STATISTICAL ANALYSIS PLAN
APL-2
PHASE II

A Phase 2 Study to Evaluate the Safety and Biologic Activity of APL-2 in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease)

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I confirm that I have reviewed this document and agree with the content.

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AH50	Complement alternative pathway assay
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
C3G	C3 Glomerulopathy
CKD	Chronic Kidney Disease
dsDNA	Double-stranded DNA (deoxyribonucleic acid)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FSH	Follicle stimulating hormone
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
Hib	Haemophilus influenza Type B
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
IgAN	Immunoglobulin A Nephropathy
MedDRA	Medical Dictionary For Regulatory Activities
MN	Membranous Nephropathy
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PI	Primary Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
QTcB	QT Interval Corrected For Heart Rate Using Bazett's Formula
QTcF	QT Interval Corrected For Heart Rate Using Fridericia's Formula
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMC	Safety Monitoring Committee
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment-Emergent Adverse Event
uPCR	Urine protein to creatinine ratios
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes detailed statistical methods to be used for analysis and data presentation for reporting safety and biologic activity data of investigational infusion of APL-2 for Apellis study protocol APL2-201 for Part B only.

The planned length of participation in the study Part A (Core Study Phase) for each subject is 76 weeks, including an approximate 4-week screening period, 48-week treatment period and 24-week follow-up period. Following Day 336 and the completion of Part A, any subject who, in the opinion of the investigator, is experiencing clinical benefit from APL-2 administration will be invited to participate in Part B, a Long-Term Extension Phase in order to continue to receive treatment with APL-2 until it is commercially available for the disease under treatment. If invited to participate in Part B, the subject can enter the Long-Term Extension Phase as soon as they complete the 48-week treatment period and do not need to participate in the 24-week follow-up period.

Statistical Analysis Plan Version 1.0 was used to produce the Part A (Core Study Phase) analysis. This SAP will present the results for the final analysis for subjects who rolled over into Part B, presenting the safety and efficacy results of Part B (Long-Term Extension Phase) and Part A + B as Part B subjects in Part B data and as well as Part A data. Definitions for the study days and baselines are outlined in Section 13. This document has been prepared according to study protocol amendment 7.0 dated 07 July 2022.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objectives of this study are to establish preliminary efficacy and safety of APL-2 in patients with complement-mediated glomerulopathies: Immunoglobulin A Nephropathy (IgAN), Lupus Nephritis (LN), C3G (C3 Glomerulopathy)

2.1.1. Efficacy Endpoints

- Proteinuria reduction over time based on urinary protein to creatinine ratio (uPCR)
- Change and % change from baseline in disease specific biomarkers over time:
    - Complement biomarkers (Serum C3, C3a, C4, C5a, AH50 and CH50, Plasma sC5b-9)
    - Serum albumin levels
- Complete clinical remission: defined as normalization of proteinuria as defined by <200 mg/g uPCR over time
- Stabilization or improvement in eGFR over time: defined as no more than a 25% decrease relative to baseline
- Changes and percentage changes from baseline in eGFR over time
- Time to the composite clinical outcome (first occurrence of any of the following: sustained doubling of serum creatinine, chronic kidney disease [CKD] stage 5, end-stage renal disease [ESRD], Kidney transplantation, or death from renal or cardiovascular causes)

2.1.2. Pharmacokinetic Endpoints

- APL-2 pharmacokinetic concentrations

2.1.3. Pharmacodynamics Endpoints

- Immunogenicity: Presence of auto-antibodies to PEG and APL-2 throughout treatment and follow up periods

2.1.4. Safety Endpoints

- Physical Examination; Incidence and severity of Adverse Events (AE).
- Changes from baseline in laboratory parameters.
- Changes from baseline in ECG parameters.

3. STUDY DESIGN

3.1. Overview of Study Design

This is a prospective Phase 2 study, consisting of a single cohort with a total of approximately 48 patients among the 4 disease groups. This is an open label study, with 48 patients clinically diagnosed with IgAN, LN, Primary MN, or C3G (with 6-12 patients per disease). Each clinical diagnosis must be confirmed by renal biopsy prior to dosing with APL-2. Subject participation will include a Part A Core Study Phase that consists of an approximate 4-week screening period, 48-week treatment period, and 24-week safety follow-up. During the treatment period, patients will receive subcutaneous (SC) once daily infusions of 360 mg APL-2. Following the completion of 48-week treatment period in Part A Core Study Phase, if invited, subjects may participate in Part B, the Long-Term Extension Phase, in order to continue to receive treatment with APL-2 until it is commercially available for the disease under treatment. If they are invited to participate in Part B, they do not need to complete the 24-week follow-up period.

