be provided for the ITT set.

5.2. Demographic and Other Baseline Characteristics

The following baseline demographic characteristics will be summarized and listed using the ITT and Safety sets (if these two sets are different, otherwise will only generate for ITT): age at screening, age group (≤ 65 years vs > 65 years, alternative grouping based on age distribution may be considered if necessary), sex, ethnicity, race, weight, height, body mass index (BMI), and blood pressure.

The following baseline disease characteristics will be summarized and listed using the ITT and Safety sets (if these two sets are different, otherwise will only generate for ITT): underlying disease based on screening biopsy (C3G including C3GN and DDD, or IC-MPGN), indication per disease-specific medical history form, potential risk factors of C3G/IC-MPGN, disease manifestations, drusen, prior kidney transplant (Y/N), time since last kidney transplant, total number of kidney transplants, prior dialysis (Y/N), baseline 24h uPCR, baseline uPCR (triplicate first-morning spot urine), baseline eGFR, annualized historical eGFR slope, baseline creatinine, baseline serum albumin, baseline serum C3, time since diagnosis of C3G/IC-MPGN, time since most recent post-transplant recurrence, and time from last kidney transplant to the most recent post-transplant recurrence.

Time since diagnosis of C3G/IC-MPGN will be calculated as:

Time since diagnosis of C3G/IC-MPGN (years) = (day 1 date – start date of indication)/365.25.
Note: for native kidney participants, the source of "start date of indication" comes from the case report form's question "Start date of indication" from the disease specific medical history form. For post-transplant participant, the source of "start date of indication" comes from the derived variable "date of most recent post-transplant recurrence", which is obtained through programmatic search from medical history.

Time since last kidney transplant will be calculated as:

Time since last kidney transplant (years) = (day 1 date – date of last kidney transplant)/365.25.

Time since most recent post-transplant recurrence will be calculated as:

Time since most recent post-transplant recurrence (years) = (day 1 date – date of most recent post-transplant recurrence)/365.25.

Time from last kidney transplant to the most recent post-transplant recurrence will be calculated as:

Time from last kidney transplant to the most recent post-transplant recurrence (years) = (date of most recent post-transplant recurrence – date of last kidney transplant)/365.25.

Note in the above time since calculations, day 1 date will be replaced with randomization date if participants are not dosed.

The following baseline biopsy characteristics will be summarized and listed using the ITT and Safety sets (if these two sets are different, otherwise will only generate for ITT): C3 staining, number of glomeruli, light microscopic patterns, glomerular crescents, global sclerosis, interstitial fibrosis, tubular atrophy, deposits by electron microscopy (absent/present, characters of deposits, locations of deposits, degree of foot process effacement), total activity score, total chronicity score, and Banff score (post-transplant only).

For baseline demographic characteristics and baseline disease characteristics, additional subgroup tables will be provided separately for adults vs adolescents.

For baseline demographic characteristics, baseline disease characteristics and baseline biopsy characteristics, additional subgroup tables will be provided separately for C3G vs IC-MPGN.

5.3. Medical History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. For participants in the Safety Set, medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) and listed. Each participant will be counted only once in each SOC or SOC/PT summary.

In the summary table, medical history will be presented by decreasing frequency of participants overall within each SOC and then similarly by decreasing frequency of participants overall within each PT. In the cases of SOCs or PTs with equal frequencies, medical history will be sorted alphabetically.

Vaccination will be summarized for the Safety Set and listed. Kidney transplant history will be listed for the Safety Set.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest World Health Organization (WHO) Drug Dictionary version available. Summaries of prior and concomitant medications will be presented by Anatomical Therapeutic Class (ATC) level 2 (therapeutic main group) and preferred term with numbers and percentages by treatment groups and overall for participants in the Safety Set. A participant who takes more than one medication will be counted only once if these medications belong to the same ATC level 2 classification.

In the summary tables, prior medications and concomitant medications will be presented by decreasing frequency of participants overall within each ATC level 2 class and then similarly by decreasing frequency of participants overall within each preferred term. In cases of ATC level 2 classes or preferred terms with equal frequencies, medications will be sorted alphabetically.

Prior medications are defined as those medications that started prior to the first administration of study drug. Concomitant medications are defined as those medications taken on/after the date of first administration of study drug. Medications started before the first dose of study drug and continuing after will be considered as both prior and concomitant medications. A data listing of prior and concomitant medications will be provided for the Safety Set.

5.5. Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using the latest MedDRA version available. Summaries of prior and concomitant procedures will be presented by SOC and PT with numbers and percentages by treatment groups and overall for participants in the Safety Set. Prior procedures are defined as those that started prior to the first administration of study drug. Concomitant procedures are defined as those that started on/after the date of first administration of study drug. Procedures that started before the first dose of study drug and continuing after will be considered as both prior and concomitant procedures. A data listing of all procedures will be provided for the Safety Set.

5.6. Exposure to Investigational Product

The following parameters will be summarized using the Safety Set and listed:

- Total dose administered (mg)
- Duration of treatment (days), defined as (last infusion date – first infusion date + 1)
- Number and percentage of participants who received at least one infusion
- Number and percentage of participants with any infusions missed
- Number and percentage of participants with one or more incomplete infusions
- Number and percentage of participants with any infusions interrupted

5.7. Measurements of Treatment Compliance

Percent compliance will be summarized using the Safety Set and listed. Compliance is calculated as follows: Compliance (%) = total number of study infusions taken / total number of expected infusions, multiplied by 100.

The number and percentage of participants who had a percentage of drug compliance range by increment of 10% (<80%, ≥ 80% - < 90%, ≥ 90 - ≤100%, and >100%) will also be summarized.

5.8. Protocol Deviations

All protocol deviations will be reviewed and documented before database lock. Protocol deviations are being captured in accordance with the protocol deviation management plan. They may also be identified through programmable checks of the data.

The CRO/Apellis will classify major and minor protocol deviations per the agreed Protocol Deviation Handling Plan. The Apellis study team will review the protocol deviations and their classification throughout the study and before database lock.

The number and percentage of participants with protocol deviations will be summarized by importance of deviation for ITT Set and listed.

6. EFFICACY ANALYSES

Efficacy analysis including primary, key secondary, additional secondary, and exploratory analysis will be performed primarily using the ITT set, with participants grouped according to the treatment assigned at randomization. Available data from all randomized participants regardless of adherence to the protocol will be included in the efficacy analysis, this includes data from participants who discontinued study drug early but continued with study assessments. All efficacy data will be listed for the ITT set.

All statistical tests will be performed at 2-sided 5% level of significance and all confidence intervals will be two-sided 95% confidence intervals.

Unless otherwise noted, the following randomization stratification factors will be adjusted for in analysis of efficacy endpoints in the overall population:

- Participants with posttransplant recurrence versus nontransplant participants
- Participants with baseline renal biopsies versus participants without baseline renal biopsies

If participants are found to have had the incorrect stratum assigned at randomization, they will be analyzed according to the randomization stratum.

For potential treatment imbalance, will check imbalance between treatment and placebo. In case there are major imbalances on important prognostic factors other than those already included in the analysis model, additional sensitivity analyses may be performed to adjust any or all of these factors if appropriate. Data will be verified for outliers. Sensitivity analyses may be performed using more robust approaches or excluding outliers.

6.1. Analysis Models

In general, data will be analyzed using the approaches described below.

Mixed-effect model for repeated measures (MMRM) for continuous outcomes

Longitudinal assessments for changes from baseline in continuous outcomes will be analyzed using a mixed-effect model for repeated measures (MMRM). The model will include fixed categorical effects for treatment group, visit, disease type (C3G vs. IC-MPGN), baseline immunosuppressants use (yes vs. no, to add this effect for primary endpoint analysis only), stratification factors, and the visit-by-treatment group interaction, as well as the continuous, fixed covariate of the baseline value of the endpoint. The least square (LS) means with standard errors (SEs) and 95% confidence intervals (CIs) of the change from baseline will be presented by treatment group and visit; between-treatment differences and 95% CIs and p-values will be presented by visit. LS means (±SE) will be plotted over time by treatment group.

A common unstructured covariance matrix will be used. If the model fails to converge, the following covariance structures will be fit in this order until convergence is met: (*i*) heterogenous autoregressive ARH(1), (*ii*) autoregressive AR(1), (*iii*) compound symmetry CS. The sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters.

Logistic regression model for binary outcomes

Binary outcomes will be analyzed using a logistic regression model. The model will include treatment group as independent variable and adjusted for baseline value of the variable(s) used to define the endpoint, disease type, and stratification factors. Point estimates for proportions and difference in proportions will be presented. The p-value and odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group with associated 95% CI will be provided. In situations where event rates are low leading to convergence issue for the logistic regression model, alternative methods such as removal of covariates may be considered when appropriate.

Analysis of covariance (ANCOVA)

Analysis of covariance (ANCOVA) will be used to analyze C3G histologic index activity score, FACIT-Fatigue score, and KDQOL score with treatment as a fixed effect, adjusted for baseline score of the endpoint, disease type, and stratification factors. LS means will be presented for each treatment group, along with the between-treatment difference and 95% CI.

Mixed effects model for slope analysis of continuous outcomes

For slope analysis of continuous outcomes, a mixed effects model using the baseline and all postbaseline assessments will be used and will include treatment group, disease type, baseline immunosuppressants use (to add this effect for primary endpoint analysis only), and stratification factors as fixed effects, time (study week, continuous assuming linearity), and the time-by-treatment interaction. A common unstructured covariance matrix will be used. If the model fails to converge, the following covariance structures will be fit in this order until convergence is met: (*i*) heterogenous autoregressive ARH(1), (*ii*) autoregressive AR(1), (*iii*) compound symmetry CS. The sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters.

6.2. Multiplicity Adjustment

The primary endpoint of the study will be tested at the 2-sided 0.05 level, and if the null hypothesis for the primary endpoint is rejected, the secondary endpoints will be tested. The key secondary and additional secondary endpoints will be tested sequentially in the order in which they are presented in Section 2.2.2 and Section 2.2.3; the testing will stop once a null hypothesis is not rejected.
This fixed-sequence testing procedure will ensure that trial-wise error rate is controlled to be 0.05.

6.3. Estimands

The primary objective of this study is to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared with that of placebo in patients with primary C3G or IC-MPGN on the basis of a reduction in proteinuria.

The estimands and their attributes for the primary and all comparative key secondary and additional secondary endpoints are shown in Table 1 below. This includes strategies for addressing the following intercurrent events (ICEs):

- ProhibiRescue = use of prohibited concomitant medication specified in Protocol Section 8.3.3, or use of rescue therapies defined in Protocol Section 8.3.2
- RenalReplace = start renal replacement therapy (dialysis and/or renal transplant)
- DisctTrt = permanent discontinuation of study treatment

Table 1: Estimands and Attributes for Primary, Key Secondary, and Additional Secondary Endpoints

For all estimands: **A. Population**: participants with C3G or IC-MPGN defined through the study inclusion/exclusion criteria in the ITT Set **B. Treatment regimens of interest:** • Twice-weekly SC doses of pegcetacoplan for 26 weeks of treatment • Twice-weekly SC doses of placebo for 26 weeks of treatment		
C: Variable (or endpoint)	**D: Strategies for addressing ICEs (event†: strategy‡)**	**E: Population-level summary**
Primary Estimand		
Log-transformed ratio of uPCR at week 26 compared to baseline	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of log-transformed uPCR from baseline to week 26 (measured by equal-weighted average over weeks 24, 25, and 26) between the pegcetacoplan group and the placebo group.
Key Secondary Estimands (for comparative endpoints)		
The proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a composite renal endpoint for the pegcetacoplan group to achieving a composite renal endpoint for the placebo group at week 26.
The proportion of participants with a reduction of at least 50% from baseline in uPCR at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving a reduction of at least 50% from baseline in uPCR for the pegcetacoplan group to achieving a reduction of at least 50% from baseline in uPCR for the placebo group at week 26.
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score at week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change from baseline to week 26 in activity score between the pegcetacoplan group and the placebo group.

Table 1: Estimands and Attributes for Primary, Key Secondary, and Additional Secondary Endpoints

The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of showing decreases in C3c staining for the pegcetacoplan group to showing decreases in C3c staining for the placebo group at week 26.
Change from baseline in eGFR at week 26	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change of eGFR from baseline to week 26 between the pegcetacoplan group and the placebo group.
Additional Secondary Estimands (for comparative endpoints)		
The proportion of participants achieving proteinuria <1 g/day at week 24	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving proteinuria <1 g/day for the pegcetacoplan group to achieving proteinuria <1 g/day for the placebo group at week 24.
For participants with serum albumin levels below LLN at baseline, the proportion of participants with normalization of serum albumin levels at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving normalization of serum albumin for the pegcetacoplan group to achieving normalization of serum albumin for the placebo group at week 26.
For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN at week 26	ProhibiRescue, RenalReplace, DisctTrt: composite strategy	Odds ratio of achieving serum C3 levels above the LLN for the pegcetacoplan group to achieving serum C3 levels above the LLN for the placebo group at week 26.
The change from baseline in FACIT–Fatigue Scale score	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change from baseline to week 26 in FACIT-Fatigue Scale score between the pegcetacoplan group and the placebo group.
The change from baseline in KDQOL score	ProhibiRescue: hypothetical strategy RenalReplace: hypothetical strategy DisctTrt: treatment policy strategy	Difference in mean change from baseline in KDQOL score between the pegcetacoplan group and the placebo group.

Table 1: Estimands and Attributes for Primary, Key Secondary, and Additional Secondary Endpoints

†ICE definitions:

- ProhibiRescue = use of prohibited concomitant medication specified in Protocol Section 8.3.3, or use of rescue therapies defined in Protocol Section 8.3.2
- RenalReplace = start renal replacement therapy (dialysis and/or renal transplant)
- DisctTrt = permanent discontinuation of study treatment

‡Strategies:

- Composite strategy: the endpoint status at or after the initiation of the ICEs will be regarded as non-responder.
- Hypothetical strategy: (for ICEs due to ProhibiRescue) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed using copy reference imputation. (for ICEs due to RenalReplace) all measurements after the ICEs will be set to missing. Missing data resulting from the ICEs will be imputed based on the worst change of all participants across visits plus a random error.
- Treatment policy strategy: all measurements after the ICEs will be used as is. Missing data resulting from the ICEs will be imputed using copy reference imputation.

6.4. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the log-transformed ratio of uPCR at week 26 compared to baseline. The null ($H_{1,0}$) and alternative ($H_{1,1}$) hypotheses for the primary efficacy analysis are:

$H_{1,0}$: There is no difference in log-transformed ratio of uPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups.

$H_{1,1}$: There is a difference in log-transformed ratio of uPCR at week 26 compared to baseline between the pegcetacoplan and placebo treatment groups.

uPCR values are expected to be highly skewed so that the values will be natural log-transformed in analysis and presentation. For the primary efficacy endpoint, sensitivity analyses (Section 6.4.2), supplemental analyses (Section 6.4.3), and subgroup analyses (Section 6.4.4) will be performed.

