STATISTICAL ANALYSIS PLAN

Pegcetacoplan (APL-2)
Phase 2

An Open-Label, Randomized, Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Pegcetacoplan (APL-2) in the Treatment of Post-Transplant Recurrence of C3G or IC-MPGN

PROTOCOL IDENTIFIER: APL2-C3G-204

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REVISION HISTORY

Version	Issue date	Summary of changes
1.0	30 March 2023	Original
2.0	10 January 2024	Fixed a typo in serum creatinine threshold when defining stabilization or improvement
		Added analysis plan details for selected Part A Non-Controlled Portion outputs
		Updated and clarified definition of PD Set
		Provided further details on the analysis of ADA data
		Added clarification languages

APPROVAL SIGNATURES

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CV	Coefficient of Variation
DDD	Dense Deposit Disease
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
INR	International Normalized Ratio
ITT	Intention-To-Treat
LLOQ	Lower Limit of Quantification
MedDRA®	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental Analysis
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PT	Preferred Term (MedDRA)
QTcB	QT Interval Corrected for Heart Rate Using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SMC	Safety Monitoring Committee
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
uPCR	Urine Protein-to-Creatinine Ratio
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic/pharmacodynamic data as described in the study protocol Amendment 3 dated 03 February 2022. Specifications for tables, figures, and listings are contained in a separate document.

There are two parts of this study: Part A includes an approximate 8-week screening period to be followed by a 52-week main period, during which time Group 1 will have pegcetacoplan administration for all 52 weeks and Group 2 will receive pegcetacoplan administration only following the Week 12 biopsy through the remainder of the main period. All subjects then enter the 8-week follow-up period or the long-term extension (Part B).

The total duration of participation is up to 68 weeks (not including the Part B long-term extension).

For analysis purposes, data will be summarized by treatment groups and overall. When applicable (and it will be specified in the following sections), the summary tables will be further separated by the 3 treatment phases (Part A Controlled Portion, Part A Noncontrolled portion, and Part B long-term extension) and combined.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of pegcetacoplan in improving the underlying pathophysiology of C3G/IC-MPGN after 12 weeks of treatment.

2.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- to evaluate the effect of pegcetacoplan on key clinical manifestations of the disease after 52 weeks of treatment
- to evaluate the safety of pegcetacoplan for up to 52 weeks in subjects with recurrent C3G/IC-MPGN in a renal allograft

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, including pegcetacoplan pharmacokinetic, pharmacodynamic, and immunogenicity in patients with C3G/IC-MPGN.

2.2. Endpoints

2.2.1. Primary Endpoint

The primary efficacy endpoint is the proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks of treatment with pegcetacoplan.

2.2.2. Secondary Endpoints

The secondary endpoints are as follows:

Safety:

- Safety measured by AEs, clinical laboratory tests, vital signs, and ECGs

Efficacy:

- The proportion of subjects with reduction in C3c staining on renal biopsy after 52 weeks of treatment
- Changes from baseline biopsy in C3c staining over time
- The proportion of subjects with stabilization or improvement in estimated glomerular filtration rate (eGFR) over time
- The proportion of subjects with stabilization or improvement of serum creatinine concentration over time
- Changes and percentage changes from baseline in eGFR and serum creatinine concentration over time

2.2.3. Exploratory Endpoints

The exploratory endpoints are as follows:

- For subjects with baseline proteinuria above the upper limit of normal (ULN), the proportion of subjects achieving at least a 50% reduction in proteinuria over time
- For subjects with baseline proteinuria above the ULN, the proportion of subjects achieving complete clinical remission of proteinuria after 12 and 52 weeks of treatment, defined as normalization of proteinuria
- Changes and percentage changes in proteinuria over time
- Change over time in additional key biopsy features, including:
    - Glomerular myeloid cell infiltration
    - Glomerular macrophage infiltration (as measured by CD68 staining)
    - Glomerular crescents (in subjects with crescents)
    - Mesangial expansion and hypercellularity
    - Deposits by electron microscopy
    - Activity score (based on C3G histologic index)
    - Chronicity score (based on C3G histologic index)
- Ophthalmology:
    - Change in maximum drusen size at Week 52
    - Number of intermediate or large drusen at baseline and Week 52
- The number and incidence of rejection episodes in each group
- The number and incidence of graft loss in each group
- Pegcetacoplan serum concentrations over time
- Change in complement biomarkers (50% classical hemolytic complement pathway activity [CH50] and 50% alternative hemolytic complement pathway activity [AH50]) over time
- Immunogenicity: The incidence of anti-pegcetacoplan antibodies and incidence of anti-PEG antibodies (including treatment-emergent and treatment-boosted responses) throughout the treatment and follow-up periods