For each disease group, patients whose underlying renal disease is stable for at least 2 months prior to the first dose may enter the study. In this trial, stable renal disease should include stable eGFR, proteinuria and blood pressure, as well as a stable and optimized treatment regimen for their renal disease, in the opinion of the PI (See Protocol Section 10.1 for the complete detailed eligibility information). Upon completion of the screening period, patients who meet all of the inclusion and none of the exclusion criteria will begin the treatment phase of the study.
The treatment phase will consist of once daily, self-administered, SC dosing of 360 mg APL-2 at home, with the exception of all scheduled clinic visits. During scheduled Visit 4 only, the site staff will assist in administering the first SC dose of APL-2. At Visits 5-15, subjects will self-administer APL-2 in the presence of the site staff and undergo various safety and efficacy assessments by qualified site staff. Subjects may be switched over to twice weekly dosing as early as Week 24. Any subject who is invited to participate in Part B who has not already switched over to twice weekly dosing of 1080 mg, must do so at the beginning of Part B. If a subject transitions to the twice weekly dosing, they need to follow the dose transition visits (T1, T2, and T3) as outlined in Protocol Section 10.1, Table 2 (during Part A) or Protocol Section 18, Table 6 (for Part B). The change in proteinuria from baseline through the end of treatment will be assessed as the primary endpoint. Urinary PCR will be used to measure changes in proteinuria for the primary endpoint.

After completion of the 48-week treatment period, each subject will have the opportunity to enter Part B, the Long-Term Extension Phase, at the discretion of the investigator. If the subject does not enter Part B, he or she will enter a 24 week follow up period, consisting of 6 clinic visits at weeks 50, 52, 54, 60, 66, and 72 (Exit Visit). Various safety assessments will be undertaken during these clinic visits, and follow-up phone calls will be performed to gain relevant safety information. Patients will be maintained on their baseline treatment regimen during treatment and the follow-up period, as determined by the Principal Investigator (PI) in consultation with the medical monitor. During the study, changes to the baseline treatment regimen should be avoided to the extent possible and made only when required for the well-being of the patient, in the opinion of the PI.

Safety summaries will be presented over the screening period, 48 weeks of treatment and 24 weeks of follow-up, as well as the overall duration of the study.

An external, independent Safety Monitoring Committee (SMC) will assess the safety or tolerability data of the study.

Subject level discontinuation will occur for any subject who develops SAE due to infection confirmed to be caused by encapsulated organisms (see Protocol Section 8.3 for further information) or any subject with a sustained and significant reduction in renal function, as defined by one of the following: initiation of chronic dialysis, a confirmed and sustained eGFR ≤15 mL/min/1.73 m2 or a confirmed and sustained reduction in eGFR of at least 30% which is drug-related in the opinion in the PI. A reduction in eGFR would be considered confirmed if present on two separate consecutive measurements and sustained if the two measurements are at least 1 week or apart. Subject level discontinuation can also occur for any individual for whom the PI deems it in the best interest of the patient to not continue in the study. Disease Group level discontinuation will occur if two or more subjects in a particular disease group are discontinued by these criteria.

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened. The timeframe and scope of eligibility reassessment will be determined by the Sponsor. Any requests to rescreen an individual more than one time must be approved by the sponsor. For each rescreening, the individual must sign a new ICF and will be assigned a new identification number. Record of the subject's prior identification number and screening should be maintained with the source documents. Subjects who received vaccinations per protocol within two years of their rescreening date do not need to have the respective vaccination repeated but may do so at the discretion of the investigator.

3.2. Sample Size

Only those subjects who completed the 48-week treatment period and wiling to continue to receive treatment with APL-2 until it is commercially available for the disease under treatment, will be offered the opportunity to enter Part B, the Long-Term Extension Phase, at the discretion of the investigator.

4. STATISTICAL ANALYSIS SETS

4.1. Screened Population

The Screened Population will include all patients who signed the informed consent form, are screened for participation. This set will be used only for summaries of disposition from Part A through Part B and the end of study.

4.2. Safety Population/Intent-to-Treat (ITT) Population

Safety Set will only include the subjects who roll over to Part B and receive at least one dose of 1080 mg APL-2.

The definition of Intent-to-Treat (ITT) Population is the same as Safety Population. It will be used for efficacy endpoint analysis.

4.3. Per Protocol Population

The Per Protocol (PP) Population will only include subjects who were in the PP set in Part A and roll over to Part B and have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment while on study in Part B.