6.4.1. Main Analysis of Primary Efficacy Endpoint

The primary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

Baseline uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 first-morning spot urine (FMU) samples collected between the start of screening and day 1, inclusive. The uPCR values used to calculate baseline should include those from the samples collected on day −2, day −1, and before dosing on day 1. In situations where less than 6 samples or more than 9 samples were collected, the average of all collected samples will be used for baseline derivation. For scheduled visits where 3 collections are expected for calculating averages, if there are missing collections, the average will be based on those available collections; if there are more than 3 collections available (e.g., additional unscheduled collections), the selection of 3 collections to be used for average calculation will follow data handling conventions as specified in Section 13.4.

An MMRM model will be used to analyze the primary endpoint. The model will include fixed categorical effects for treatment group, visit, disease type (C3G vs. IC-MPGN), baseline immunosuppressants use (yes vs. no), stratification factors, and the visit-by-treatment group interactions, as well as the continuous, fixed covariate of baseline log-transformed uPCR. As the primary estimate, the difference between treatment groups using a composite contrast of equal-weighted average over weeks 24, 25, and 26 will be estimated (refer to sample SAS code section for more details) with its 95% CI and corresponding p-value. Further details on the presentation of the results are described in Section 6.1above. In addition, the geometric means and geometric mean ratios relative to baseline will also be presented after converting the log-transformed values back to the original unit.

ICEs strategy and handling are listed in Table 1. Imputation for the non-monotone missing pattern (ie, arbitrary missing pattern) will be performed prior to the multiple imputation for the monotone missing pattern (ie, where a missing uPCR measurement at a visit for a participant implies that uPCR measurements at all subsequent visits for that participant are missing).

For the non-monotone missing pattern, missing value(s) between two visits with uPCR measurements will be imputed using the MCMC method based on the MAR assumption, which was first proposed by Li (1988) and Liu (1993) described the algorithm. Multiple imputation will then be carried out for monotone missing pattern. For ICEs due to renal replacement therapy (dialysis and/or renal transplant), missing data will be imputed based on the worst change of all participants across visits plus a random error. For other ICEs, missing data will be imputed based on copy reference imputation:

- Participants with monotone missing data in the placebo arm will have missing data imputed based on the observed values in the placebo arm.
- For the active treatment arm, participants with monotone missing data due to prohibited medication, rescue therapies, or treatment discontinuation will have missing data imputed based on the placebo arm.
- For the active treatment arm, participants with monotone missing data that are not due to prohibited medication, rescue therapies, or treatment discontinuation will have missing data imputed based on the observed values in the active treatment arm.

The number and percent of participants without monotone missing data (separated further by non-monotone missing vs. complete data), the number of participants with monotone missing data and a breakdown of reasons will be reported.

The imputation method will be implemented in SAS using the three standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step. The randomization seed to be used is CCI .

- The missing data are filled in 100 times to generate 100 complete datasets.
- The 100 complete datasets are analyzed by using the MMRM approach described above.
- The results from the 100 complete datasets are combined for inference using Rubin's rule.

The observed values for uPCR will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

The mean change from baseline in uPCR (±SE) will be plotted over time by treatment group.

All uPCR data will be listed for the ITT set.

6.4.2. Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis results. Analyses will be performed for the overall population based on the outcome of the primary analyses including all participants in the ITT set.

The following sensitivity analysis will be performed, as appropriate, using the same statistical approach as the one used in the primary analysis:

- Imputation based on MAR: Participants with missing data, regardless of the reason being the ICEs or not, will be handled implicitly within the MMRM analysis under the assumption of missing at random (MAR).
- Tipping point analysis: Participants with a monotone missing data pattern due to the ICEs will have missing data after the last assessment explicitly imputed by multiple imputation using a tipping point analysis method assuming missing not at random (MNAR).

The tipping point analysis method (a delta-adjusted stress testing approach) will be implemented for the active treatment arm under the MNAR assumption by searching for a tipping point that reverses the conclusion regarding positive treatment effect (O'Kelly and Ratitch 2014).
The following strategy will be used:

- For the control arm, participants will have missing data imputed based on the observed values in the control arm.
- For the active treatment arm, participants with monotone missing data that are not due to the ICEs will have missing data imputed based on the observed values in the active treatment arm.
- For the active treatment arm, participants with monotone missing data due to the ICEs will have missing data imputed based on the available values (observed values and values imputed for non-monotone missing data) in the active treatment arm with a shift parameter added to the imputed values. Multiple imputation will be implemented with the shift parameter allocated to the missing data point(s) proportionally across timepoints. (eg, for a shift parameter of 0.26 at week 26, incremental shifts of 0.04 would apply to week 4, …, and week 24, respectively, then a shift of 0.01 would apply to week 25 and week 26, respectively. 0.04 × 6 visits+ 0.01 × 2 visits= 0.26) The range of the shift parameters will be from 0.13 to 0.65 by increments of 0.13 for week 26. A tipping point may not exist within reasonable clinical assumptions.

To generate inference from imputed data, the same three standard steps as described in the main analysis will be implemented.

6.4.3. Supplemental Analyses of Primary Efficacy Endpoint

6.4.3.1. Per Protocol Set

The main analysis described in Section 6.4.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand. Missing data (regardless of the reason being the ICEs or not) will be handled implicitly within the MMRM analysis under the assumption of missing at random (MAR).

6.4.3.2. Slope Analysis

The mean rate of change (ie, slope) in observed log-transformed uPCR values will be compared between treatment groups using the linear mixed effects model for slope analysis of continuous outcomes described above in Section 6.1. The mean rate of change (slope), standard errors, and confidence interval will be estimated for the baseline to week 26 period for each treatment group. In addition, the estimated difference in slopes between the treatment groups along with the 95% CIs and p-value will be reported. Strategies for addressing ICEs are the same as the ones described in Section 6.4.1.

6.4.4. Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses will be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. Analyses will be performed for the primary efficacy endpoint for each of the following subgroups (as appropriate per actual subgroup sample size, levels with low sample size may be pooled to allow for an analysis to be conducted):

- Age group: adolescent, adult
- Sex: male, female
- Race: Caucasian, non-Caucasian
- Geographic region: United States, Rest of World
- Disease type: C3G, IC-MPGN
- Transplant history: nontransplant, posttransplant
- Baseline FMU uPCR: <3000 mg/g, ≥3000 mg/g
- Baseline eGFR: <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2
- Baseline C3 level: normal, below the LLN
- Baseline immunosuppressants use: yes, no (based on ATC level 2 of "IMMUNOSUPPRESSANTS" and/or "CORTICOSTEROIDS FOR SYSTEMIC USE")

The estimated treatment effects and corresponding 95% CIs and p-values from the models will be displayed graphically for each level of the subgroups specified via forest plots.

6.5. Analyses of Key Secondary Efficacy Endpoints

The following subsections describe the analyses of the key secondary efficacy endpoints of the study. All analyses of the key secondary efficacy endpoints will be done primarily using the ITT set.

6.5.1. The Proportion of Participants Who Meet the Criteria for Achieving a Composite Renal Endpoint

The key secondary efficacy endpoint of the proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 will be examined with the following null ($H_{2,0}$) and alternative ($H_{2,1}$) hypotheses:

$H_{2,0}$: There is no difference in proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 between the pegcetacoplan and placebo treatment groups.

$H_{2,1}$: There is a difference in proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 between the pegcetacoplan and placebo treatment groups.

A participant meets the requirements of the composite renal endpoint if they satisfy:

(1) A stable or improved eGFR compared to baseline (≤15% reduction in eGFR), and
(2) A ≥50% reduction in uPCR compared to baseline.

For requirement (1), the eGFR status at week 26 will be calculated using the following steps:

1. Baseline eGFR value will be calculated using the last non-missing assessment prior to first dose.
2. Week 26 eGFR value will be calculated based on the week 26 assessment result.
3. Each participant will be categorized as either a "stable or improved" or not "stable or improved" according to whether the change from baseline in eGFR calculated from steps 1 and 2 is a reduction of no more than 15%.

For requirement (2), the uPCR response status at week 26 will be calculated using the following steps:

1. Baseline uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive.
2. Week 26 uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26.
3. Each participant will be categorized as either a success or a failure according to whether the change from baseline in uPCR calculated from steps 1 and 2 is a reduction of at least 50%.

6.5.1.1. Main Analysis

The key secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the key secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline eGFR values, baseline log-transformed uPCR values, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1.

A composite strategy will be used for addressing the ICEs listed in Table 1. In the composite strategy, the composite renal endpoint status at or after the occurrence of any of these ICEs will be regarded as non-responder. Additionally, participants with missing eGFR and/or uPCR values at week 26 for reasons other than those listed as ICEs will be regarded as non-responder.

The numbers and proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 will be tabulated by treatment group, including detailed breakdown on each of the two requirements.

All composite renal endpoint achievement data will be listed for the ITT set.

6.5.1.2. Supplemental Analyses

6.5.1.2.1. Per Protocol Set

The main analysis described in Section 6.5.1.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand.

6.5.1.3. Subgroup Analyses

Subgroup analyses will be performed for this key secondary endpoint to evaluate the consistency of the results across the subgroups specified in Section 6.4.4 above.

6.5.2. The Proportion of Participants With a Reduction of at least 50% from Baseline in uPCR

The key secondary efficacy endpoint of the proportion of participants with a reduction of at least 50% from baseline in uPCR at week 26 will be examined with the following null ($H_{3,0}$) and alternative ($H_{3,1}$) hypotheses:

$H_{3,0}$: There is no difference in proportion of participants who have a reduction of at least 50% from baseline in uPCR at week 26 between the pegcetacoplan and placebo treatment groups.

$H_{3,1}$: There is a difference in proportion of participants who have a reduction of at least 50% from baseline in uPCR at week 26 between the pegcetacoplan and placebo treatment groups.

The uPCR response status at week 26 will be calculated using the following steps:

1. Baseline uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive.
2. Week 26 uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26.
3. Each participant will be categorized as either a success or a failure according to whether the change from baseline in uPCR calculated from steps 1 and 2 is a reduction of at least 50%.

6.5.2.1. Main Analysis

The key secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the key secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline log-transformed uPCR values, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1 above. Strategies for addressing ICEs are the same as the ones described in Section 6.5.1.1.

The numbers and proportion of participants with a reduction of at least 50% from baseline at week 26 will be tabulated by treatment group.

All the uPCR response status data will be listed for the ITT set.

6.5.2.2. Supplemental Analyses

6.5.2.2.1. Per Protocol Set

The main analysis described in Section 6.5.2.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand.

6.5.2.3. Subgroup Analyses

Subgroup analyses will be performed for this key secondary endpoint to evaluate the consistency of the results across the subgroups specified in Section 6.4.4 above.

6.5.3. Change From Baseline in the Activity Score of the C3G Histologic Index Score

For participants with evaluable renal biopsies, the key secondary efficacy endpoint is the change from baseline in the activity score of the C3G histologic index score at week 26. It will be examined with the following null ($H_{4,0}$) and alternative ($H_{4,1}$) hypotheses:

$H_{4,0}$: There is no difference in mean change from baseline to week 26 in activity score between the pegcetacoplan and placebo treatment groups.

$H_{4,1}$: There is a difference in mean change from baseline to week 26 in activity score between the pegcetacoplan and placebo treatment groups.

6.5.3.1. Main Analysis

The key secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

An ANCOVA model will be used to analyze the key secondary endpoint. The model will include treatment as a fixed effect, adjusted for baseline C3G histologic index activity score, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.4.1. The randomization seed to be used is CCI. Note that because adolescents are not required to provide week 26 biopsies, this endpoint will be analyzed based on adult participants only.

The observed values for activity score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit. In situations where an adjudication is needed (the difference of total activity score >3.5 between the primary pathologist and the secondary pathologist), the final score based on adjudication will be used for analysis; if an adjudication is not needed (the difference of total activity score <=3.5 between the primary pathologist and the secondary pathologist), the average of the two pathologists' scores will be used for analysis.

All activity score data will be listed for the ITT set.

6.5.3.2. Sensitivity Analyses

The tipping point analysis method described in Section 6.4.2 will be repeated for the key secondary endpoint. The range of the shift parameters will be from 1.3 to 6.5 by increments of 1.3.

6.5.3.3. Supplemental Analyses

6.5.3.3.1. Per Protocol Set

The main analysis described in Section 6.5.3.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand.

6.5.3.4. Subgroup Analyses

Subgroup analyses will be performed for this key secondary endpoint to evaluate the consistency of the results across the subgroups specified in Section 6.4.4 above.

6.5.4. The Proportion of Participants Showing Decreases in C3c Staining From Baseline

For participants with evaluable renal biopsies, the key secondary efficacy endpoint of the proportion of participants showing decreases in C3c staining (defined as decrease of at least 2 orders of magnitude of intensity) from baseline at week 26 will be examined with the following null ($H_{5,0}$) and alternative ($H_{5,1}$) hypotheses:

$H_{5,0}$: There is no difference in proportion of participants who show decreases in C3c staining from baseline at week 26 between the pegcetacoplan and placebo treatment groups.

$H_{5,1}$: There is a difference in proportion of participants who show decreases in C3c staining from baseline at week 26 between the pegcetacoplan and placebo treatment groups.

6.5.4.1. Main Analysis

The key secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the key secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline C3c staining, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.5.1.1. Since adolescents are not required to provide week 26 biopsies, this endpoint will be analyzed based on adult participants only.

The numbers and proportion of participants who meet the criteria of showing decreases in C3c staining at week 26 will be tabulated by treatment group. A shift table of changes in C3c staining from baseline to week 26 will also be tabulated.

All C3c staining data will be listed for the ITT set.

6.5.4.2. Supplemental Analyses

6.5.4.2.1. Per Protocol Set

The main analysis described in Section 6.5.4.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand.

6.5.4.3. Subgroup Analyses

Subgroup analyses will be performed for this key secondary endpoint to evaluate the consistency of the results across the subgroups specified in Section 6.4.4.

6.5.5. Change From Baseline in eGFR

The key secondary efficacy endpoint of change from baseline in eGFR at week 26 will be examined with the following null ($H_{6,0}$) and alternative ($H_{6,1}$) hypotheses:

$H_{6,0}$: There is no difference in mean change from baseline to week 26 in eGFR between the pegcetacoplan and placebo treatment groups.

$H_{6,1}$: There is a difference in mean change from baseline to week 26 in eGFR between the pegcetacoplan and placebo treatment groups.

6.5.5.1. Main Analysis

The key secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A MMRM model will be used to analyze the key secondary endpoint. The model will include fixed categorical effects for treatment group, visit, disease type (C3G vs IC-MPGN), stratification factors, and the visit-by-treatment group interactions, as well as the continuous, fixed covariate of baseline eGFR values. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.4.1. The randomization seed to be used is [redacted].

The observed values for eGFR will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

The mean change from baseline in eGFR (±SE) will be plotted over time by treatment group.

All eGFR data will be listed for the ITT set.

6.5.5.2. Sensitivity Analyses

The two sensitivity analyses method described in Section 6.4.2 will be repeated for the key secondary endpoint. For tipping point analysis, the range of the shift parameters will be from −1.3 to −6.5 by increments of −1.3.

6.5.5.3. Supplemental Analyses

6.5.5.3.1. Per Protocol Set

The main analysis described in Section 6.5.5.1 will be repeated using the PP set to investigate the impact of changing the population in the estimand. Missing data (regardless of the reason being the ICEs or not) will be handled implicitly within the MMRM analysis under the assumption of missing at random (MAR).