3. STUDY DESIGN

This Phase 2, multicenter, open-label, randomized, controlled clinical study is designed to evaluate the safety and efficacy of pegcetacoplan in subjects who have post-transplant recurrence of C3G or IC-MPGN. There will be up to 12 subjects enrolled in this study. This study has two parts.

Part A (Core Study):

- Screening Period: an up to 8-week screening period, during which a screening renal allograft biopsy will occur
- Main Period: a 52-week study period that contains 2 portions (Controlled and Non-Controlled) during which subjects will be randomized to either Group 1 or Group 2 at the Week 1 visit:
    - Controlled Portion: Weeks 1-12 of the study
        - Group 1: Up to 9 subjects will be randomized to this treatment group and will receive pegcetacoplan treatment throughout the entire study; biopsies will occur at Week 12
        - Group 2: Up to 3 subjects will be randomized to this treatment group and will not receive pegcetacoplan treatment during the Controlled Portion; biopsies will occur at Week 12
    - Non-Controlled Portion: Weeks 13-52 of the study
        - Group 1: Subjects will continue to receive pegcetacoplan treatment; biopsies will occur at Week 52
        - Group 2: Subjects will receive pegcetacoplan treatment following their Week 12 renal allograft biopsy; biopsies will occur at Week 52
- Follow-up Period: an 8-week follow-up period.

Part B:

Any subject who, in the opinion of the investigator is experiencing clinical benefit from pegcetacoplan administration may participate in Part B, a long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study. If invited to participate, the subject can enter Part B as soon as his/her 52-week treatment period has ended and does not need to participate in the 8-week follow-up period.

3.1. General Description

This is an open-label, randomized, controlled, Phase 2 study, consisting of a single cohort of up to 12 subjects with clinical and pathologic evidence of recurrent C3G or IC-MPGN in a renal allograft. Subjects will be randomized 3:1 to Group 1 (pegcetacoplan treatment throughout the Main Period) or Group 2 (no pegcetacoplan treatment for the first 12 weeks of the Main Period, followed by pegcetacoplan treatment), respectively. The visit schedule will be the same, regardless of randomization.

Pathologic evidence of recurrence requires a biopsy-based diagnosis of C3G or IC-MPGN in the renal allograft, confirmed by a central pathologist. The diagnosis need not be the same in the native kidney and the renal allograft; for example, a subject with C3G in the native kidney and IC-MPGN post-transplant is still eligible for the study.

Subjects with either preexisting disease recurrence or upon initial identification of clinical and pathologic recurrence of disease will be invited to enter screening. Subjects must also have an eGFR of at least 15 mL/min/1.73m2 and no more than 50% fibrosis on renal biopsy.

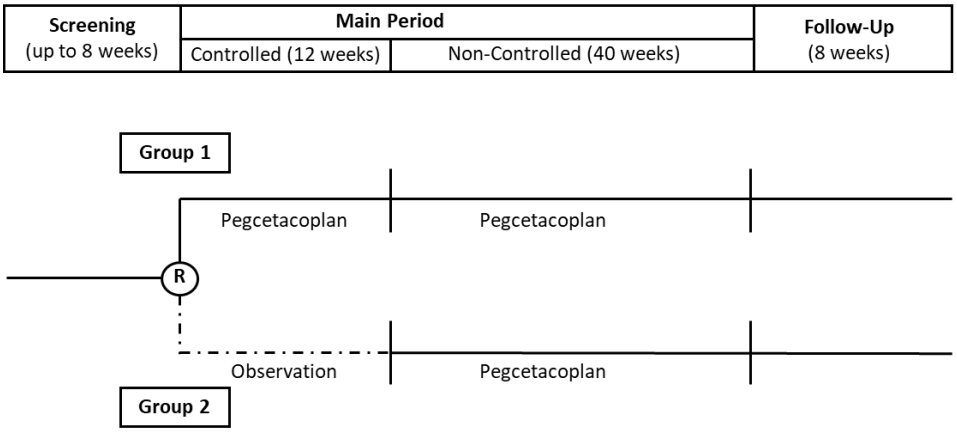
The study will require a total of 3 renal allograft biopsies, during screening, Week 12, and Week 52. Flexibility has been built-in for each biopsy as described below:

- Screening renal allograft biopsy: must occur within 4 weeks leading up to the day of randomization
    - A non-study biopsy may be used as the baseline biopsy provided it meets the following criteria:
        - it was performed no more than 12 weeks prior to Week 1
        - the subject has remained clinically stable since the biopsy with no changes in medication regimens that would be expected to significantly alter the baseline biopsy findings
        - the prior biopsy is available for central pathology review and includes all the required components of a study baseline biopsy.
- Week 12 renal allograft biopsy: must occur at a time point between Weeks 12 and 14, inclusive; Group 2 subjects cannot begin pegcetacoplan administration until after the biopsy occurs
- Week 52 renal allograft biopsy: must occur at a time point between Weeks 48 and 52, inclusive, but after completion of the 24-hour urine collection scheduled for Week 48.

In the event that a subject has a biopsy for clinical cause within the timeframe allowed for a study biopsy, this clinical biopsy may be able to serve as one of the protocol biopsies, provided it includes all required components for this study. If it is not able to serve as a protocol biopsy, then information from that biopsy should still be collected within the study database, if possible.

After completion of the 52-week Main Period, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the Long-Term Extension Phase in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study (see Protocol Section 15). Those who do not continue on pegcetacoplan in the long-term extension protocol will enter a Follow-Up period of a minimum of 8 weeks.

Figure 1: Study Design



Abbreviation: R = randomization.

3.2. Randomization

Subjects will be randomized 3:1 to Group 1 (pegcetacoplan treatment throughout the Main Period) or Group 2 (no pegcetacoplan treatment for the first 12 weeks of the Main Period, followed by pegcetacoplan treatment), respectively.

3.3. Blinding

This is an open-label study (not blinded).

3.4. Sample Size

Given the exploratory nature of the study, no formal statistical hypothesis testing will be performed; therefore, the sample size is not based upon statistical power of the study. Up to 12 subjects will be enrolled into this study.

3.5. Analysis Timing

The analysis of data from the Part A Controlled Portion of the study will be performed when all subjects have completed the Part A Controlled Portion or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized, and the Week 12 Analysis database locked. At that time, the primary analysis will be performed, which will include all efficacy and safety analyses for the Part A Controlled Portion. For Week 12 Analysis, all summary tables will be presented by randomized group.

The analysis of data from the Part A Non-Controlled Portion will be performed once all subjects have completed the Part A Non-Controlled Portion or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized, and the Week 52 Analysis database locked. For disposition, baseline summary, and efficacy analysis, tables will be presented similarly as Week 12 Analysis.

The table summaries for protocol deviations, concomitant medications, study drug exposure and compliance, as well as all AE summaries will be presented in 5 columns: (1) Group 1's Part A Controlled Portion results; (2) Group 1's Part A Non-Controlled Portion results; (3) Group 2's Part A Non-Controlled Portion results; (4) Part A Non-Controlled Portion 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). More details on the summary layout are provided in the separate table shell document.

4. STATISTICAL ANALYSIS SETS

4.1. Screened Set

The screened set includes all subjects who provide written informed consent.

This set will be used for the summary of analysis sets.

4.2. Intent-to-Treat Set

The intent-to-treat (ITT) set consists of all subjects who are randomized.

The ITT set will be used for the summary of demographics, baseline characteristics, subject disposition, and analysis of all efficacy data.

4.3. Safety Set

The safety set includes all subjects who receive at least 1 dose of pegcetacoplan, and subjects who are randomized into Group 2.

All safety analyses will be conducted using the safety set.

4.4. Pharmacokinetic Set

The PK set includes all subjects in the ITT set who receive pegcetacoplan and have at least 1 evaluable postdose PK measurement.

All PK analyses will be conducted using the PK set.

4.5. Pharmacodynamic Set

The PD set includes all subjects in the ITT set who had at least 1 evaluable postscreening PD measurement.

All PD analyses will be conducted using the PD set.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

For summary of analysis sets, the number and percentage of subjects 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 subjects 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. This summary will be further separated by treatment phases and combined. Variables to be summarized within each treatment phase will be adjusted accordingly to reflect the specific treatment phase.