The PP Set will be used in efficacy analyses for Part B and Part A + B.

4.4. Pharmacokinetic Population

The Pharmacokinetic (PK) Population is defined as all subjects in the ITT Population who rolled over into Part B and have at least one evaluable post-dose PK measurement.

4.5. Pharmacodynamic Population

The Pharmacodynamic (PD) Population is defined as all subjects in the ITT Population who rolled over into Part B and have at least one evaluable post-dose PD measurement.

5. STUDY SUBJECTS

Unless otherwise specified, study subjects will be summarized by disease group for Part B and Part A + B. The disease groups are defined throughout as patients with IgAN, LN, or C3G. For subjects from the other disease group, all efficacy data will be listed in the listings.

5.1. Disposition of Subjects

The subject disposition will summarize All Screened Subjects from Screening prior to Part A through the end of Part B. The following disposition categories will be tabulated by disease group:

- Number of subjects screened
- Number of subjects who received at least one dose of APL-2 in Part A
- Number of subjects in the Part A PP set
- Number of subjects with ≥ 1 post-dose PK assessment in Part A
- Number of subjects with ≥ 1 post-dose PD assessment in Part A
- Number of subjects who completed Part A
- Number of subjects who withdraw from treatment during the Part A
- Reason for withdrawal from Part A treatment
- Number of subjects who completed Part A treatment but withdrew from study before entering Part B
- Reason for withdrawal from study before entering Part B
- Number of subjects who received at least one dose of APL-2 in Part B (Safety/ITT Analysis Set)
- Number of subjects in the Part B PP set
- Number of subjects with ≥ 1 post-dose PK assessment in Part B
- Number of subjects with ≥ 1 post-dose PD assessment in Part B
- Number of subjects who completed Part B
- Number of subjects who withdraw from study during the Part B
- Reason for withdrawal from Part B

5.2. Demographic and Other Baseline Characteristics

If the Safety Population is the same as the PP Population, then only results from Safety Population needs to be presented.

5.2.1. Demographic Characteristics at Part A+B Baseline

The demographic data will be summarized for the Safety Population and PP Population by disease group at Part A+B baseline including:

- Age at screening (years)
- Age in categories (≤65 years and > 65 years)
- Sex
- Race
- Ethnicity
- Weight (kg) at baseline
- Height (cm) at baseline
- Body Mass Index (BMI, kg/m2), defined as weight(kg)/(height(m))2

5.2.2. FSH, HIV, HCV or HBsAg Lab Tests at Part A+B Baseline

Number and percentage of subjects will be summarized for the following variables for the Safety Population by disease group at Part A + B baseline:

- FSH
- HIV
- HCV
- HBsAg

5.2.3. Baseline Disease Characteristics at Part A+B Baseline

Number and percentage of subjects will be summarized for the following variables for the Safety Population and PP Population by disease group at Part A + B baseline:

- uPCR from 24-hour urine
- Total protein from 24-hour urine
- Serum C3
- Serum Creatinine
- eGFR
- Serum albumin
- Serum albumin categories: < LLN and >= ULN
- Systolic Blood Pressure and Diastolic Blood Pressure
- Years since diagnosis
- C3G only: C3 nephritic factor (Part A only)
- LN only: anti-dsDNA (Listing only)
- IgAN only: Anti-GdIgA1 and anti-glycan

5.2.4. Vaccinations Received at Part A+B Baseline

Number and percentage of subjects who received vaccines at screening or within 2 years prior to Day -14 will be tabulated for Safety Population by disease group at Part A + B baseline:

- Within 2 years prior to Day -14
    - Neisseria meningitides types A, C, W, Y
    - Neisseria meningitidis type B
    - Streptococcus pneumoniae PSV23
    - Streptococcus pneumoniae PSV13
    - Haemophilus influenza Type B (Hib)
- Neisseria Meningitidis Vaccine/s administered during screening

5.3. Medical History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1. Summaries will be presented by System Organ Class (SOC) and Preferred Term (PT) with numbers and percentages for Safety Population by disease group at Part A + B baseline. 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.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest WHO Drug Dictionary version available. Medication will be presented by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with numbers and percentages by disease group for Safety Population. A subject who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification.

Prior and Concomitant medications will be analysed for Part B and Part A + B for Safety Population.

Prior medications are defined as those medications started prior to the administration of the first study drug.

Concomitant medications are defined as:

Part B: Any medication taken during Part B of the study. This can include prior medications that were taken continuously into Part B of the study. Concomitant medications taken in Part A but ended prior to Part B will not be considered as concomitant medications during Part B.