6.5.5.3.2. Slope Analysis

The mean rate of change (ie, slope) in observed eGFR values will be compared between treatment groups using the linear mixed effects model for slope analysis of continuous outcomes described above in Section 6.1. The mean rate of change (slope), standard errors, and confidence interval will be estimated for the baseline to week 26 period for each treatment group.
In addition, the estimated difference in slopes between the treatment groups along with the 95% CIs and p-value will be reported.

6.5.5.4. Subgroup Analyses

Subgroup analyses will be performed for this key secondary endpoint to evaluate the consistency of the results across the subgroups specified in Section 6.4.4.

6.6. Analyses of Additional Secondary Efficacy Endpoints

The following subsections describe the analyses of the additional secondary efficacy endpoints of the study. All analyses of the additional secondary efficacy endpoints will be done on the ITT set.

6.6.1. The Proportion of Participants Achieving Proteinuria <1 g/day

The additional secondary efficacy endpoint of the proportion of participants achieving proteinuria <1 g/day (assessed by 24-hour urine protein) at week 24 will be examined with the following null ($H_{7,0}$) and alternative ($H_{7,1}$) hypotheses:

$H_{7,0}$: There is no difference in proportion of participants who achieve proteinuria <1 g/day at week 24 between the pegcetacoplan and placebo treatment groups.

$H_{7,1}$: There is a difference in proportion of participants who achieve proteinuria <1 g/day at week 24 between the pegcetacoplan and placebo treatment groups.

The additional secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the additional secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline proteinuria values, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.5.1.1.

The numbers and proportion of participants achieving proteinuria <1 g/day at week 24 will be tabulated by treatment group.

All 24-hour urine protein data will be listed for the ITT set.

6.6.2. The Proportion of Participants With Normalization of Serum Albumin Levels

For participants with serum albumin levels below LLN at baseline, the additional secondary efficacy endpoint of the proportion of participants with normalization of serum albumin levels at week 26 will be examined with the following null ($H_{8,0}$) and alternative ($H_{8,1}$) hypotheses:

$H_{8,0}$: There is no difference in proportion of participants who achieve normalization of serum albumin levels at week 26 between the pegcetacoplan and placebo treatment groups.

$H_{8,1}$: There is a difference in proportion of participants who achieve normalization of serum albumin levels at week 26 between the pegcetacoplan and placebo treatment groups.

The serum albumin levels status at week 26 will be calculated using the following steps:

1. Baseline serum albumin value will be calculated as the average of up to 2 serum albumin measurements preceding and including day 1. Participants will be included in the denominator of this calculation only if the baseline albumin value is below the LLN.
2. Week 26 serum albumin values will be calculated as the average of up to 2 serum albumin measurements preceding and including week 26, no earlier than week 20 measurement.

3. Each participant will be categorized as either a success or a failure according to whether the week 26 serum albumin values as calculated in Step 2. Values greater than or equal to the LLN will be categorized as a success; values less than the LLN will be categorized as a failure.

The additional secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the additional secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline albumin value, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.5.1.1.

For participants with serum albumin levels below the LLN at baseline, the numbers and proportion of participants with normalization of serum albumin levels at week 26 will be tabulated by treatment group. The observed values for serum albumin will be summarized by treatment group and visit.

All serum albumin data will be listed for the ITT set.

6.6.3. The Proportion of Participants With Serum C3 Levels Above the LLN

For participants with serum C3 levels below the LLN at baseline, the additional secondary efficacy endpoint of the proportion of participants with serum C3 levels above the LLN at week 26 will be examined with the following null ($H_{9,0}$) and alternative ($H_{9,1}$) hypotheses:

$H_{9,0}$: There is no difference in proportion of participants with serum C3 levels above the LLN at week 26 between the pegcetacoplan and placebo treatment groups.

$H_{9,1}$: There is a difference in proportion of participants with serum C3 levels above the LLN at week 26 between the pegcetacoplan and placebo treatment groups.

The serum C3 levels status at week 26 will be calculated using the following steps:

1. Baseline serum C3 value will be calculated as the average of up to 2 serum C3 measurements preceding and including day 1. Participants will only be included in the denominator of this calculation if the baseline C3 value is below the LLN.
2. Week 26 serum C3 value will be calculated as the average of up to 2 serum C3 measurements preceding and including week 26, no earlier than week 20 measurement.
3. Each participant will be categorized as either a success or a failure based on whether the week 26 serum C3 value as calculated in Step 2. Values greater than or equal to the LLN will be categorized as a success; values less than the LLN will be categorized as a failure.

The additional secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

A logistic model will be used to analyze the additional secondary endpoint. The model will include treatment group as the independent variable and adjusted for baseline serum C3 level, disease type (C3G vs IC-MPGN), and stratification factors.

Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.5.1.1.

For participants with low serum C3 levels at baseline, the numbers and proportion of participants with serum C3 levels above the LLN at week 26 will be tabulated by treatment group.
The observed values for serum C3 will be summarized by treatment group and visit.

All serum C3 level data will be listed for the ITT set.

6.6.4. Change From Baseline in FACIT-Fatigue Scale Score

The additional secondary efficacy endpoint is the FACIT-Fatigue score at week 26. It will be examined with the following null ($H_{10,0}$) and alternative ($H_{10,1}$) hypotheses:

$H_{10,0}$: There is no difference in mean change from baseline to week 26 in FACIT-Fatigue score between the pegcetacoplan and placebo treatment groups.

$H_{10,1}$: There is a difference in mean change from baseline to week 26 in FACIT-Fatigue score between the pegcetacoplan and placebo treatment groups.

The additional secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

The FACIT-Fatigue score is constructed as the total score of the 13 questions. Each question has 5 possible responses as “Not at all” (0), “A little bit” (1), “Somewhat” (2), “Quite a bit” (3) and “Very much” (4). Before calculating the total score, some responses are reversed to ensure that the higher score corresponds to a higher quality of life.

An ANCOVA model will be used to analyze the additional secondary endpoint. The model will include treatment as a fixed effect, adjusted for baseline FACIT-Fatigue score, disease type (C3G vs IC-MPGN), the stratification factor of transplant status, and age group (adults vs. adolescents). Further details on the presentation of the results are described in Section 6.1.
Strategies for addressing ICEs are the same as the ones described in Section 6.4.1.
The randomization seed to be used is CCI

The observed values for FACIT-Fatigue score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit. Note that the FACIT-Fatigue questionnaires have two versions, one for adults and one for adolescents. The summaries will be pooled together regardless of the different versions. Additional analysis on modeling the adults and adolescents separately will also be performed.

All FACIT-Fatigue score data will be listed for the ITT set.

6.6.5. Change From Baseline in KDQOL Score

The additional secondary efficacy endpoint is the KDQOL score at week 26. It will be examined with the following null ($H_{11,0}$) and alternative ($H_{11,1}$) hypotheses:

$H_{11,0}$: There is no difference in mean change from baseline to week 26 in KDQOL score between the pegcetacoplan and placebo treatment groups.

$H_{11,1}$: There is a difference in mean change from baseline to week 26 in KDQOL score between the pegcetacoplan and placebo treatment groups.

The additional secondary endpoint will be analyzed in the ITT set with participants grouped according to the treatment assigned at randomization.

The KDQOL score is constructed as the KDQOL-36 Summary Score (KSS) by averaging the 24 items from Burden of Kidney Disease, Symptoms and Problems of Kidney Disease, and Effects of Kidney Disease on 0-100 scale (Peipert et al. 2019).

An ANCOVA model will be used to analyze the additional secondary endpoint. The model will include treatment as a fixed effect, adjusted for baseline KDQOL score, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. Strategies for addressing ICEs are the same as the ones described in Section 6.4.1. The randomization seed to be used is CCI .

The observed values for KDQOL score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

All KDQOL score data will be listed for the ITT set.

6.7. Analyses of Exploratory Efficacy Endpoints

All primary, key secondary, and additional secondary endpoints will be evaluated at week 52 as exploratory efficacy endpoints. In addition, the following exploratory endpoints will also be evaluated. Note that this SAP focuses on the analysis of the randomized controlled period (RCP) data only. The analysis for interim data post-week 26 at the time of the datacut will be detailed in an SAP addendum.

6.7.1. The Change From Baseline in uPCR Using the 24-Hour Urine Collections

The observed values for uPCR measured by 24-hour urine collections will be summarized by treatment group and visit using ITT Set. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

An MMRM model will be used to analyze the exploratory efficacy endpoint up to week 24. The model will include fixed categorical effects for treatment group, visit, disease type (C3G vs IC-MPGN), stratification factors, and the visit-by-treatment group interactions, as well as the continuous, fixed covariate of baseline 24-hour uPCR values. Further details on the presentation of the results are described in Section 6.1. No multiple imputations will be applied. ICE strategies will be simplified where missing data after the ICEs will be imputed implicitly within the MMRM in a hypothetical strategy under the assumption of MAR.

All 24-hour uPCR data will be listed for the ITT set.

6.7.2. The Annual Rate of Change From up to 3 Years Prior to Screening in eGFR

A generalized linear mixed model will be used to analyze the exploratory efficacy endpoint from up to 3 years prior to screening to the end of the RCP period. The model will include fixed effect for disease type, stratification factors, a common intercept, a pre-treatment (either pegcetacoplan or placebo) slope, and a change in the slope by arm after treatment. Random effects include the individual intercept and slope, and the random errors are i.i.d. normally distributed. The eGFR slope prior to treatment, the slope after pegcetacoplan treatment and the difference comparing to pre-treatment slope, the slope after placebo treatment and the difference comparing to pre-treatment slope, as well as the difference between post-pegcetacoplan slope vs. post-placebo slope, will be summarized along with their 95% CIs and p-values using the ITT set.

In situations where for a certain historical collection, the eGFR value was not collected but the components for calculating it (such as serum creatinine, age, height, etc.) were collected, then the eGFR value will be calculated based on the formula (CKD-EPI creatinine equation for adults or the Bedside Schwartz equation for adolescents) specified in protocol.

6.7.3. The Proportion of Participants With Reductions From Baseline in Proteinuria of at least 30%

The proportion of participants with reductions from baseline in proteinuria (measured by triplicate FMU uPCR) of at least 30% at week 26 will be summarized using ITT set.
The baseline and week 26 uPCR calculation will be handled the same way as in Section 6.5.1.

A logistic model will be used to analyze the exploratory efficacy endpoint. The model will include treatment group as the independent variable and adjusted for baseline log-transformed uPCR values, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. ICE strategies will be the same as those specified in Section 6.5.1.1.

A data listing for each participant's reduction status at week 26 will be provided using ITT set.

6.7.4. The Proportion of Participants With Normalization of Proteinuria

The proportion of participants with normalization of proteinuria (measured by triplicate FMU uPCR) at week 26 will be summarized using ITT set. The baseline and week 26 uPCR calculation will be handled the same way as in Section 6.5.1. Normalization of proteinuria is defined as test result values within the normal reference range.

A logistic model will be used to analyze the exploratory efficacy endpoint. The model will include treatment group as the independent variable and adjusted for baseline log-transformed uPCR values, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. ICE strategies will be the same as those specified in Section 6.5.1.1.

A data listing for each participant's normalization status at week 26 be provided using ITT set.

6.7.5. Time to 50% Reduction in uPCR With a Stable or Improved eGFR

Time to 50% reduction in uPCR with a stable or improved eGFR (a.k.a., achieving the composite renal endpoint as defined in Section 6.5.1) will be summarized using ITT set with the Kaplan-Meier method (Kaplan and Meier 1958), using plots and presentation of median (and 95% CIs) for time-to-event. Participants who did not have the event at or prior to Week 26 in study will be censored at the minimum of the last date of contact or their treatment discontinuation date, or their Week 26 visit or first dose date+182 if Week 26 is missing. Participants who were randomized but did not receive any treatment will be censored at Day 1. Time to vent (or censor) will be calculated as date of event (or censor date) – Day 1 date +1. Event rates at week 12 and week 26 will also be presented in the summary tables. Comparisons between treatment groups will be done using Cox proportional hazard models (Cox 1976) stratified by disease type (C3G vs IC-MPGN) and stratification factors, and adjusted for baseline eGFR values and baseline log-transformed uPCR values. The hazard ratio, 95% CI, and p-value will be presented for the pegcetacoplan group over placebo group.

A data listing for each participant's time to achieve 50% reduction in uPCR with a stable or improved eGFR will be provided using ITT set.

6.7.6. Time to Normalization for Selected Parameters for Participants in Whom the Parameter is Abnormal at Baseline

For parameters serum C3, uPCR (measured by triplicate FMU), serum albumin, and blood pressure (both SBP and DBP), time to normalization (in weeks) will be summarized using ITT set with the Kaplan-Meier method, using plots and presentation of median (and 95% CIs) for time-to-event. Participants who did not have the event at or prior to Week 26 in study will be censored at the minimum of the last date of contact or their treatment discontinuation date, or their Week 26 visit or first dose date+182 if Week 26 is missing. Participants who were randomized but did not receive any treatment will be censored at Day 1. Time to vent (or censor) will be calculated as date of event (or censor date) – Day 1 date +1. Event rates at week 12 and week 26, as well as p-values from the log-rank test (stratified by disease type and stratification factors) will also be presented in the summary tables. The analyses will be based on participants whose test result being abnormal at baseline.

A data listing for each participant's time to normalization for these parameters will be provided using ITT set.

6.7.7. The Change From Baseline in Glomerular Macrophage Count

The observed values for glomerular macrophage count, determined by CD68 staining, will be summarized by treatment group and visit using ITT set. The categories for glomerular macrophage count are: 0 = None, 1 = Mild (<25% glomeruli), 2 = Moderate (26 to 50 % glomeruli), 3 = Severe (>50 – 75 % glomeruli), and 4 = Extensive (>75%).

All glomerular macrophage count results will be listed for the ITT set.

6.7.8. The Change From Baseline in PGIC Score

A shift table of changes in PGIC score from baseline to week 26 will be tabulated by treatment group.

All PGIC score results will be listed for the ITT set.

6.7.9. The Change From Baseline in EQ-5D-5L Score

The observed values for EQ-5D-5L score (based on visual analog scale) will be summarized by treatment group and visit using ITT set. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

An ANCOVA model will be used to analyze the exploratory endpoint. The model will include treatment as a fixed effect, adjusted for baseline EQ-5D-5L score, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. No multiple imputations will be applied. ICE strategies will be simplified where participants with missing data at week 26 (whether due to ICE or not) will be excluded from the modeling. Alternative approaches on the construction of EQ-5D-5L score may be explored as post-hoc analysis if necessary.

All EQ-5D-5L score results will be listed for the ITT set.

6.7.10. The Change From Baseline in WPAI Score

The observed values for WPAI score will be summarized by treatment group and visit using ITT set. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit.

The WPAI score is constructed based on the responses to the 6 questions: Q1=currently employed, Q2=hours missed due to specified problem, Q3=hours missed other reasons, Q4=hours actually worked, Q5=degree problem affected productivity while working, Q6=degree problem affected regular activities. Each response will be multiplied by 100 to express in percentages. And the WPAI score is constructed as Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)], which indicates percent overall work impairment due to problem.