5.2. Demographic and Other Baseline Characteristics

The following baseline demographic characteristics will be summarized and listed using the ITT set: age at screening, age group(<= 65 years vs > 65 years), sex, ethnicity, race, weight, height, BMI, blood pressure.

The following baseline disease characteristics will be summarized and listed using the ITT set: underlying disease (C3GN, DDD or IC-MPGN) based on screening biopsy, underlying disease per medical history, potential causes 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, baseline creatinine, baseline serum albumin, baseline serum C3, and time since post-transplant recurrence.

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 post-transplant recurrence will be calculated as:

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

The following baseline biopsy characteristics will be summarized and listed using the ITT set: C3 staining, number of glomeruli, light microscopic patterns, Crescents (%), global sclerosis, interstitial fibrosis, tubular atrophy, total activity score, total chronicity score, and Banff score.

5.3. Medical History

Medical history will be coded using the latest MedDRA coding dictionary. For subjects in the Safety Set, medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) and listed. Each subject 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 subjects overall within each SOC and then similarly by decreasing frequency of subjects overall within each PT. In 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.

Outputs in this section will also be provided using the ITT Set if the ITT set differs from the Safety Set.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest WHO Drug Dictionary version available. Summaries of prior and concomitant medications will be presented by ATC level 2 (therapeutic main group) and preferred term with numbers and percentages by treatment groups and overall for subjects in the Safety set. A subject 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 subjects overall within each ATC level 2 class and then similarly by decreasing frequency of subjects 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 started prior to the administration of study drug for subjects in Group 1 or prior to Day 1 for subjects in Group 2. Concomitant medications are defined as those medications taken on/after the date of first administration of study drug for Group 1 subjects or on/after Day 1 for Group 2 subjects. Hence medications started before receiving study drug (or Day 1 for Group 2 subjects) but continuing after will be considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

Outputs in this section will also be provided using the ITT Set if the ITT Set differs from the Safety Set.

5.5. Exposure to Investigational Product

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

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

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

5.7. 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 management 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 subjects with protocol deviations will be summarized by importance of deviation for ITT Set and listed.

6. EFFICACY ANALYSIS

6.1. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with reduction in C3c staining on renal biopsy at Week 12.

The baseline renal allograft biopsy will be taken as defined per Protocol Section 9.1.3.
The proportion of subjects with reduction in C3c staining at Week 12 will be tabulated, along with the 95% confidence intervals (CIs).

Categories for C3c staining are: 0 (including negative and trace), 1, 2, 3, and NA (meaning no C3c staining available or no glomeruli in the sample stained for C3c). Reduction in C3c staining is defined as decrease of at least 2 orders of magnitude of intensity from baseline (e.g., baseline result being 3 and Week 12 result being 1 or 0). Missing or NA results at Week 12 will be listed separately. A composite strategy will be used for addressing intercurrent events. The C3c staining status at or after the initiation of any of intercurrent events, including but not limited to, the use of prohibited concomitant medication, starting renal replacement therapy due to worsening of underlying disease, use of rescue therapies, premature withdrawal from the treatment, will be regarded as non-reduction. The initiation of intercurrent events will be reviewed by medical team and provided to biostatistics team.

Sensitivity analysis such as using treatment policy strategy for handling intercurrent events, meaning that Week 12 C3c staining status will be collected and analyzed regardless of an intercurrent event has occurred or not, will also be performed. Supportive analysis may be conducted based on those who have both baseline and Week 12 C3c staining results.

6.2. Analyses of Secondary Efficacy Endpoints

The proportion of subjects with reduction in C3c staining on renal biopsy at Week 52, change from baseline biopsy in C3c staining over time, the proportion of subjects with stabilization or improvement in eGFR or serum creatinine concentration over time, change and percentage change from baseline in eGFR and serum creatinine concentration over time, are the secondary efficacy endpoints.

The proportion of subjects with reduction in C3c staining on renal biopsy at Week 52 will be tabulated. The strategies to handle intercurrent events are same as for the primary endpoint by using composite strategy and treatment policy strategy. Changes from baseline biopsy in C3c staining over time will be summarized. A spaghetti plot of C3c staining throughout the study will be provided.