Part A + B: Any medication taken during Part A or Part B of the study. This can include prior medications that were continued into Part A and Part B of the study.

Hence medications started before receiving APL-2 but continuing after will be considered as both prior and concomitant medications.

The listing of medications will identify prior and concomitant medications for Part B and Part A + B.

In the summary tables, prior medication 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 ATC level 5 class. In cases of ATC level 2 classes or ATC level 5 classes with equal frequencies, medications will be sorted alphabetically.

Concomitant medications will be summarized using the Safety Population by disease group.

5.5. Exposure to Study Drug

The following parameters will be calculated and presented by disease group for Part B and Part A + B using the Safety Population:

- Total dose administered (mg)
- Duration of APL-2 dosing (days) (overall) defined as (last infusion date – first infusion date + 1)
- Duration of APL-2 dosing (days) for the 360 mg daily group / 1080 mg twice weekly group / 1080 mg every 3 days group defined as the sum of each period of the respective dosing group.
- Number and percentage of subjects who received at least one infusion
    - Number and percentage of subjects with all planned infusions administered
    - Number and percentage of planned bi-weekly infusions administered
    - Number and percentage of planned daily infusions administered
    - 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 all infusions administered as prescribed

If the investigator instructed the subject to stop taking study medication for a period of time, e.g. due to an adverse event, then this period will not be included in the denominator for the exposure calculation.

5.6. Measurements of Treatment Compliance

Percent compliance by dose regimen and dose frequency (360 mg daily, 1080 twice weekly, and/or 1080 mg every 3 days) will be calculated for Part B and Part A + B, by disease group using the Safety Population as follows:

$$\textbf{Part A Compliance}\ (\%) = \frac{\textbf{number of completed study doses administered during Part A}}{\textbf{total number of expected study doses during Part A}} \times \mathbf{100}$$

Unless otherwise noted, during the Part A, the number of expected doses is the number of days during Part A for subjects that did not roll over into Part B. For subjects that rolled over into Part B, the expected number of doses is the number of days during Part A minus 1 to account for the skipped dose prior to the dose transition.

$$\textbf{Part B Compliance}\ (\%) = \frac{\textbf{number of completed study doses administered during Part B}}{\textbf{total number of expected study doses during Part B}} \times \mathbf{100}$$

That is, when subjects receive twice weekly dosage, percentage compliance will be calculated as:

$$\textbf{Compliance}\ (\%) = \frac{\textbf{actual number of completed study doses administered}}{(\boldsymbol{last\ dose\ date - first\ dose\ date} + 3.5)/7) \times 2} \times \mathbf{100}$$

When subjects receive every 3 days dosage, percentage compliance will be calculated as:

$$\textbf{Compliance}\ (\%) = \frac{\textbf{actual number of completed study doses administered}}{(\boldsymbol{last\ dose\ date - first\ dose\ date})/3 + 1} \times \mathbf{100}$$

Part A + B compliance will be calculated as:

$$\textbf{Part A + B Compliance}\ (\%) = \frac{\textbf{number of completed study doses administered during Part A} + \textbf{number of completed study doses administered during Part B}}{\textbf{total number of expected study doses during Part A} + \textbf{total bumber of expected study doses during Part B}} \times \mathbf{100}$$

If the investigator instructed the subject to stop taking study medication for a period of time, e.g. due to an adverse event, then this period will not be included in the denominator for the compliance calculation.

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 then be presented in a table by disease group.

By-subject listings will be produced for treatment compliance and exposure.

5.7. Protocol Deviations

All protocol deviations will be reviewed and documented before database lock. Protocol deviations will be recorded by the site staff separately from the clinical database. They may also be identified through programmable checks of the data.

Key protocol deviations include any violations of inclusion and exclusion criteria. This includes unknown violations at enrollment and on-study violations, such as taking a prohibited medication.

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.

Number and percentage of subjects with protocol deviation will be tabulated by importance of deviation for Part B and Part A + B, and by disease group for the Safety Population.

6. EFFICACY ANALYSES

Unless otherwise stated, all efficacy analyses will be summarized per disease groups (C3G and IgAN) by analysis visit (see Section 13.4). For subjects from the other disease group, all efficacy data will be listed in the listings.

No formal inferential statistics will be applied to data collected in the study.

The following plots with (±SE) error bars will be provided for primary and secondary efficacy endpoints outlined below over time based on the analysis visit (see Section 13.4) per disease group:

- Mean with individual subject plots overlaid
- Percentage change from baseline with individual subject plots overlaid

Where applicable, the area for ULN and LLN will be shaded on each graph. Also, the number of subjects contributing to each mean value at a visit will be presented above the x-axis.