An ANCOVA model will be used to analyze the exploratory endpoint. The model will include treatment as a fixed effect, adjusted for baseline WPAI score, disease type (C3G vs IC-MPGN), and stratification factors. Further details on the presentation of the results are described in Section 6.1. No multiple imputations will be applied. ICE strategies will be simplified where participants with missing data at week 26 (whether due to ICE or not) will be excluded from the modeling.

All WPAI score results will be listed for the ITT set.

6.7.11. Correlation Analysis on Reduction in uPCR and Change in eGFR

An exploratory correlation analysis exploring the relationship between the reduction in uPCR and change in eGFR will be considered at week 26, with correlation coefficients provided. The analysis may be repeated based on alternative populations (such as ITT or subgroups based on baseline level) or uPCR reduction metrics (such as change from baseline, percentage change from baseline, or absolute levels) if needed.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Safety variables include AEs, clinical laboratory data, vital signs, and ECGs. For each safety variable, the last value collected before the first dose of the investigational product will be used as a baseline for all analyses of that safety variable.

All safety analyses will be conducted according to the treatment the participant actually received.

7.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs that develop or worsen after the first dose of double-blinded investigational product and up to 56 days beyond the last dose of investigational product. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing.

All reported AEs will be coded using the current version of MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). All summaries by SOC and PT will be ordered by decreasing frequency of participants within each SOC and then similarly by decreasing frequency of participants within each PT based on the pegcetacoplan group. In the case of equal frequency of number of participants in SOCs or PTs, summaries of TEAEs will be sorted alphabetically. Rules for handling missing severity, relationship to study drug, relationship to infusion procedure, outcome, and missing dates of AEs are described in Section 13.

If a PT was reported more than once for the same participant, that participant would only be counted once in the incidence for that PT. For participants experiencing the same PT at multiple severities, the occurrence of the AEs with the greatest severity will be used in the analysis of incidence by severity. For participants experiencing the same PT at multiple relationship levels, the occurrence of the AEs with the strongest relationship to study drug will be used in the analysis of incidence by relationship to study drug.

The AE summaries will be presented by treatment group. In addition, the incidence of death, stratified by transplant history will be summarized.

In post-transplant participants, the number and incidence of rejection episodes at week 26 will be tabulated by treatment group. Additionally, if the number of participants is sufficient, the results for treatment groups will be compared using Fisher's exact test (or a stratified Cochran-Mantel-Haenszel χ-square test as appropriate).

In participants who are posttransplant, the number and incidence of graft loss at week 26 will be tabulated by treatment group. Additionally, if the number of participants is sufficient, the results for treatment groups will be compared using Fisher's exact test (or a stratified Cochran-Mantel-Haenszel χ-square test as appropriate).

An overall summary for TEAEs, including number of participants who experience a TEAE, number of total TEAEs, and number of unique TEAEs, will be provided:

- TEAE
- Treatment-related TEAE
- Infusion-related TEAEs
- Serious TEAE
- Maximum severity of TEAEs
- Infusion site reaction
- TEAE leading to treatment withdrawn
- TEAE leading to dose interruption
- TEAE leading to study discontinuation
- TEAE leading to death
- Rejection episodes (for posttransplant only, based on PTs of "KIDNEY TRANSPLANT REJECTION", "RENAL AND PANCREAS TRANSPLANT REJECTION", "MULTIPLE ORGAN TRANSPLANT REJECTION", "SOLID ORGAN TRANSPLANT REJECTION")
- Graft loss (for posttransplant only, based on PTs of "TRANSPLANT FAILURE", "ENGRAFT FAILURE", "RENAL TRANSPLANT FAILURE", "REMOVAL OF RENAL TRANSPLANT", "GRAFT LOSS")

The following summaries will be provided:

- TEAEs by SOC and PT
- TEAEs by PT in decreasing order of frequency
- Treatment-related TEAEs by SOC and PT
- Infusion-related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAE by SOC, PT and maximum severity
- TEAE leading to treatment discontinuation by SOC and PT
- TEAE leading to dose interruption by SOC and PT
- TEAE leading to study discontinuation by SOC and PT
- TEAE leading to death by SOC and PT
- Treatment-emergent adverse events of special interest (AESIs) by SOC and PT
- Serious treatment-emergent AESIs by SOC and PT
- Exposure-adjusted incidence TEAEs by SOC and PT
- Exposure-adjusted incidence serious TEAEs by SOC and PT

Exposure-adjusted incidence rate of an AE is defined as the number of events divided by the total duration of exposure of the participants at risk during treatment, which is computed as following:

Exposure-adjusted incidence rate = n*100/EY,

where n is the number of participants impacted; the exposure year (EY) = (sum of time to onset of the event)/365.25, where time to onset of the event = date of onset of event – Day 1 date +1. For participants without the event, time to onset is censored as follows: time to onset of the event = (last dose date + 56 days) – Day 1 date +1. For participants who experienced the same event on multiple occasions: time to onset of the event = date of onset at the first occasion – Day 1 date +1.

The following listings will be provided:

- All AEs
- Serious adverse events (SAEs)
- AEs leading to study drug discontinuation
- Death
- Treatment-related adverse events
- Infusion-related adverse events

7.2. Clinical Laboratory Data

All laboratory results will be standardized by converting values in original units to values in standard units and classified as normal, abnormal low, or abnormal high on normal ranges supplied by the local laboratories and upon employing standardization.

When a certified local laboratory is used instead of a central laboratory due to COVID-19 pandemic, the units and normal ranges might be different. Therefore, all local laboratory values will be standardized to a central laboratory value using the following formula:

$$X_S = L_S + \frac{U_S - L_S}{U_X - L_X} \times (X - L_X)$$

Where,

X: local lab value

X_S: standardized value of X

L_S: Low normal range for central lab

U_S: High normal range for central lab

L_X: Low normal range for local lab

U_X: High normal range for local lab

Specifications will be developed to detail all the steps necessary for developing the standardized laboratory values and to address issues like missing normal ranges or negative standardized laboratory values.

Observed and change from baseline of clinical laboratory data (hematology, serum chemistry, coagulation and continuous urine chemistry parameters) will be summarized at each analysis visit by treatment group and overall. Categorical urine chemistry data will also be tabulated at each analysis visit when applicable.

In addition, liver abnormalities will be summarized at each analysis visit including following variables by treatment group and overall:

- ALT or AST ≥ 3×ULN
- ALT or AST ≥ 3×ULN and (TBL >2×ULN or INR >1.5)
- ALT or AST ≥ 5×ULN
- ALT or AST >8×ULN

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in the table below:

Table 2: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria
Hematology	
WBC (total) (x10^9/L)	< 3.0 > 16
Lymphocyte (x10^9/L)	< 0.5 < 0.8 > 12
Neutrophils (x10^9/L)	< 1.0 < 1.5 > 12
RBC (x10^12/L)	< 3.3 > 6.8
Hemoglobin (g/dL)	< 10
Platelet count (x10^9/L)	< 100 > 600

Table 2: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria
Serum Chemistry	
ALT	> 1.5xULN > 3.0xULN
AST	> 1.5xULN > 3.0xULN
ALP	> 1.5xULN > 3.0xULN
Total Serum Bilirubin	> 1.5xULN
GGT	> 3.0xULN
ALT or AST > 3xULN and concurrent elevated total bilirubin defined as	> 2.0xULN

For the following serum chemistry parameters: creatinine; LDH; creatine kinase (CK); uric acid; glucose; sodium; potassium; and chloride, abnormal values will be used as potentially clinically significant.

The number and percentage of participants with post-baseline PCS laboratory values will be tabulated by treatment group and overall. A listing of participant data with at least one post-baseline PCS value will be provided.

All laboratory values will be listed for each participant.

7.3. Vital Signs

Observed and change from baseline in vital signs (pulse rate, respiratory rate, systolic and diastolic blood pressure, temperature, and weight) will be summarized by treatment group and overall at each analysis visit.

Additionally, the number and percentage of participants with post-baseline potentially clinically significant (PCS) vital sign values will be tabulated. Vital signs are potentially clinically significant (PCS) if they meet the PCS criteria listed in the table below:

Table 3: Criteria for Potentially Clinically Significant Vital Signs

VS parameter	Criteria
HR	≥100 BPM <40 BPM
SBP	≥130 mm Hg ≥160 mm Hg ≥180 mm Hg >20 mm Hg increase from baseline <90 mm Hg ≥20 mm Hg decrease from baseline
DBP	≥90 mm Hg ≥15 mm Hg increase from baseline <40 mm Hg ≥15 mm Hg decrease from baseline
Temp	≥38°C

All vital sign values and change from baseline values will be listed. In the listing, potentially clinically significant vital sign values will be flagged.

7.4. Electrocardiogram (ECG)

Observed and change from baseline in ECGs (heart rate, PR interval, QRS duration, QT interval, and QTc interval which is corrected by Fridericia's method) will be summarized by treatment group and overall at each analysis visit.

Additionally, the number and percentage of participants with post-baseline potentially clinically significant (PCS) ECG values will be tabulated. ECGs are potentially clinically significant (PCS) if they meet the PCS criteria listed in the table below:

Table 4: Criteria for Potentially Clinically Significant ECGs

ECG parameter	Criteria
HR	<40 bpm >100 bpm
PR	>200 msec
QRS	>120 msec
QTcF	>450 msec >480 msec >500 msec
QTcF increase from baseline	>30 msec >60 msec

All ECG values and change from baseline values will be listed. In the listing, potentially clinically significant ECG values will be flagged.

7.5. Other Safety Data

Physical examinations will be described in a data listing.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the PK set as defined in Section 4.5.

8.1. Drug Concentration

Individual pegcetacoplan concentrations, actual sampling times and deviations from nominal sampling times will be presented in a data listing for all participants included in the PK set. Placebo samples will also be included in the data listing if they are analyzed but will not be summarized.

Pegcetacoplan concentrations will be summarized by treatment group at each scheduled time point using descriptive statistics (including mean, SD, coefficient of variation (CV), median, min, max, geometric mean/%CV). The number of participants with a BLQ concentration at each scheduled time point will also be tabulated. The handling of BLQ concentrations in the summary tables is described in Section 8.2. Missing values will be omitted from the calculation of descriptive statistics.

Linear and semilogarithmic individual concentration-time profiles will be generated using actual sampling times. Linear and semilogarithmic mean (±SE) and median concentration-time profiles will be generated using nominal sampling times. The number of participants contributing to each mean or median value at a visit will be presented above the x-axis.

8.2. Handling BLQ Values

8.2.1. Handling of BLQ Concentrations in Summary Tables

BLQ concentrations prior to first dosing (day 1): Pre-treatment pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as zero for the computation of descriptive statistics, except geometric mean. Geometric mean cannot be calculated and will be reported as “N/A” or “-”.

BLQ concentrations occurring at any time after first dosing: Pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as half the lower limit of quantification (LLOQ/2).

8.2.2. Handling of BLQ Concentrations in Figures

BLQ concentrations prior to first dosing (day 1): Pre-treatment pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to half the lower limit of quantification (LLOQ/2) for semilogarithmic plots.

BLQ concentrations occurring at any time after first dosing: Pegcetacoplan concentrations reported as BLQ will be taken as half the lower limit of quantification (LLOQ/2) for both linear and semilogarithmic plots.

9. PHARMACODYNAMIC ANALYSIS

9.1. Pharmacodynamic Data

All summaries and analyses of the pharmacodynamic data will be based on the PD set as defined in Section 4.6.

Observed values, changes from baseline, and percentage changes from baseline in C3, AH50, CH50, C3b/iC3b, sC5b9, C4, and C3a will be summarized at each protocol-specified time point using descriptive statistics.

Individual observed values and individual changes from baseline will be presented graphically. Actual sampling times will be used for the graphical presentation of individual data. The mean (± SE) of the observed values, mean changes from baseline, and mean percentage changes from baseline will also be presented graphically. Nominal sampling times will be used for the mean plots.

PD parameters will be listed together with changes from baseline and percentage changes from baseline by treatment group.

In addition to the analyses outlined above, all PK and complement biomarker concentration data may be used to develop the population PK and exposure-response models in conjunction with other clinical study data. The methods and procedures will be described in a separate Analysis Plan if needed. The results from population modeling will be reported separately.

10. IMMUNOGENICITY

Immunogenicity data will be listed and summarized using safety set separately for anti-pegcetacoplan peptide antibody and anti-PEG antibody results. A sample and participant level summary table will be presented as described below.

Sample Level Summary

The number of evaluable (ADA-positive, ADA-negative, and ADA-inconclusive) and unevaluable samples will be summarized by treatment group and overall. The number and percentage of each ADA sample classification will be summarized by treatment group and overall in the evaluable samples. In addition, the number and percentage of baseline and post-dose ADA positive samples along with the titer range for each will also be summarized by treatment group and overall in samples that are ADA positive.

ADA samples will be classified as follows:

- ADA-Positive Sample – when the sample is positive in the confirmatory assay
- ADA-Negative Sample – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that does not interfere with the ADA method.
- ADA-Inconclusive Sample – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that interferes with the ADA method, then the sample is considered inconclusive. Note that the drug is considered at a level that interferes with the ADA method if the corresponding visit's PK concentration is greater than or equal to: (a)1000 ug/mL for anti-pegcetacoplan peptide antibody; or (b) 5000 ug/mL for anti-PEG antibody.
- Unevaluable Sample – when a sample could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.

Participant Level Summary

The number and percentage of participants with pre-existing ADAs will be summarized by treatment group and overall in the participants with a baseline sample result. In addition, the number and percentage of participants with an ADA positive response, ADA negative response, and ADA inconclusive response, as well as the type and kinetics of the positive ADA response, will be summarized by treatment group and overall in the evaluable participants. The participant summary table will include a summary by treatment group and overall for the ADA population parameters. For participants with an ADA positive response, association with changes in PK, efficacy, and safety may be explored.

Pre-existing ADA will be defined as follows: any participant with an ADA positive baseline sample from the total participants with a baseline sample result.

Evaluable participants will be defined as follows: a participant with at least one sample taken with a reportable result after first dosing during the treatment or follow-up period.

Evaluable participants will be classified as follows for ADA response:

- ADA-Positive Participant – An evaluable participant with at least one pre-dose sample and one treatment-emergent or treatment-boosted ADA-positive sample at any time after dosing
- ADA-Negative Participant – An evaluable participant without a treatment-emergent or treatment-boosted ADA-positive sample during the treatment or follow-up period
- ADA-Inconclusive Participant – An evaluable participant who cannot be classified as either ADA-positive or ADA-negative (eg, assay drug tolerance issues, post-dose positive without a baseline sample, positive baseline and positive post-dose sample without a titer value, etc.)