The proportion of subjects with stabilization or improvement in eGFR (defined as no more than a 25% decrease relative to baseline) over time will be tabulated. The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) creatinine equation for adults will be used to calculate eGFR. Changes and percentage changes from baseline in eGFR will be summarized over time.

The proportion of subjects with stabilization or improvement in serum creatinine concentration (defined as no increase or an increase of no more than 25% from baseline) over time will be tabulated. Changes and percentage changes from baseline in serum creatinine concentration will be summarized over time.

6.3. Analyses of Exploratory Efficacy Endpoints

For subjects with baseline proteinuria above the upper limit of normal (ULN), the proportion of subjects achieving at least a 50% reduction in proteinuria over time, and the proportion of subjects achieving complete clinical remission of proteinuria (defined as normalization of proteinuria, which is <200 mg/g) at Week 12 and Week 52, will be tabulated. Changes and percentage changes from baseline in proteinuria will be summarized over time. Since proteinuria will be assessed in two separate ways (one using the mean of the triplicate first-morning spot urine, the other using the 24-hour urine collection), there will be two sets of tables for the proteinuria summaries described in this paragraph. In addition, changes and percentage changes from baseline in proteinuria will also be summarized descriptively based on the subgroup of baseline uPCR < 1000 mg/g vs. baseline uPCR >= 1000 mg/g.

Additional key biopsy features, including glomerular leukocyte infiltration (Total #, percentage, score), glomerular macrophage infiltration as measured by CD 68 staining, glomerular crescents (total #, percentage, score), Mesangial hypercellularity (total #, percentage, score), Deposits by electron microscopy (absent/present, characters of deposits, locations of deposits, degree of foot process effacement), and C3G histologic index (activity score, chronicity score), will be summarized and listed. Changes over time will also be summarized for the numeric biopsy features.

Ophthalmologic features including change in maximum drusen size (measured by total volume of drusen) at baseline and Week 52, and change in number of intermediate or large drusen at Week 52, will be summarized for subjects who have both baseline and on-study ophthalmologic evaluations and listed. In situations where no subjects had on-study ophthalmologic evaluations, outputs will still be generated for those baseline evaluations. Summaries will further be separated by left eye and right eye, respectively.

7. SAFETY ANALYSIS

7.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs that develop or worsen after the first dose of study medication (or after randomization in Group 2) and up to 56 days beyond the last dose of study medication. 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 subjects within each SOC and then similarly by decreasing frequency of subjects within each PT. In the case of equal frequency of number of subjects 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 subject, that subject would only be counted once in the incidence for that PT. For subjects 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 subjects 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 and overall. The number and incidence of rejection episodes and graft loss will also be summarized.

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

- TEAE
- Treatment-related TEAE
  - Related
  - Not related
- Infusion-related TEAEs
  - Related
  - Not related
- Serious TEAE
- Maximum severity of TEAEs
- Infusion site reaction (yes/no)
- TEAE leading to treatment discontinuation
- TEAE leading to dose interruption
- TEAE leading to study discontinuation
- TEAE leading to death

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

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 urinalysis parameters) will be summarized at each analysis visit by treatment group and overall. Categorical urinalysis 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 1: 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 1: 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; estimated Glomerular Filtration Rate (using CKD-EPI formula) –screening only; Albumin; LDH; Creatine kinase (CK); Uric acid; Glucose; Sodium; Potassium; and Chloride, abnormal values will be used as potentially clinically significant.

Similarly, for Urinalysis parameters, Protein; Glucose; Blood; Nitrite; and Leukocyte esterase, abnormal values will be used as potentially clinically significant.

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

All laboratory values will be listed for each subject.

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 subjects 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 2: 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 post-baseline ≥15 mm Hg decrease from baseline
Temp	≥ 38℃

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. Electrocardiograms (ECGs)

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

Additionally, the number and percentage of subjects 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 3: 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

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 subjects included in the PK Population.

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 subjects with a below the limit of quantification (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 subjects 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 below the limit of quantification (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

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 (PD) 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 (antidrug antibody [ADA]) data will be listed and summarized separately for anti-pegcetacoplan peptide antibody and anti-PEG antibody results using the safety set. A sample and subject 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 positive samples will be further classified into neutralizing antibody (NAb) positive, NAb negative, or NAb inconclusive for anti-pegcetacoplan peptide antibody and summarized by treatment group and overall.

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
- 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.