In addition, plot with (±SE) error bars will also be provided for percentage change in mean uPCR.

The primary and secondary efficacy endpoint analyses will be performed for both the ITT Population and Per Protocol Population. Exploratory analysis will only be performed for the ITT Population. In addition, when ITT Population is the same as Per Protocol Population, data will only be presented by ITT Population.

Change from baseline are defined as change from Part B baseline and change from Part A + B baseline, which are:

Part A + B baseline: baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug in Part A (Study Day 1). Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

Part B baseline: baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug during Part B.

For categorical data, proportions will be based on the number of subjects who have the opportunity to be assessed at that visit.

6.1. Analysis of Primary Efficacy Endpoints

Changes from Part A + B baseline and Part B baseline in proteinuria (24 Hour Urine Collection and mean of triplicate uPCR), percentage changes from Part A + B baseline and Part B baseline in proteinuria will be summarized by visits and by disease groups for both the ITT Population and the Per Protocol Population.

6.2. Analysis of Secondary Efficacy Endpoints

Changes from Part A + B baseline and Part B baseline and percentage change from Part A + B baseline and Part B baseline will be summarized in the same fashion with the primary efficacy endpoints for following endpoints:

- eGFR
- Complement biomarkers including serum C3, C3a, C4, C5a, AH50, CH50, and sC5b-9 (see Section 9.1)
- Serum albumin

Additional disease parameters and/or biomarkers may also be analyzed.

eGFR will be calculated using CKD-EPI (2021) formula as:

$$\text{eGFR} = 141 \text{ x } \min(\text{SCr}/\text{K}, 1)^{a} \text{ x } \max(\text{SCr}/\text{K}, 1)^{-1.209} \text{ x } 0.993^{Age} \text{ x } 1.018 \text{ [if female]x } 1.159 \text{ [if black]}$$

where SCr is standardized serum creatinine in mg/dL, K is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males.

In addition, stabilization or improvement in eGFR from baseline, which is defined as GFR no more than 25% less than the baseline, will be tabulated by analysis visit including the following categories:

- Stable GFR: no more than 25% (+/-) change
- Improvement in GFR: >25% increase
- Worsening of GFR: >25% decrease
- Stabilized or Improved eGFR: <=25% decrease

Complete clinical remission, defined as normalization of proteinuria as defined by < 200 mg/g uPCR, will be tabulated by visit.

In addition, a responder analysis summarizing those patients with uPCR < 500 mg/g by each visit will be provided as well as a responder analysis by visit summarizing those patients with a uPCR reduction from baseline by 30% and 50%. However, subjects who have missing data, or have taken prohibited med, or received dialysis or renal transplant will be identified as non-responder.

6.3. Analyses of Exploratory Endpoints

Changes and percentage of changes from Part A + B baseline and Part B baseline will be summarized by visits using both the ITT Population and PP Population for the following disease specific biomarkers:

- IgAN: autoantibodies to Gd-IgA1 and antiglycan antibodies
- LN: autoantibodies to dsDNA, C3 and C1q (listing only)
- C3G: C3 nephritic factor (C3NeF)

Additional disease parameters and/or biomarkers may also be analyzed.

Finally, the time to the composite clinical outcome will be summarized by disease group using Kaplan-Mier (KM) method. The detail of definition and search criteria is provided in the following table:

Composite clinical outcome category	Definition	Search criteria
Doubling of serum creatinine	Doubling of the serum creatinine level from Part A baseline sustained for at least 30 days	Search post-baseline creatinine that is twice of Part A baseline, and the following assessment that is >=30 days away and is also twice of baseline; if 2nd assessment is missing but the subject discontinues treatment after 1st doubling creatinine, this is also counted as an event. Any local lab can also be used for confirmation. Only assessments on or before treatment discontinuation will be used.
Disease progression	Treatment discontinued due to disease progression	Search treatment discontinued reason due to disease progression
Progression to chronic kidney disease stage 5	An estimated GFR of <15 ml per minute per 1.73 m2 confirmed by a second measurement after ≥30 days	Search for eGFR<15/min/1.73m2, and the following assessment that is >=30 days away and is also<15/min/1.73m2; if 2nd assessment is missing but the subject discontinues treatment then it is also counted as an event. Any local lab can also be used for confirmation. Only assessments on or before treatment discontinuation will be used.
End-stage renal disease	Onset of end-stage kidney disease (defined as maintenance dialysis for ≥30 days)	Search concomitant procedure for dialysis and check (End Date-Start Date)>=30
Kidney transplantation	Kidney transplantation	Search concomitant procedure for transplantation
Death	Death from renal or cardiovascular causes	Search death with cause related to renal or cardiovascular

7. SAFETY ANALYSIS

Safety endpoints include AEs, clinical laboratory variables, vital signs, ECG variables including ECG interpretation, and physical examination.