ADA positive responses will be classified as follows:

- Treatment-Boosted ADA Response – An evaluable participant with a baseline ADA positive sample and a post-dose ADA positive sample that is ≥ 4x the baseline titer (eg, baseline titer of 10 vs. post-dose titer of 40)
- Treatment-Emergent ADA Response – An evaluable participant with a baseline ADA negative sample and an ADA positive sample after treatment, ADA developed *de novo*

The kinetics of ADA positive responses will be classified as follows:

- Transient ADA Response
  - Treatment-emergent positive participants are classified as having a transient response if they have only a single ADA positive sample (that was not the last assessment), or more than 1 ADA positive sample where the first and last ADA positive samples are separated by a period of less than 112 days (16 weeks), irrespective of any negative and positive samples in between.
  - Treatment-boosted ADA positive participants are classified as having a transient response if they have only a single ADA boosted sample (that was not the last assessment), or more than 1 positive boosted sample where the first and last ADA positive samples are separated by a period of less than 112 days (16 weeks), irrespective of any negative and positive samples in between.
- Persistent ADA Response
  - Treatment-emergent positive participants are classified as having a persistent response if they have more than 1 positive ADA sample ≥ 112 days (16 weeks) apart, or a positive ADA sample at the last timepoint with no further results available
  - Treatment-boosted ADA positive participants were classified as having a persistent response if they have more than 1 positive boosted sample ≥ 112 days (16 weeks) apart, or a positive boosted sample at the last timepoint with no further results available
- Unclassified Response
  - Any ADA positive participant that cannot be defined as having a transient or persistent ADA response

ADA population parameters are derived as follows:

- ADA Prevalence – The proportion of all ADA positive participants, including pre-existing ADA, computed as a percentage of the total number of evaluable and unevaluable participants
- ADA Incidence – The sum of all ADA positive treatment-emergent and treatment-boosted participants computed as a percentage of the total number of evaluable participants

  Note: This population parameter is the same as the percentage of participants with an ADA positive response.

11. INTERIM ANALYSIS

No formal interim analysis is planned for this study.

12. DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) will review cumulative safety/tolerability data (eg, physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) and efficacy data. The DMC will have the responsibility to conduct a thorough safety assessment at regular pre-defined intervals during the treatment period of the study.

DMC meetings will be held according to the schedule in the DMC charter. An ad hoc DMC data review may be recommended by the DMC or requested by the sponsor at any time during the study.

The remit, roles, and responsibilities of the DMC will be specified in a separate DMC charter. There will be a separate DMC SAP covering the presentation and analyses for the DMC.

13. DATA HANDLING CONVENTIONS

13.1. General Data Reporting Conventions

All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

Categorical variables will be tabulated as number of participants and percentage of total number of participants in the given analysis set as noted for each category. Descriptive statistics will be used to summarize continuous variables including number of participants, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Mean, Q1, Q3, and median will be reported to 1 more decimal place than the raw data, while the SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

Participant specific listings will be provided by treatment group, participant ID, study period and visit, if applicable.

13.2. Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as number of days relative to the first dose date of study drug, which is designated as day 1, and the preceding day is day −1, the day before that is day −2, etc.

- For assessments on/after study day 1, study days are calculated as:
  - (date of assessment– date of study day 1 + 1)
- For assessments before study day 1, study days are calculated as:
  - (date of assessment – date of study day 1)

13.3. Definition of Baseline, RCP, and OLP

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of study drug. Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

In by-visit summary tables, the baseline will be summarized using all available data, but also for each visit using only the baseline data from participants with available data at the visit; hence the mean change from baseline will equal the mean visit value – mean baseline value.

Throughout this document ‘change from baseline’ refers to the actual change from baseline (ie, visit value – baseline value).

The date when a participant receives first administration of OLP drug will be defined as the start date of the participant’s OLP, and that date minus one day will be the end date of the participant’s RCP.

13.4. Definition of Analysis Visit Windows

Unless otherwise specified, the actual scheduled nominal post-baseline visit will be used for all summaries across time. Post-baseline unscheduled visits, follow-up visits, and early termination visits will be mapped to a scheduled visit and will be used in the analysis only if the nominal scheduled visit result is missing. Table 5 presents the analysis visit window mapping for unscheduled and early term visits for assessments done mostly every 4 weeks (central lab, vital sign, PK). For other assessments that do not follow Table 5 schedule (such as 24-hour urine, triplicate FMU uPCR, ECG, PD, ADA, etc.), the analysis visit window mapping will be adjusted accordingly. In the case that multiple unscheduled or early termination visits are in the same analysis window, the one closest to the target date will be used. In the event that the windowed visit is mapped to an illogical sequence of visits when considering nearby scheduled visits (ie, windowed visit is higher than the subsequent visit or lower than the preceding visit), the windowed visit will be set to the logical scheduled visit.

Table 5: Analysis Visit Windows for Unscheduled and Early Termination Visits for Assessments Done Mostly Every 4 Weeks

Study period	Analysis visit	Target day	Analysis window	Interval
Screening	Week -10 to -4	-49	-77 - < -21	56
	Week -2	-14	-21 – ≤ -1	21
Randomized controlled period	Day 1	1	1	1
	Week 4	28	2 – < 42	40
	Week 8	56	42 – < 70	28
	Week 12	84	70 – < 98	28
	Week 16	112	98 – < 126	28
	Week 20	140	126 – < 154	28
	Week 24	168	154 – < 175	21
	Week 26	182	175 – < OLP start date	NA
Open-label period	Week 28	196	OLP start date – <210	NA
	Week 32	224	210 – < 238	28
	Week 36	252	238 – < 273	35
	Week 42	294	273 – < 315	42
	Week 48	336	315 – < 350	35
	Week 52 (for roll-over participants)	364	350 – < 434	84
	Week 52 (for non-roll-over participants)	364	350 – < 371	21

Table 5: Analysis Visit Windows for Unscheduled and Early Termination Visits for Assessments Done Mostly Every 4 Weeks

Study period	Analysis visit	Target day	Analysis window	Interval
Follow-up period (for participants not entering long term extension)	Week 54	378	371 – < 385	14
	Week 56	392	385 – < 406	21
	Week 60	420	406 – < 434	28

13.5. Repeated or Unscheduled Assessments of Safety Parameters

For safety parameters, if a participant has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for Potentially Clinically Significant (PCS) value determination and all assessments will be presented in the data listings.

13.6. Handling of Missing, Unused, and Spurious Data

Missing data is addressed in the relevant sections elsewhere. Spurious data will be discussed with data management and others as appropriate to address queries to sites or vendors.
In general, all data will be used as reported (and after query resolutions); any decisions to remove data would be made and documented prior to unblinding.

13.6.1. Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a participant in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date will be used in the calculation of treatment duration.

13.6.2. Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed.
When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

13.6.2.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

13.6.2.1.1. Missing Day, Month, and Year

In this case, no start date will be imputed. However, the medication will be assumed to be a prior medication. If the stop date is missing or if the stop date is on or after the date of the first dose of investigational product, the medication will also be considered a concomitant medication.

13.6.2.1.2. Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

13.6.2.1.3. Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.6.2.1.4. Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

13.6.2.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

13.6.2.2.1. Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

13.6.2.2.2. Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.6.2.2.3. Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

13.6.3. Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, eg, AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (ie, partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a participant, impute the start date first.

- Rules to impute incomplete start date are the same as stated in Section 13.6.2.1.
- Rules to impute incomplete stop date are the same as stated in Section 13.6.2.2.

13.6.4. Missing Severity Assessment for Adverse Events

- If severity is missing for an AE starting prior to the date of study day 1, then a severity of “Mild” will be assigned.
- If the severity is missing for an AE starting on or after the date of study day 1, then a severity of “Severe” will be assigned.

The imputed values for severity assessment will be used for incidence summaries, while the actual values will be presented in data listings.

13.6.5. Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of study day 1, a causality of "related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

13.6.6. Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. If the laboratory results are collected as < or > a numeric value, 0.0000000001 will be subtracted or added, respectively to the value. However, the actual values as reported in the database will be presented in data listings.

14. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS on a suitably qualified environment.

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

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17. APPENDICES

17.1. Schedule of Assessments

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	–10 to –4	–2	1	4	8	12	16	20	24	26	28	32	36	42	48	52	54	56	60 Exit
Study day	–70	–14	1	28	56	84	112	140	168	182	196	224	252	294	336	364	378	392	420
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Visit window (± days)	N/A[b]		0	3	7	7	7	7	3	3	3	7	7	7	7	7	3	3	7
Assessments																			
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Post-transplant immunosuppression plan documentation		X																	
Inclusion/exclusion	X	X	X																
Vaccination[d]		X[b]				X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full)[e]	X		X							X[e]						X			
Physical examination (brief)[e]		X		X	X	X	X	X	X		X[e]	X	X	X	X		X	X	X
12-lead ECG	X		X		X		X		X	X	X		X		X	X	X		X
Chest radiography		X[b]								X						X			
Renal biopsy[f]	X[b]									X[g]						Xh			
Randomization			X																
Study drug administration[i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Infusion site/pump safety assessment[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital sign measurements[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL1		X								X						X			

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	–10 to –4	2	1	4	8	12	16	20	24	26	28	32	36	42	48	52	54	56	60 Exit
Study day	–70	–14	1	28	56	84	112	140	168	182	196	224	252	294	336	364	378	392	420
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Visit window (± days)	N/A[b]		0	3	7	7	7	7	3	3	3	7	7	7	7	7	3	3	7
Urine																			
24-hour urine collection[m]	X					X			X				X		X				X
Triplicate FMU uPCR[n]	X	X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In-clinic (random) uPCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (dipstick & microscopic)[p]	X																		
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood																			
Hematology[p] & chemistry[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA assaysq			X	X			X		X				X			X	X		X
Serum complement profilep	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
Plasma complement profile[p]	X		X		X		X		X	X	X		X		X	X	X		X
eGFRr	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (β-HCG)	X																		
Screening assayss	X																		
Optional assessments																			
Ophthalmologic evaluations[t]		Xt												Xt					
Measured GFR[u]			Xu							X[u]				Xu					

Abbreviations: Ab = antibodies; ADA = antidrug antibodies; AE = adverse events; AH50 = 50% alternative hemolytic complement pathway activity; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies, β HCG = beta human chorionic gonadotropin, CH50 = 50% classical hemolytic complement pathway activity, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, EQ-5D-5L = 5-Level EuroQol-5 Dimension; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FMU = first-morning spot urine; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; KDQOL = Kidney Disease Quality of Life; N/A = not applicable; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; SC = subcutaneous; SD OCT = spectral domain optical coherence tomography; SPEP = serum protein electrophoresis; uPCR = urine protein-to-creatinine ratio; WPAI = Work Productivity and Activity Impairment.

NOTE: When multiple assessments/procedures occur at the same visit, order should be: vital signs, ECGs, blood collection/sampling, study drug dosing.

a. All visit 2 assessments need not occur in a single visit and visit 2 can be split into multiple visits (eg, visit 2a, visit 2b).
b. Vaccinations, baseline renal biopsy, and screening chest radiography can occur any time during screening after confirmation of eligibility based on visit 1 data.
c. For transplant participants only. Must be documented prior to assignment to study treatment.
d. Vaccine series should be initiated at least 14 days prior to randomization; additional vaccines may be required at visit 6. Please see Protocol Section 8.2 for more details on vaccination requirements. Vaccination serum samples will be collected on the day of vaccination before receiving vaccinations on that visit. These samples will be analyzed to evaluate response to vaccinations in the event that the participant has a positive infection for Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae.
e. A full physical examination is required at visits 1, 3 (week 1), 10 (week 26), and 16 (week 52). A full physical examination should also be conducted on the first day of open-label dosing, if that is not at the week 26 visit. Brief physical examinations, including weight (kg) and assessment of edema, will be conducted at all other visits noted. A symptom-driven physical examination may be performed at any time, at the investigator's discretion. Body height (cm) will be measured only during screening for adults but will be measured at screening and every 12 weeks throughout the study for adolescents; weight (kg) will be measured throughout study, during brief and full physical examinations for all participants. Both body weight and height will be assessed without shoes on; height will be measured using a calibrated stadiometer. Edema should be assessed at every visit.
f. Renal biopsies will not be required for participants younger than 18 years provided that they have adequate previous renal biopsies to establish the diagnosis as per the central pathology laboratory.
g. The week 26 renal biopsy need not occur on the same day as all other assessments for that visit. However, the week 26 triplicate FMU uPCR collections must occur before the renal biopsy. In addition, the week 26 biopsy must occur before the first visit of the open-label period at week 28. Participants younger than 18 years are not required to provide renal biopsies and may advance to the open-label period upon completion of all assessments for weeks 24 through 26 other than the renal biopsy.
h. The week 52 renal biopsy is optional for all participants. If performed it should be after collection of the week 48 24-hour urine and FMU samples, and not more than 8 weeks after the week 52 visit. In the event that a participant has a renal biopsy as part of their clinical management within this window, it may serve as the week 52 biopsy provided that it includes the required components for this study.
i. Study drug will be self-administered by the participant or administered by their caregiver, after receiving appropriate training and sign-off by a research nurse (or other qualified personnel) in their first treatment week, as described in Protocol Section 9.5. Once qualified, the participant or caregiver should administer study drug at site visits (as done at home) on those days when a clinic visit occurs on a dosing day. If a home nurse is administering study drug on nonvisit days, the site staff may administer study drug on days of site visits.
j. Between site visits, participants will be instructed to report any infusion site reactions to the study staff. Pump use safety will be reviewed by licensed health care professionals (eg, investigator or nurse) for each study drug administration at clinic visits and during at-home qualification.
k. Vital signs should be measured a maximum of 2 hours before study drug infusion. On day 1 and on the first day of open-label dosing (week 26 or week 28, depending on whether a week 26 renal biopsy is required and when it is performed), vital signs should also be measured approximately 30 minutes to 1 hour after the first infusion of study drug dosing, timed from the completion of the study drug administration. Blood pressure and heart rate should be evaluated after the participant has been resting in a seated position for at least 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs, or if deemed necessary by the investigator.
l. FACIT-Fatigue, EQ-5D-5L, KDQOL, PGIC, and WPAI.
m. The screening 24-hour urine collection may be done any time between screening visit 1 and screening visit 2. After week 1, collections should be within ±1 week of the visit (except for the week 24 collection, which cannot be earlier than week 24). Courier arrangements can be made to pick up the collection container from the participant, or the participant may return the container directly to the site.
n. Triplicate FMU samples will be collected by the participant at home on 3 consecutive days throughout the duration of the study. These should be the first urinary output of the day. An additional triplicate FMU uPCR sample will be collected at week 25. Samples should be collected within ±1 week of the clinic visit (except for weeks 24 through 26, when sample collection should be within ±3 days of the clinic visit). Courier arrangements can be made to pick up the collection containers from the participants, or the participant may return the containers directly to the site. At every visit, enough uPCR collection containers should be dispensed to the participant to enable all at-home uPCR collections until the next clinic visit.
o. The day 1 triplicate FMU uPCR samples should be collected before the first dose of study drug (eg, day –2, day –1, and before dosing on day 1).
p. Serum complement profile includes AH50, CH50, and C3NeF; C3NeF will only be assayed in samples collected at the baseline (screening) visits. Plasma complement profile includes C3a, C3b/iC3b, C5a, and sC5b 9. See laboratory assessments (Protocol Table 4) for more details.
q. The day 1 samples should be collected before dosing with study drug. Participants who discontinue dosing will have ADA samples collected at 2 and 8 weeks after the last treatment. Participants who have a treatment-emergent or treatment-boosted ADA response at any time will have ADA samples collected approximately every 6 months until the antibody levels revert to baseline.
r. eGFR will be calculated using the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation for adults or the Bedside Schwartz equation for adolescents. For each participant, eGFR will be calculated using the same formula for the duration of the study; the choice of formula will be determined by the participant's age at study entry.
s. Serum FSH (to be measured in female participants only), hepatitis B panel, hepatitis C panel, HIV antibodies, SPEP (adult participants only), ANA, and ANCA (see Protocol Table 4 and laboratory manual for more details).
t. Ophthalmologic evaluations are optional and will be performed at selected sites. If evaluations are performed, each participant should have a baseline ophthalmologic evaluation, including a basic ophthalmologic examination, SD-OCT, and color fundus photography, at an approved ophthalmologic clinical site at any time during the screening period. For participants who have drusen before pegcetacoplan administration, a follow-up ophthalmologic evaluation, including an SD-OCT and color fundus photography, should occur at a convenient time between weeks 44 and 52.
u. Measured GFR is an optional assessment that, if performed, should occur at 3 time points: once on day 1 or within 10 weeks before day 1, again at week 26, and a third time between week 44 and week 52, inclusive. Measured GFR should only be done at sites where it is routinely performed, as per the site's standard protocol.