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.

Subject Level Summary

The number and percentage of subjects with pre-existing ADAs will be summarized by treatment group and overall in the subjects with a baseline sample result. In addition, the number and percentage of subjects 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 subjects. The subject summary table will include a summary by treatment group and overall for the ADA population parameters. The subject summary table will also include the number and percentage of subjects with a positive NAb result either pre- or post-dose in the subjects with at least one pre- or post-dose sample result.

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

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

Evaluable subjects will be classified as follows for ADA response:

- ADA-Positive Subject – An evaluable subject with at least one pre-dose sample and one treatment-emergent or treatment-boosted ADA-positive sample at any time after dosing
- ADA-Negative Subject – An evaluable subject without a treatment-emergent or treatment-boosted ADA-positive sample during the treatment or follow-up period
- ADA-Inconclusive Subject – An evaluable subject 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 subject 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 subject 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 subjects 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 subjects 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 subjects 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 subjects are 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 subject 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 subjects, including pre-existing ADA, computed as a percentage of the total number of evaluable and unevaluable subjects
- ADA Incidence – The sum of all ADA positive treatment-emergent and treatment-boosted subjects computed as a percentage of the total number of evaluable subjects

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

11. INTERIM ANALYSIS

No formal interim analysis is planned for this study.

12. SAFETY MONITORING COMMITTEE

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

The first SMC meeting will be scheduled 4 months after the first subject is dosed with study drug and at further 4-monthly intervals until all subjects complete the Main Period. An ad hoc SMC data review may be recommended by the SMC or requested by the Sponsor at any time during the study.

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

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 subjects and percentage of total number of subjects in the given analysis set as noted for each category. Percentages will be reported to one decimal place. Descriptive statistics will be used to summarize continuous variables including number of subjects, 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.

Subject specific listings will be provided by treatment group, subject 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 Study Day 1 visit 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

For all evaluations unless otherwise noted, baseline is defined as the most recent non- missing measurement prior to the first administration of study drug (Study Day 1 for treatment group 1), or prior to/on the randomization date (Study Day 1 for treatment group 2). 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 subjects 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 (i.e. visit value – baseline value).

13.4. Definition of Analysis Visit Windows

Safety lab, vital sign, and ECG data will be assigned to analysis visit based on windowing (see table below). If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis. If two assessment dates are at the same distance from the target day, the first assessment with non-missing data will be considered for analysis.

Study period	Analysis visit	Target day	Analysis window	Interval
Screening	Week -8 to -4	-28	-56 - < -21	NA
	Week -2	-14	-21 – ≤ -1	21
Main Period Controlled Portion	Day 1	1	1	1
	Week 2	14	2 – < 21	19
	Week 4	28	21 – < 42	21
	Week 8	56	42 – < 70	28
	Week 12	84	70 – < 91	21
Main Period Noncontrolled Portion	Week 14	98	91 – < 105	14
	Week 16	112	105 – < 126	21
	Week 20	140	126 – < 154	28
	Week 24	168	154 – < 189	35
	Week 30	210	189 – < 231	42
	Week 36	252	231 – < 273	42
	Week 42	294	273 – < 315	42
	Week 48	336	315 – < 350	35
	Week 52	364	350 – < 371	21
Follow-up Period (for subjects not entering Part B)	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 subject 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

13.6.1. Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject 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

When the start date and the stop date are both incomplete for a subject, impute the start date 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.

- Missing Day and Month
  - If the year of the incomplete start date is the same as the year of the date of Study Day 1, then the day and month of the date of Study Day 1 will be assigned to the missing fields
  - If the year of the incomplete start date is before the year of the date of Study Day 1, 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 Study Day 1, then 01 January will be assigned to the missing fields.
- Missing Month Only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- 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 Study Day 1, then the day of the date of Study Day 1 will be assigned to the missing day
  - If either the year is before the year of the date of Study Day 1 or if both years are the same but the month is before the month of the date of Study Day 1, 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 Study Day 1 or if both years are the same but the month is after the month of the date of Study Day 1, 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.

- 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.
- Missing Month Only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- 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, e.g. 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 (i.e., 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 subject, 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 used 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.

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. In addition, pharmacokinetic analyses will be performed using Phoenix WinNonlin version 6.2 or higher (Pharsight Corporation, Mountain View, California, USA).

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

16. REFERENCES