Unless otherwise specified, all safety analysis will be performed by disease group (IgAN and C3G), according to the treatment the subject actually received using the Safety Population. For subjects from the other disease group, all safety data will be only listed in the listings.

All data will be presented for Part B and Part A + B. Change from baseline is defined as change from Part B baseline and change from Part A + B baseline.

For categorical data, proportions will be based on the number of subjects who have the opportunity to be assessed at that visit.

7.1. Adverse Events

Adverse events (AEs) will be coded using the most recent version of MedDRA.

Severity of AEs will be assessed and classified into mild, moderate, severe, life-threatening or death by investigators. Handling rules for missing severity of AEs are described in Section 13.6.4.

Treatment emergent adverse events (TEAEs) are defined as those AEs that develop or worsen after the first dose of study medication and up to 56 days beyond the last dose of study drug.

AEs are classified as related if AEs are definitely related, probably related or possibly related to study drug; Any AEs with missing or unknown relationship will be considered as related to study drug.

All summaries of AEs described in this section will be on TEAEs. All summaries will be ordered by decreasing frequency of number of subjects in PT within SOC. In the case of equal frequency of number of subjects in SOCs or PTs, then summaries of AEs will be sorted alphabetically.

All summary tables will be presented for Part B and Part A + B, where AEs will be categorized by the Part in which the AE started, i.e. an AE which began during the Part A will be categorized under Part A even if it continues into Part B.

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

- TEAE
- APL-2-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 APL-2 withdrawn
- TEAE leading to dose interruption
- TEAE leading to death

The following summary will be provided by disease group for Part B and Part A + B:

- TEAEs by SOC and PT
- APL-2 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 APL-2 discontinuation by SOC and PT
- TEAE leading to dose interruption by SOC and PT
- TEAE leading to death by SOC and PT

If a SOC or PT was reported more than once for a subject, the subject would only be counted once in the incidence for that SOC or 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 following listings will be provided for the Safety Population:

- All AEs
- Serious Adverse Events
- AEs leading to study drug discontinuation
- AEs leading to study discontinuation
- Death
- APL-2 Related TEAEs
- Infusion-Related TEAEs

7.2. Clinical Laboratory Data

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

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 disease group.

Urinalysis categorical data will also be tabulated at each analysis visit by disease group, if applicable.

Shift table of normal, abnormal low and abnormal high from baseline by analysis visit will also be summarized for hematology and chemistry (including coagulation) data (scheduled or unscheduled) by disease. Denominator will be based on number of subjects who have non-missing baseline values.

All summary tables will be presented for Part B and Part A + B.

Clinical laboratory data will be listed by disease group. The listing will include changes from Part A + B and Part B baseline values and values that are outside the reference range will be flagged. Out of range laboratory results with their corresponding changes from baseline will also be listed.

In addition, liver abnormality will be summarized at each analysis visit including following variables by disease group:

- ALT or AST $\geq$ 3×ULN
- ALT or AST $\geq$ 3×ULN and (TBL >2×ULN or INR >1.5)
- ALT or AST $\geq$ 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 Table 1 below:

Table 1: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria Lower limit Higher limit
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
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

7.3. Vital Signs

Observed and change from baseline of vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature and body weight) will be summarized at each analysis visit by disease group. All summary tables will be presented for Part B and Part A + B.

Values and changes from Part A + B and Part B baseline values will be listed by disease group. In the listing, values of potential clinical importance will be flagged. These are defined in Table 2:

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 or ≥15 mm Hg decrease from baseline
Temp	≥ 38°C

7.4. Electrocardiogram (ECG)

For triplicate ECGs, the average value will be used.

Observed and changes from baseline for ECG variables (including heart rate (hr), PR interval, QRS interval, QT interval, QTcB and QTcF interval) will be summarized by analysis visit. QTc interval will be calculated using both Bazett (QTcB=QT/(RR)1/2) and Fridericia (QTcF=QT/(RR)1/3) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula.

ECG interpretation will be summarized at each analysis visit by disease group. Abnormality shift of normal, abnormal but not clinically significant and abnormal and clinically significant from baseline at each analysis visit will be presented. All summary tables will be presented for Part B and Part A + B.