17.2. Sample SAS code

```
* The SAS codes in this section are shown as examples
* Some modifications (such as variables used in the model statement)
* may require further changes to reflect the methods specified in the
* SAP and analysis data structure
```

17.2.1. Mixed Effect Model for Repeated Measure

```
*-----------------------------------------------------
* Read Analysis data
*-----------------------------------------------------
* In this example, repeated measures are available at
* avisitn = 0 (baseline), 4 (Week 4), 8 (Week 8), 12 (Week 12), 16 (Week 16),
*   20 (Week 20), 24 (Week 24), 25 (Week 25), and 26 (Week 26)
*-----------------------------------------------------;

data upcr;
 set adam.adeff;
 if paramcd = 'LNUPRCRF' and basetype = 'NORMAL' and
 avisitn in (0, 4, 8, 12, 16, 20, 24, 25, 26) and
 ANL01FL = 'Y';

 * avisitc will be used in PROC TRANSPOSE;
 if avisitn = 0 then avisitc = '00'; * Baseline;
 if avisitn = 4 then avisitc = '04'; * Week 4;
 if avisitn = 8 then avisitc = '08'; * Week 8;
 if avisitn = 12 then avisitc = '12'; * Week 12;
 if avisitn = 16 then avisitc = '16'; * Week 16;
 if avisitn = 20 then avisitc = '20'; * Week 20;
 if avisitn = 24 then avisitc = '24'; * Week 24;
 if avisitn = 25 then avisitc = '25'; * Week 25;
 if avisitn = 26 then avisitc = '26'; * Week 26;
run;

*******************************;
*** ANALYSIS using MMRM assuming MAR (e.g., Section 6.4.2(1) )***;
*******************************;

proc sql;
      select avg(base) into: abs
      from upcr_t; * upcr_t is the upcr dataset but in long format;
run;

%put abs=&abs;   * this will be used for the "estimate" statement, similarly
to obtain the empirical weight for each stratification factor and disease
type and baseline immune use, namely stra1_wt, stra1_wt_rev, stra2_wt,
stra2_wt_rev, distype_wt, distype_wt_rev, immunobl_wt, immunobl_wt_rev to be
used in next procedure;


proc mixed data=upcr method=reml covtest empirical;
  where avisitn NE 0; * exclude rows for baseline;
  * stra1 (stratification factor 1)
  * 0 = post-transplant recurrence
  * 1 = non-transplant
```

```
  * stra2 (stratification factor 2)
  * 0 = Without Baseline Renal Biopsy
  * 1 = With Baseline Renal Biopsy
  * distype (disease type)
  * 0 = IC-MPGN
  * 1 = C3G
  * immunobl (baseline immunosuppressants use)
  * 0 = No
  * 1 = Yes
  class trtpn avisitn usubjid stra1 stra2 distype;
  model chg = trtpn stra1 stra2 distype immunobl avisitn trtpn*avisitn
base/cl;
  repeated avisitn / subject=usubjid type=un r;
  lsmeans trtpn*avisitn/pdiff cl e om alpha=.05;
  ods output diffs= diff1 LSMeans= LSMean1;

estimate 'PEG Week 24-25-26 Avg LSMean' intercept 1 stra1 &stra1_wt_rev
&stra1_wt stra2 &stra2_wt_rev &stra2_wt distype &distype_wt_rev
&distype_wt immunobl &immunobl_wt_rev &immunobl_wt trtpn 1 0
BASE &abs
avisitn 0 0 0 0 0 0.333 0.333 0.334
trtpn*avisitn 0 0 0 0 0 0.333 0.333 0.334
              0 0 0 0 0 0 0 0 /cl ;
estimate 'PEG vs PBO Difference Week 24-25-26 Avg' trtpn 1 -1
trtpn*avisitn 0 0 0 0 0 0.333 0.333 0.334
              0 0 0 0 0 -0.333 -0.333 -0.334 /cl ;
ods output estimates = est;
run;


data lsmeans1;
 set lsmeans;
 geo_estimate = exp(estimate);     * = LS Geometric mean;
 geo_lower = exp(lower);           * = lower bound of the 95%CI for the
LS Geometric mean;
 geo_upper = exp(upper);           * = upper bound of the 95%CI for the
LS Geometric mean;
run;

data diffs1;
 set diffs;
 geo_estimate = exp(estimate);     * = LS Geometric mean ratio;
 geo_lower = exp(lower);           * = lower bound of the 95%CI for the
LS Geometric mean ratio;
 geo_upper = exp(upper);           * = upper bound of the 95%CI for the
LS Geometric mean ratio;
run;

data est1;
 set est;
 geo_estimate = exp(estimate);     * for composite results;
 geo_lower = exp(lower);
 geo_upper = exp(upper);
run;
```

17.2.2. Multiple Imputation

```
*******************************;
*** MAIN ANALYSIS (e.g., Section 6.4.1 )***;
*******************************;

*******************************;
*** RESHAPE DATA FOR PROC MI ***;
*******************************;

proc sort data= upcr;
 by usubjid stra1 stra2 distype immunobl trtpn base avisitc;
run;

proc transpose data= upcr out= upcr_t(drop= _NAME_ _LABEL_) prefix=V;
 by usubjid stra1 stra2 distype immunobl trtpn base;
 id avisitc;
 var aval;
run;

* Examine the missing patterns of the data;
proc mi data=upcr_t nimpute=0;
 var stra1 stra2 distype immunobl trtpn v00 - v26;
 ods output missPattern=pattern;
run;

*************************************;
*** MCMC (impute nonmonotone missing) ***;
*************************************;

* Below statements invoke MCMC procedure and specify IMPUTE=MONOTONE
 to turn the arbitrary missing patterns to monotone missing patterns
 under missing at random (MAR) assumption;

proc mi data=upcr_t out=upcr_t_mono seed= CCI nimpute=100;
 mcmc chain=multiple impute= monotone disp        t
     initial=em(itprint);
 var stra1 stra2 distype immunobl trtpn v00 - v26;
run;

* Examine the missing patterns of the data;
proc mi data=upcr_t_mono nimpute=0;
 var stra1 stra2 distype immunobl trtpn v00 - v26;
 ods output missPattern=pattern;
run;

*********************************************************************;
*** Control-based pattern imputation(impute monotone missing) ***;
*********************************************************************;
data upcr_t_mono2;
      set upcr_t_mono;
      **Identify the subjects in the active groups we want to keep
  imputed as MAR;
      if ICEDT1>. or ICEDT2>. or ICEDT3>. then MAR = 'N';
      else MAR = 'Y';
      if trt01 = 2 then MAR = 'N';
```

```
      run;

**First impute general MAR based on regression method for all subjects to get
the true MAR;
proc mi data=upcr_t_mono2 out=upcr_step1 nimpute=1 seed=CCI ;
 by _Imputation_;
 class trtpn;
 monotone reg(v00 - v26/details);
 var stra1 stra2 distype immunobl trtpn v00 - v26;
run;

**Identify and keep the data from the subjects in the active group that
should remain as a MAR;
data upcr_step2;
      set upcr_step1;
      if Mar = "Y";
      run;

**Update the dataset and keep the MAR imputed data for the subjects in the
active group that should remain as a MAR, all others remain to be imputed
with control based imputation;
data upcr_t_mono3;
      update upcr_t_mono2 upcr_step2;
      by _Imputation_ subjid;
      run;

**Fill out the remaining missing where missing data should be imputed based
on the controls;
proc mi data=upcr_t_mono3 out=upcr_t_cbp nimpute=1 seed=CCI ;
 by _imputation_;
 class trtpn;
 var stra1 stra2 distype immunobl v00 - v26;
 monotone reg(/details);
 mnar model(v04 - v26 / modelobs= (trtpn='2'));
run;

**if there are ICEs of renal transplant/dialysis (ICEDT2>.) then need to
impute based on worst change;

** first, transpose the above upcr_t_cbp back to long format upcr_cbp(omit
the details), then, collect details on worst percentage across all visits
based on original data (e.g., name the variable as worstpchg), also, identify
for those subjects who had ICEDT2>., their first visit that should be imputed
based on worst percent change (e.g., name the variable as startavisit), plus,
for all 100 imputations, calculate the average log(uPCR) for each avisit
(e.g., name the variable as visit_avg), then;

data upcr_cbp_worst;
      merge upcr_cbp worstpchg startavisit visit_avg;
      by subjid;
      if avisitn>startavisit>. then aval = base*(1+ worstpchg/100) + (aval-
visit_avg);
      **Note, the "base*(1+ worstpchg/100)" part is worst change, the "(aval-
visit_avg)" is random error;
      run;

** lastly, transpose it back to the wide format;
```

```
proc transpose data= upcr_cbp_worst out= upcr_t_cbp_worst (drop= _NAME_
_LABEL_) prefix=V;
 by usubjid stra1 stra2 distype immunobl trtpn base;
 id avisitc;
 var aval;
run;



*****************************************************************;
*** Delta-Adjusted Pattern Imputation (tipping point analysis) ***;
*****************************************************************;
**First identify the subjects in the active treatment groups that we want to
apply the shift parameter if they have monotone missing data;
data upcr_t_mono2;
      set upcr_t_mono;

      **ICEDT1=. is just an example of a reason that we do not want to
  apply the shift parameter. The actual reasons are in the text;
      if ICEDT1=. then flag = 1;
      else flag = 0;

      if trtpn = 1 and flag = 0 then adjustthis = 1;
      else adjustthis = 0;
run;

proc mi data=upcr_t_mono2 out=upcr_t_tip nimpute=1 seed=[CCI redacted];
 by _imputation_;
 class trtpn adjustthis;
 var stra1 stra2 distype immunobl trtpn v00 -- v12;
 monotone reg(/details);
 mnar adjust(v04 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v08 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v12 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v16 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v20 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v24 / shift=0.04 adjustobs=(adjustthis = '1' ))
  adjust(v25 / shift=0.01 adjustobs=(adjustthis = '1' ))
  adjust(v26 / shift=0.01 adjustobs=(adjustthis = '1' ));
run;



*****************************************************;
*** SAS macro to run MIANALYZE on outputs from MMRM *;
*****************************************************;

%macro mi_results(in, lsm, dif); ** Note this macro is for individual visits
such as W4, W8,…,W24,W25,W26, see next macro for composite contrast of W24-
W25-W26 average;


proc transpose data= &in
    out= upcr_mi (rename= (_NAME_ = AVISITN COL1 = AVAL));
 by _imputation_ usubjid trtpn base stra1 stra2 distype immunobl;
```

```
 var V00 - V26;
run;

data upcr_mi;
 set upcr_mi;
 label AVISITN = 'AVISITN';
  chg = aval - base;
  * baseline record is not used in MMRM;
 if AVISITN = 'V00' then delete;
run;

proc sort; by _imputation_; run;

proc mixed data=upcr_mi method=reml covtest empirical;
 by _imputation_;
 class trtpn avisitn usubjid stra1 stra2 distype immunobl;
 model chg=trtpn stra1 stra2 distype immunobl avisitn trtpn*avisitn base /cl;
 repeated avisitn / subject=usubjid type=UN;
 lsmeans trtpn*avisitn / pdiff cl om alpha=.05;
 ods output diffs= diffs lsmeans= lsmeans;
run;

* In the final step, the analysis results obtained from PROC MIXED
  procedure are combined into a single estimation with standard error
  using PROC MIANALYZE;

proc sort data=lsmeans;
 by avisitn trtpn _imputation_;
run;
proc mianalyze parms=lsmeans;
 by avisitn trtpn;
 modeleffects trtpn*avisitn;
 ods output ParameterEstimates=&lsm;
run;

proc sort data=diffs (where= (_trtpn= 2 and (avisitn = _avisitn)));
 by avisitn trtpn _trtpn _imputation_;
run;

proc mianalyze parms=diffs;
 by avisitn trtpn _trtpn;
 modeleffects trtpn*avisitn;
 ods output ParameterEstimates=&dif;
run;

proc sql; *** LSMEANS using Multiple Imputation;
  select Parm as Effect, AVISITN, TRTPN, Estimate, StdErr, DF,
    tValue, Probt, LCLMean as L95, UCLMean as U95
 from &lsm;

  select Parm as Effect, AVISITN, TRTPN, _TRTPN, Estimate, StdErr, DF,
    tValue, Probt, LCLMean as L95, UCLMean as U95
 from &dif;
quit;
%mend;

%mi_results(in= upcr_t_cbp, lsm= lsm_cbp, dif=dif_cbp );
```

```
%mi_results(in= upcr_t_cbp_worst, lsm= lsm_cbp, dif=dif_cbp );


%macro mi_results(in, lsm, dif); ** Note this macro is for composite contrast
of W24-W25-W26 average;

proc sql;
      select avg(base) into: abs
      from &in
      group by _imputation_;
run;
%put abs=&abs;   * this will be used for the "estimate" statement, similarly
to obtain the empirical weight for each stratification factor and disease
type, namely stra1_wt, stra1_wt_rev, stra2_wt, stra2_wt_rev, distype_wt,
distype_wt_rev, immunobl_wt, immunobl_wt_rev to be used in next procedure;


proc transpose data= &in
    out= upcr_mi (rename= (_NAME_ = AVISITN COL1 = AVAL));
 by _imputation_ usubjid trtpn base stra1 stra2 distype immunobl;
 var V00 - V26;
run;

data upcr_mi;
 set upcr_mi;
 label AVISITN = 'AVISITN';
  chg = aval - base;
  * baseline record is not used in MMRM;
 if AVISITN = 'V00' then delete;
run;

proc sort; by _imputation_; run;

proc mixed data=upcr_mi method=reml covtest empirical;
 by _imputation_;
 class trtpn avisitn usubjid stra1 stra2 distype immunobl;
 model chg=trtpn stra1 stra2 distype immunobl avisitn trtpn*avisitn base /cl;
 repeated avisitn / subject=usubjid type=UN;
 lsmeans trtpn*avisitn / pdiff cl alpha=.05 om;
estimate 'PEG Week 24-25-26 Avg LSMean' intercept 1 stra1 &stra1_wt_rev
&stra1_wt stra2 &stra2_wt_rev &stra2_wt distype &distype_wt_rev &distype_wt
immunobl & immunobl_wt_rev & immunobl_wt trtpn 1 0
BASE &abs
avisitn 0 0 0 0 0 0.333 0.333 0.334
trtpn*avisitn 0 0 0 0 0 0.333 0.333 0.334
               0 0 0 0 0 0 0 0 /cl ;
estimate 'PEG vs PBO Difference Week 24-25-26 Avg' trtpn 1 -1
trtpn*avisitn 0 0 0 0 0 0.333 0.333 0.334
               0 0 0 0 0 -0.333 -0.333 -0.334 /cl ;
  ods output estimates = est;
run;

proc mianalyze data=est(where=(label='PEG Week 24-25-26 Avg LSMean'));
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=&lsm;
run;
```

```
proc mianalyze data=est(where=(label='PEG vs PBO Difference Week 24-25-26
Avg'));
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=&dif;
run;

proc sql; *** LSMEANS using Multiple Imputation;
  select Parm as Effect, Estimate, StdErr, DF,
       tValue, Probt, LCLMean as L95, UCLMean as U95
    from &lsm;

  select Parm as Effect,  Estimate, StdErr, DF,
       tValue, Probt, LCLMean as L95, UCLMean as U95
    from &dif;
quit;
%mend;

%mi_results(in= upcr_t_cbp, lsm= lsm_cbp, dif=dif_cbp );
%mi_results(in= upcr_t_cbp_worst, lsm= lsm_cbp, dif=dif_cbp );
```