Observed and changes from Part A +B baseline and Part B baseline values will be listed by disease group. In this listing, values of potentially clinically significant ECG (scheduled or unscheduled) will be flagged. These are defined in Table 3:

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

7.5. Physical Examination

Physical examination will be listed only.

8. PHARMACOKINETIC ANALYSIS

8.1. Drug Concentration

The observed values of APL-2 concentrations will be evaluated using the PK population. APL-2 concentrations will be summarized by disease groups at each scheduled time point using descriptive statistics. Moreover, APL-2 concentrations will be summarized by disease groups (if at least 2 subjects within a particular disease group) and dose groups at each scheduled time point using descriptive statistics. In addition, APL-2 concentrations will be summarized by dose groups across all patients at each scheduled time point using descriptive statistics (including at least mean, SD, CV, Min, Max, Geometric Mean/%CV). The number of subjects with a BLQ value will also be tabulated. The handling of BLQ in the summary table is described in Section 8.2.

Linear and log-linear individual concentration profile plots against the actual study visit will be produced by disease group with each subject being identifiable by disease group.

Linear and log-linear Mean (± SE) concentration plots against the actual study visit will be generated by disease group. The number of subjects contributing to each median value at a visit will be presented above the x-axis.

A listing of concentration data will be presented by disease group and dose. The actual time, deviation, and percent deviation from nominal time will be listed.

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Population defined in Section 4.4.

8.2. Handling BLQ Values

APL-2 concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

Population PK and PD Modelling

In addition to the analyses outlined above, all PK and complement marker (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.

9. PHARMACODYNAMIC ANALYSIS

9.1. Pharmacodynamic Data

The PD endpoints will be evaluated using the PD Population.

Observed values, changes from baseline and percentage changes from Part A + B baseline and Part B baseline in C3, C3a, C4, C5a, AH50, CH50, and sC5b-9 will be summarized by disease group at each protocol specified time point using descriptive statistics for Part B and Part A + B. Moreover, this summary of PD parameters will be repeated by disease groups (if at least 2 subjects within a particular disease group) and dose groups at each scheduled time point using descriptive statistics for Part A and Part B. In addition, the above PD parameters will be summarized by dose group across all patients at each scheduled time point using descriptive statistics for Part B and Part A + B.

Individual observed values and individual changes from Part A + B baseline and Part B baseline will be presented graphically for each disease group. Actual sampling times will be used for the graphical presentation of individual data.

The mean (± SE) of the observed values, mean changes from Part A + B baseline and Part B baseline, and mean percentage changes from baseline will also be presented graphically by disease group. 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 group.

10. OTHER ANALYSES

10.1. Immunogenicity

This data will be summarized in listing(s).

11. INTERIM ANALYSIS

No interim analyses are planned.

12. SAFETY MONITORING COMMITTEE/REVIEW COMMITTEE

No SMC are planned for Part B.

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, minimum and maximum. Mean 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.

In general, all analyses will be performed for Part B and Part A + B unless otherwise specified. Subject specific listings will be provided by disease group, subject ID, Study Part and visit, if applicable.

13.2. Definition of Study Days

Part A + B: Study Day 1 for Part A + B will be the day a subject takes the first dose of APL-2, which will be calculated as:

For events that occurred on the day of or after administration of the first APL-2 dose:

Part A + B Study Day = visit date – date of first APL-2 dose + 1

For events that occurred on days before administration of the first APL-2 dose:

Part A + B Study Day = visit date – date of first APL-2 dose

Part B: Study Day 1 for Part B will be the day of first 1080 mg APL-2 dose during Part B, which will be calculated as:

For events that occurred on the day of or after administration of the first 1080 mg APL-2 dose in Part B:

Part B Study Day = visit date – date of first 1080 mg APL-2 dose + 1

For events that occurred on days before administration of the first 1080 mg APL-2 dose in Part B:

Part B Study Day = visit date – date of first 1080 mg APL-2 dose

13.3. Definition of Baseline

Part A + B baseline: baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug in Part A (Study Day 1). Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

Part B baseline: baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug during Part B.

13.4. Definition of Visit Windows

Data will be summarized and analyzed based on the list of visits specified in the schedule of assessments of the protocol. All the records post-baseline will be assigned to an appropriate analysis visit using the following:

- For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits.
- If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit.
- If the interval separating 2 scheduled visits is an even number of days, the middle day will be included in the lower bound of the next visit.
- If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis.
- If 2 records are tied before and after the middle of the interval, the earlier record will be used in the analysis.