17.2.3. Rate of Change Models

```
*******************************;
*** Rate of Change analyses ***;

* In this example, repeated measures are available at
* avisitn = 0 (baseline), 4 (Week 4), 8 (Week 8), 12 (Week 12)
*   16 (Week 16), 20 (Week 20), 24 (Week 24), 25 (Week 25) and 26 (Week 26)
*
* AVAL is the actual average of triplicate FMU uPCR at the corresponding
visit.
* t is equivalent to AVISITN
*
* The data is read in from the control base imputation upcr_t_cbp, then
calling another macro to generate the "Week 0 to 26" slope for each arm as
well as the difference in slope between two arms
*******************************;

*******************************;
*This is the example if not based on multiple imputation
*******************************;

proc mixed data=upcr method=reml covtest empirical;
      class subjid trtpn stra1 stra2 distype immunobl t;
      model aval = trtpn stra1 stra2 distype immunobl avisitn trtpn*avisitn
            /cl solution;
      repeated t /type=un sub=subjid r ;

      **Week 0 to 26;
  estimate 'PEG Week 0 to 26 slope' trtpn*avisitn 26 0   avisitn 26 /cl;
  estimate 'PBO Week 0 to 26 slope' trtpn*avisitn 0 26   avisitn 26 /cl;

  estimate 'Week 0 to Week 26 Difference in slope PEG - PBO'   trtpn*avisitn
26 -26 /cl;
run;


*****************************************************;
*** SAS macro to run MIANALYZE on outputs from multiple imputation dataset *;
*****************************************************;

%macro mi_results(in, lsm, dif);

proc transpose data= &in
    out= upcr_mi (rename= (_NAME_ = AVISITN COL1 = AVAL));
 by _imputation_ usubjid trtpn base stra1 stra2 distype immunobl;
 var V00 - V26;
run;

data upcr_mi;
  set upcr_mi;
  label AVISITN = 'AVISITN';
 if avisitn = 'W00' then t = 0;
 else if avisitn = 'W04' then t = 4;
 else if avisitn = 'W08' then t = 8;
 else if avisitn = 'W12' then t = 12;
```

```
 else if avisitn = 'W16' then t = 16;
 else if avisitn = 'W20' then t = 20;
 else if avisitn = 'W24' then t = 24;
 else if avisitn = 'W25' then t = 25;
 else if avisitn = 'W26' then t = 26;
  drop avisitn base;
run;

data upcr_mi;
 set upcr_mi;
 avisitn = t;
run;

proc sort; by _imputation_; run;

proc mixed data=upcr_mi method=reml covtest empirical;
 by _imputation_;
 class trtpn usubjid stra1 stra2 distype immunobl t;
 model aval=trtpn stra1 stra2 distype immunobl avisitn trtpn*avisitn /cl;
 repeated t / subject=usubjid type=UN r;

  **Week 0 to 26;
  estimate 'PEG Week 0 to 26 slope' trtpn*avisitn 26 0   avisitn 26 /cl;
  estimate 'PBO Week 0 to 26 slope' trtpn *avisitn 0 26   avisitn 26 /cl;

  estimate 'Week 0 to 26 Difference in slope PEG - PBO'   trtpn *avisitn 26 -
26 /cl;

ods output estimates = est;
run;


proc mianalyze data=est(where=(label='PEG Week 0 to 26 slope')); * change
label for the other estimate;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=&lsm;
run;

proc mianalyze data=est(where=(label='Week 0 to 26 Difference in slope PEG -
PBO'));
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=&dif;
run;

proc sql;
select Parm as Effect, Estimate, StdErr, DF,
       tValue, Probt, LCLMean as L95, UCLMean as U95
    from &lsm;

select Parm as Effect,  Estimate, StdErr, DF,
       tValue, Probt, LCLMean as L95, UCLMean as U95
    from &dif;
quit;
%mend;
```

```
%mi_results(in= upcr_t_cbp, lsm= lsm_cbp, dif=dif_cbp );
%mi_results(in= upcr_t_cbp_worst, lsm= lsm_cbp, dif=dif_cbp );
```

17.2.4. Logistic Model

```
*-----------------------------------------------------
* logistic regression, take example of FMU uPCR of at least 50% reduction
from baseline
*-----------------------------------------------------

* first select out the binary variable of the endpoint (avalc)
data upcr50;
 set ADAM.ADEFF;
 if paramcd = 'UPRTRD50';
 if ittfl='Y';
 if avisit = 'Week 26';
 if anl01fl='Y';
 keep subjid trt01p aval avalc param paramcd stragr1 stragr2p
disesbio;
run;


* then obtain the baseline variable (log-transformation) FMU uPCR value
data fmuupcr;
 set adam.adeff;
 if paramcd='LNUPRCRF';
 if ittfl='Y';
 if basetype='NORMAL';
 if avisit='Baseline';
 logbase = aval;
 keep subjid logbase;
run;

* then merge together to obtain all necessary variables
data upcr50;
 merge upcr50 fmuupcr;
 by subjid;
run;

proc sort data=upcr50; by trt01p;run;

** Descriptive summary of the data;
proc freq data=upcr50;
  by trt01p;
  tables avalc/nocol nopercent nocum;
run;


** logistic regression that produces Proportion (SE), CI, odd ratio
and CI, and p-value;
proc logistic data=upcr50;
 class trt01p(ref='Placebo') stragr1 stragr2p disesbio/param=glm;
 model avalc(event='Y') = trt01p logbase stragr1 stragr2p disesbio /
clodds=wald orpvalue;
 oddsratio trt01p;
```

```
 lsmeans trt01p / ilink e cl;
 store LogFit;
 ods output coef=Coeffs;
run;

** calling macro to produce difference in proportion and CI of it;
%NLMeans(instore=LogFit, coef=Coeffs, link=logit, title=Differences of
Proportion)
```

17.2.5. ANCOVA Model

```
*-----------------------------------------------------
* Read Analysis data
*-----------------------------------------------------
* Example used here is the key secondary endpoint of activity score of the
C3G Histologic Index at Week 26.
* Note the main analysis should be performed based on multiple imputation
dataset with ICE addressed (see sample code under 1.2.2), here is only an
illustration of the key code using data without the multiple imputation.
*-----------------------------------------------------;

data activity;
 set ADAM.ADMI;
 if paramcd = 'C3HISACT';
 if ittfl='Y';
 if avisit = 'Week 26';
 if anl01fl='Y';
 keep usubjid trt01p chg base stragr1 stragr2p disesbio;
run;


proc mixed data=activity;
 by <subgroup>; *note: to add this line if for subgroup analysis;
 class trt01p disesbio stragr1 stragr2p;
 model chg = trt01p base disesbio stragr1 stragr2p;
 lsmeans trt01p /om cl pdiff;
run;
```

17.2.6. Time-to-Event Analysis

```
proc lifetest data=adtte;
 time aval*cnsr(1);
 strata stragr1 stragr2p disesbio / group=trt01p;
run;

proc phreg data=adtte;
 class trt01p/ param=reference ref=last;
 model aval*cnsr(1) = trt01p loguPCR_BL eGFR_BL/rl ties=efron;
 strata stragr1 stragr2p disesbio;
run;
```

STATISTICAL ANALYSIS PLAN (FINAL)
Statistical Analysis Plan: 2.0
Protocol Number: APL2-C3G-310

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT ADDENDUM

Pegcetacoplan (APL-2)
PHASE 3

A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis

PROTOCOL IDENTIFIER: VALIANT

Study Sponsor(s):	Apellis Pharmaceuticals, Inc 100 5th Ave, Waltham, MA 02451
Author:	PPD
Protocol:	Amendment 4 dated 25 April 2024
SAP Version #:	2.0
SAP Date:	10 February 2025
Status:	Final

REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	27 June 2024	New document to describe the primary analysis (Week 26) CSR addendum analyses
2.0	10 February 2025	This update describes the analyses for the final database lock with all available Week 52 data. Please refer to Version 1.0 for analyses related to the primary (Week 26) analyses. • Updated to remove Week 52 Set and replace with ITT Set. • Added shift table summary of FMU uPCR by categories. • Removed biopsy-related analysis at Week 52 given the Week 52 biopsy being optional. • Revised slope analysis at Week 52 for primary endpoint and key secondary endpoint of eGFR. • Revised 24-hour uPCR modeling by using log-transformed uPCR values. • Revised analysis for time to normalization of serum C3. • Revised analysis for PGIC score and EQ-5D-5L score. • Added more details on AEs of special search summaries and rejection episode definition. • Removed individual plots for PK and PD analysis due to redundancy. • Added clarification languages.

APPROVAL SIGNATURES

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AH50	50% alternative hemolytic complement pathway activity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	autoregressive
ARH	heterogenous autoregressive
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BLQ	below limit of quantification
BMI	body mass index
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CH50	50% classical hemolytic complement pathway activity
CI	confidence interval
CKD-EPI	Chronic Kidney Disease–Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CS	compound symmetry
CV	coefficient of variation
DBP	diastolic blood pressure
DDD	dense deposit disease
DMC	data monitoring committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	5-Level EuroQol-5 Dimension
FACIT	Functional Assessment of Chronic Illness Therapy
FMU	first-morning spot urine
GGT	gamma-glutamyltransferase
IC-MPGN	immune-complex membranoproliferative glomerulonephritis

Term	Definition
ICE	intercurrent event
INR	international normalized ratio
ITT	intention-to-treat
KDQOL	kidney disease quality of life
LLN	lower limit of normal
LLOQ	lower limit of quantification
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
MNAR	missing not at random
OLP	open-label period
PCS	potentially clinically significant
PD	pharmacodynamic
PEG	polyethylene glycol
PGIC	patient global impression of change
PK	pharmacokinetic
PP	per-protocol
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RCP	randomized controlled period
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event

Term	Definition
ULN	upper limit of normal
uACR	urine albumin-to-creatinine ratio
uPCR	urine protein-to-creatinine ratio
WBC	white blood cell
WHO	World Health Organization
WPAI	work productivity and activity impairment

1. INTRODUCTION

This statistical analysis plan (SAP) addendum provides a technical and detailed elaboration of the statistical analyses of efficacy and safety, supplementing what is described in the main SAP of the primary analysis (Week 26) and overall (combined with Week 26 SAP) clinical study report (CSR). The specified analyses to be performed as part of this SAP addendum do not supersede or replace any previously specified analyses, unless specified otherwise.

The specified analyses in this SAP addendum will serve the purposes of the planned analyses for the open-label period (OLP) reporting once all participants have completed the open-label treatment period or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized, and the database is locked.

The analyses of the OLP data associated with the primary CSR (dated 05 December 2024) were described in Version 1.0 of the SAP Addendum.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

Refer to main SAP Section 2.1.1 for the primary objective for the study.

2.1.2. Secondary Objectives

Refer to main SAP Section 2.1.2 for the secondary objectives for the study.

2.1.3. Exploratory Objectives

Refer to main SAP Section 2.1.3 for the exploratory objectives for the study.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

Refer to main SAP Section 2.2.1 for further details of the primary efficacy endpoint for the study.

2.2.2. Key Secondary Efficacy Endpoints

Refer to main SAP Section 2.2.2 for further details of the key secondary efficacy endpoints for the study.

2.2.3. Additional Secondary Efficacy Endpoints

Refer to main SAP Section 2.2.3 for further details of the additional secondary efficacy endpoints for the study.

2.2.4. Exploratory Efficacy Endpoints

Refer to main SAP Section 2.2.4 for further details of the exploratory efficacy endpoints for the study.

2.2.5. Safety Endpoints

Refer to main SAP Section 2.2.5 for further details of the safety endpoints for the study.

2.2.6. Pharmacokinetic Endpoint

Refer to main SAP Section 2.2.6 for further details of the pharmacokinetic endpoint for the study.

2.2.7. Pharmacodynamics Endpoints

Refer to main SAP Section 2.2.7 for further details of the pharmacodynamic endpoints for the study.

2.2.8. Immunogenicity Endpoint

Refer to main SAP Section 2.2.8 for further details of the immunogenicity endpoint for the study.

3. STUDY DESIGN

3.1. General Description

Refer to main SAP Section 3.1 for the general description of the study design.

3.2. Randomization

Refer to main SAP Section 3.2 for randomization details.

3.3. Blinding

This is a double-blinded study. Details on unblinding are reported in main SAP Section 3.3 and Section 3.5.

3.4. Sample Size and Power Considerations

Further detail is found in main SAP Section 3.4.

3.5. Analysis Timing and Unblinding

Further details on pre-specified Week 26 and Week 52 reporting are found in main SAP Section 3.5.

In support of initial regulatory filings, additional Open-Label Period (OLP) efficacy and safety analyses was prepared for interim data post-Week 26 at the time of the Week 26 datacut. Details of these analyses can be found in the SAP Addendum version 1.0.

4. STATISTICAL ANALYSIS SETS

4.1. Screened Set

The definition of the screened set is the same as the main SAP (refer to main SAP Section 4.1).

4.2. Intent-to-Treat Set

The definition of the intent-to-treat (ITT) set is the same as the main SAP (refer to main SAP Section 4.2).

4.3. Safety Set

The definition of the safety set is the same as the main SAP (refer to main SAP Section 4.3).

4.4. Per-protocol Set

Not applicable for the Week 52 analyses.

4.5. Pharmacokinetic Set

The definition of the PK set is the same as the main SAP (refer to main SAP Section 4.5).

4.6. Pharmacodynamic Set

The definition of the PD set is the same as the main SAP (refer to main SAP Section 4.6).

4.7. OLP Set

The OLP set includes all participants in the ITT set who enter into the open-label period.
The OLP set will be used only for selected descriptive summaries as specified in Section 6.7.1 and Section 6.7.4.

5. STUDY PARTICIPANTS

5.1. Disposition of Participants

The analyses on participant disposition are the same as the main SAP (refer to main SAP Section 5.1) and will be repeated for OLP and RCP+OLP using all available data through Week 52 assessment.

5.2. Demographic and Other Baseline Characteristics

Not applicable.

5.3. Medical History

Not applicable.

5.4. Prior and Concomitant Medications

Not applicable for prior medications.

The analyses on concomitant medications are the same as the main SAP (refer to main SAP Section 5.4) and will be repeated for OLP using all available data through Week 52 assessment.

5.5. Prior and Concomitant Procedures

Not applicable for prior procedures.

The analyses on concomitant procedures are the same as the main SAP (refer to main SAP Section 5.5) and will be repeated for OLP using all available data through Week 52 assessment.

5.6. Exposure to Investigational Product

The analyses on drug exposure are the same as the main SAP (refer to main SAP Section 5.6) and will be repeated for OLP using all available data through Week 52 assessment.

5.7. Measurements of Treatment Compliance

The analyses on treatment compliance are the same as the main SAP (refer to main SAP Section 5.7) and will be repeated for OLP using all available data through Week 52 assessment.

5.8. Protocol Deviations

The analyses on protocol deviations are the same as the main SAP (refer to main SAP Section 5.8) and will be repeated for OLP using all available data through Week 52 assessment using the OLP set.

6. EFFICACY ANALYSES

Efficacy analysis including primary, key secondary, additional secondary, and exploratory analysis will be performed primarily using the ITT set, with participants grouped according to the treatment assigned at randomization. Further details of the analysis are found in main SAP Section 6.

6.1. Analysis Models

Refer to main SAP Section 6.1 for further details.

6.2. Multiplicity Adjustment

Further details of the analysis are found in main SAP Section 6.2. No formal hypothesis testing will be performed for the analysis of the OLP data.

6.3. Estimands

Refer to main SAP Section 6.3 for further details.

6.4. Analyses of Primary Efficacy Endpoint

Not applicable.

6.5. Analyses of Key Secondary Efficacy Endpoints

Not applicable.

6.6. Analyses of Additional Secondary Efficacy Endpoints

Not applicable.

6.7. Analyses of Exploratory Efficacy Endpoints

All primary, key secondary, and additional secondary endpoints will be evaluated at Week 52 as exploratory efficacy endpoints (listed below as Section 6.7.1-11). Additional exploratory endpoints (listed below as Section 6.7.12-24) will also be evaluated.

6.7.1. Primary Efficacy Endpoint at Week 52

The analyses described in Section 6.4.1 (main analysis) and Section 6.4.3.2 (slope analysis) in the main SAP will be repeated at Week 52 using all available data through the Week 52 assessment based on the ITT Set.

ICE strategies will be the same as the first sensitivity analysis as specified in the main SAP Section 6.4.2 where missing data after the ICEs will be imputed implicitly within the MMRM in a hypothetical strategy under the assumption of MAR.

In addition, the observed values for uPCR will be summarized by treatment group and visit using the OLP set. Details on the baseline derivation for OLP set are specified in Section 13.

A shift table summary of FMU uPCR by categories (>= 3 g/g, 1- <3 g/g, <1 g/g) will be generated. This also applies to the analysis for the RCP period.

For slope analysis, the mean rate of change in log-transformed uPCR will be compared between pegcetacoplan arm and control arm by use of a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model"). The analysis to be performed will be similar to what is described in the "slope model" except that a knot at the Week 26 visit will be added to both arms, which allows for the slope of log-transformed uPCR to differ between the two periods (RCP and OLP). Difference in slope will also be estimated by period.

6.7.2. The Proportion of Participants Who Meet the Criteria for Achieving a Composite Renal Endpoint at Week 52

The descriptive analysis described in Section 6.5.1.1 (main analysis) in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

ICE strategies will be the same as the main SAP where the endpoint status at or after the initiation of ICEs will be regarded as non-responder.

6.7.3. The Proportion of Participants with a Reduction of at least 50% from Baseline in uPCR at Week 52

The descriptive analysis described in Section 6.5.2.1 (main analysis) in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

ICE strategies will be the same as the main SAP where the endpoint status at or after the initiation of ICEs will be regarded as non-responder.

6.7.4. Change from Baseline in the Activity Score of the C3G Histologic Index Score at Week 52

Not applicable, given the Week 52 biopsy being optional.

6.7.5. The Proportion of Participants Showing Decreases in C3c Staining from Baseline at Week 52

Not applicable, given the Week 52 biopsy being optional.

6.7.6. Change from Baseline in eGFR at Week 52

The analyses described in Section 6.5.3.1 (main analysis) and Section 6.5.3.3.2 (slope analysis) in the main SAP will be repeated at Week 52 using all available data through the Week 52 assessment based on the ITT Set.

For slope analysis, the mean rate of change in eGFR will be compared between pegcetacoplan arm and control arm by use of a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model"). Due to the instability from MMRM analysis with large number of visits and small sample size, a random coefficients model with an unstructured covariance matrix will be used. The model will include treatment group, disease type, stratification factors, time, and time-by-treatment interaction as fixed effects, and subject-specific random intercept and slope (Vonesh et al. 2019). A knot at the Week 26 visit will be added to the control arm, which allows for the slope of eGFR to differ between the two periods (RCP and OLP). Difference in slope will also be estimated by period.

ICE strategies will be the same as the first sensitivity analysis as specified in the main SAP Section 6.5.3.2 where missing data after the ICEs will be imputed implicitly within the MMRM in a hypothetical strategy under the assumption of MAR.

In addition, the observed values for eGFR will be summarized by treatment group and visit using the OLP set. Details on the baseline derivation for OLP set are specified in Section 13.

6.7.7. The Proportion of Participants Achieving Proteinuria <1 g/day at Week 48

The descriptive analysis described in Section 6.6.1 in the main SAP will be repeated at Week 48 based on the ITT Set by using available data through the Week 48 assessment.

6.7.8. The Proportion of Participants with Normalization of Serum Albumin Levels at Week 52

The descriptive analysis described in Section 6.6.2 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

ICE strategies will be the same as the main SAP where the endpoint status at or after the initiation of ICEs will be regarded as non-responder.

6.7.9. The Proportion of Participants with Serum C3 Levels above the LLN at Week 52

The descriptive analysis described in Section 6.6.3 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

ICE strategies will be the same as the main SAP where the endpoint status at or after the initiation of ICEs will be regarded as non-responder.

6.7.10. Change from Baseline in FACIT-Fatigue Scale Score at Week 52

The descriptive analysis described in Section 6.6.4 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

6.7.11. Change from Baseline in KDQOL Score at Week 52

The descriptive analysis described in Section 6.6.5 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

6.7.12. The Change from Baseline in uPCR Using the 24-hour Urine Collections at Week 48

The descriptive analysis described in Section 6.7.1 in the main SAP will be repeated at Week 48 using all available data through the Week 48 assessment based on the ITT Set.

Note for the MMRM modeling for the RCP period, the analysis based on log-transformed 24-hour uPCR will be implemented, instead of the uPCR values on original scale.

6.7.13. The Annual Rate of Change from up to 3 Years Prior to Screening in eGFR

The analysis described in Section 6.7.2 in the main SAP will be repeated at Week 52 using all available data through the Week 52 assessment, with the adjustment that for the placebo group, eGFR data collected during the RCP period will be considered as part of the historical (a.k.a. pre-treatment) data in the analysis. This analysis will be based on the ITT Set.

In addition, the above analysis will be repeated by pooling the two treatment regimens and difference between post-peg and pre-peg will be presented with the 95% CI and p-value.

6.7.14. The Proportion of Participants with Reductions from Baseline in Proteinuria of at least 30% at Week 52

The descriptive analysis described in Section 6.7.3 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

6.7.15. The Proportion of participants with Normalization of Proteinuria at Week 52

The descriptive analysis described in Section 6.7.4 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

6.7.16. Time to 50% Reduction in uPCR with a Stable or Improved eGFR

The analysis described in Section 6.7.6 in the main SAP will be repeated based on the ITT set using all available data through the Week 52 assessment. For event-free survival, present the timepoints of week 12, week 24, week 36, and week 48.

6.7.17. Time to Normalization for Selected Parameters for Participants in Whom the Parameter is Abnormal at Baseline

The analysis described in Section 6.7.7 in the main SAP will be repeated based on the ITT set using all available data through the Week 52 assessment. For event-free survival, present the timepoints of week 12, week 24, week 36, and week 48.

Note for time to normalization of serum C3, the normalization is not applicable for this endpoint hence the analysis is revised as time to serum C3 levels being greater than or equal to the lower limit of normal (LLN). This also applies to the analysis for the RCP period.

6.7.18. The Change from Baseline in Glomerular Macrophage Count

Not applicable, given the Week 52 biopsy being optional.

6.7.19. The Change from Baseline in PGIC Score

The descriptive analysis described in Section 6.7.9 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

Note per FDA guidance, PGIC should not be collected at baseline, and therefore should not be calculated/reported in the form of “change from baseline”, this endpoint will be analyzed in a descriptive way of presenting the PGIC score at specific timepoint(s) only. This also applies to the analysis for the RCP period.

6.7.20. The Change from Baseline in EQ-5D-5L Score

The descriptive analysis described in Section 6.7.10 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

Note that the individual component score of EQ-5D-5L will also be tabulated. This also applies to the analysis for the RCP period.

6.7.21. The Change from Baseline in WPAI Score

The descriptive analysis described in Section 6.7.11 in the main SAP will be repeated at Week 52 based on the ITT Set by using available data through the Week 52 assessment.

6.7.22. Change in Drusen from Baseline

The observed values for maximum drusen size (measured by total volume of drusen) and number of intermediate or large drusen will be summarized by treatment group and visit using ITT set. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit. Summaries will further be separated by left eye and right eye, respectively.

All maximum drusen size and number of intermediate or large drusen results will be listed for the ITT set.

6.7.23. The Change from Baseline in uACR

The observed values for urine albumin-to-creatinine ratio (uACR), measured by triplicate first-morning spot urine or 24-hour urine collection, will be summarized separately by treatment group and visit based on the ITT Set by using available data through the Week 52 assessment. Summaries will present the descriptive statistics for baseline, absolute values, change and percentage change from baseline data by visit. The baseline derivation of FMU uACR will be based on the same logic as described for FMU uPCR.

7. SAFETY ANALYSIS

7.1. Adverse Events

Further detail is provided in the main SAP Section 7.1. The same summaries for RCP as in the main SAP will be repeated for OLP (except for rejection episodes and graft loss where only descriptive summaries are required at Week 52) using all available data through the Week 52 assessment.

Besides the AESI summaries as per the CRF form checkbox question "Is this event an AESI?", additional summaries for the AEs of special search will be provided based on the special search teams provided by Apellis safety team, more specifically:

- Infections: SOC-infections and infestations; HLGT- Bacterial infectious disorders, HLGT- Fungal infectious disorders, HLGT- Viral infectious disorders
- Hypersensitivity: SMQ-Hypersensitivity (narrow)
- Acute Kidney Injury: SMQ- Acute Renal Failure (narrow)
- Thrombocytopenia: HLT- Thrombocytopenias, PT-Platelet count decreased, PT-Plateletcrit decreased, PT-Platelet count abnormal

AEs will be summarized by treatment groups and period. Data will be presented in 5 columns: (1) Pegcetacoplan group's RCP results; (2) Pegcetacoplan group's OLP results; (3) Placebo group's OLP results; (4) OLP results combined (in other words, combining columns 2 and 3); (5) for all results since Pegcetacoplan injection (in other words, combining columns 1 and 4). The classification of AEs in the RCP or OLP will be based on the AE start date compared to the RCP/OLP threshold as defined in the main SAP Section 13.3.

For AE summaries that relate to rejection episodes, in addition to the preferred terms specified in the main SAP, one additional preferred term of "Transplant rejection" is also added based on Apellis team review.

7.2. Clinical Laboratory Data

Refer to main SAP Section 7.2 for further details of the analysis.

The same by-visit summaries as in the main SAP will be repeated using all available data through the Week 52 assessment.

7.3. Vital Signs

Refer to main SAP Section 7.3 for further details of the analysis.

The same by-visit summaries as in the main SAP will be repeated using all available data through the Week 52 assessment.

7.4. Electrocardiogram (ECG)

Refer to main SAP Section 7.4 for further details of the analysis.

The same by-visit summaries as in the main SAP will be repeated using all available data through the Week 52 assessment.

7.5. Other Safety Data

Physical examinations will be described in a data listing using all available data through the Week 52 assessment.

8. PHARMACOKINETIC ANALYSIS

Refer to main SAP Section 8 for further details of the analysis.

The same summaries for RCP as in the main SAP will be repeated using all available data through the Week 52 assessment.

Note the individual linear and loglinear PK plots will be removed from planned analysis, given the relevant data listings already provided sufficient information. This also applies to the analysis for the RCP period.

9. PHARMACODYNAMIC ANALYSIS

Refer to main SAP Section 9 for further details of the analysis.

The same summaries for RCP as in the main SAP will be repeated using all available data through the Week 52 assessment.

Note the individual PD and change from baseline PD plots will be removed from planned analysis, given the relevant data listings already provided sufficient information. This also applies to the analysis for the RCP period.

10. IMMUNOGENICITY

Refer to main SAP Section 10 for further details of the analysis.

The same summaries for RCP as in the main SAP will be repeated using all available data through the Week 52 assessment.

11. INTERIM ANALYSIS

An analysis was conducted for regulatory submissions when all participants have completed the randomized controlled period and the data was cleaned. No type I error adjustment was necessary. Results were reported in the CSR (dated 05 December 2024).

12. DATA MONITORING COMMITTEE

Refer to main SAP Section 12 for more details.

13. DATA HANDLING CONVENTIONS

Refer to main SAP Section 13 for more details.

In addition, for analysis based on OLP set, baseline is defined as the most recent non-missing measurement prior to the start of open-label period for both pegcetacoplan group and placebo group, with the exception of triplicate FMU uPCR, where an average of up to 9 collections from Week 24, 25, and 26 will be used for baseline derivation when applicable.

14. ANALYSIS SOFTWARE

Refer to main SAP Section 14 for more details.

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Changes in this SAP Addendum that were not described in the protocol or main SAP are:

- Added shift table summary of FMU uPCR by categories.
- Removed biopsy-related analysis at Week 52 given the Week 52 biopsy being optional.
- Revised slope analysis at Week 52 for primary endpoint and key secondary endpoint of eGFR.
- Revised 24-hour uPCR modeling by using log-transformed uPCR values.
- Revised analysis for time to normalization of serum C3.
- Revised analysis for PGIC score and EQ-5D-5L score.
- Added more details on AEs of special search summaries and rejection episode definition.
- Removed individual plots for PK and PD analysis due to redundancy.

16. REFERENCES

Vonesh E, Tighiouart H, Ying J, et al. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease [published correction appears in *Stat Med*. 2021 Jun 30;40(14):3400-3401. doi: 10.1002/sim.8974.]. *Stat Med*. 2019;38(22):4218-4239. doi:10.1002/sim.8282

17. APPENDICES

Refer to main SAP Section 17 for more details.