13.4.1. Analysis Window for 24-hour Urine Collection

Part A + B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Core Study Phase (Part A)	4	Day 1	1	1	1
	15	Week 48	336	2 - < 343	14

Part B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Long-Term Extension Phase (Part B)	15	Day 1	1	1	1
	17	Week 24	168	2 - < 252	251
	19	Week 48	336	252 - < 420	168
	21	Week 72	504	420 - < 588	168
	…	…	…	…	…

13.4.2. Analysis Window for Consecutive Spot uPCR

Part A + B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Core Study Phase (Part A)	3a	Week -4	-28	< -21	NA
	3b	Week -2	-14	-21 - 0	21
	4	Day 1	1	1	1
	5	Week 2	14	2- < 21	19
	6	Week 4	28	21 - <35	14
	6a*	Week 6	42	35 - < 49	14
	7	Week 8	56	49 - < 63	14
	7a	Week 10	70	63 - < 77	14
	8	Week 12	84	77 - < 91	14
	8a	Week 14	98	91 - < 105	14
	9	Week 16	112	105 - < 119	14
	9a	Week 18	126	119 - < 133	14
	10	Week 20	140	133 - < 147	14
	10a	Week 22	154	147 - < 161	14
	11	Week 24	168	161 - < 175	14
	11a	Week 26	182	175 - < 189	14
	11b	Week 28	196	189 - < 203	14
	12	Week 30	210	203 - < 217	14
	12a	Week 32	224	217 - < 231	14
	12b	Week 34	238	231 - < 245	14
	13	Week 36	252	245 - < 259	14
	13a	Week 38	266	259 - < 273	14
	13b	Week 40	280	273 - < 287	14
	14	Week 42	294	287 - < 301	14
	14a	Week 44	308	301 - < 315	14
	14b	Week 46	322	315 - < 329	14
	15	Week 48	336	329 - < 343	14

Part B:

When Transition Visits in Part A:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Long-Term Extension Phase (Part B)	15	Day 1	1	1	1
	15a	Week 6	42	2 - < 63	62
	16	Week 12	84	63 - < 105	42
	16a	Week 18	126	105 - < 147	42
	17	Week 24	168	147 - < 189	42
	17a	Week 30	210	189 - < 231	42
	18	Week 36	252	231 - < 273	42
	18a	Week 42	294	273 - < 315	42
	19	Week 48	336	315 - < 357	42
	…	…	…	….	42

When Transition Visits in Part B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Long-Term Extension Phase (Part B)	15	Day 1	1	1	1
	T1	Week 1	7	2 - < 11	9
	T2	Week 2	14	11 - < 21	10
	T3	Week 4	28	21 - < 35	14
	15a	Week 6	42	35 - < 63	28
	16	Week 12	84	63 - < 105	42
	16a	Week 18	126	105 - < 147	42
	17	Week 24	168	147 - < 189	42
	17a	Week 30	210	189 - < 231	42
	18	Week 36	252	231 - < 273	42
	18a	Week 42	294	273 - < 315	42
	19	Week 48	336	315 - < 357	42
	…	…	…	….	42

* "a" in Study Visit is added based on schedule of assessment in protocol.

13.4.3. Analysis Window for Other Endpoints

Part A + B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Core Study Phase (Part A)	3a	Week -4	-28	< -21	NA
	3b	Week -2	-14	-21 - 0	21
	4	Day 1	1	1	1
	5	Week 2	14	2- < 21	19
	6	Week 4	28	21 - < 42	21
	7	Week 8	56	42 - < 70	28
	8	Week 12	84	70 - < 98	28
	9	Week 16	112	98 - < 126	28
	10	Week 20	140	126 - < 154	28
	11	Week 24	168	154 - < 189	35
	12	Week 30	210	189 - < 231	42
	13	Week 36	252	231 - < 273	42
	14	Week 42	294	273 - < 315	42
	15	Week 48	336	315 - < 343	28

Part B:

When Transition Visits in Part A:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Long-Term Extension Phase (Part B)	15	Day 1	1	1	1
	16	Week 12	84	2 - < 126	125
	17	Week 24	168	126 - < 210	84
	18	Week 36	252	210 - < 294	84
	19	Week 48	336	294 - < 378	84
	…	…	…	….	84

When Transition Visits in Part B:

Part	Study visit	Mapped visit	Target day	Analysis window	Interval
Long-Term Extension Phase (Part B)	15	Day 1	1	1	1
	T1	Week 1	7	2 - < 11	10
	T2	Week 2	14	11 - < 21	10
	T3	Week 4	28	21 - < 56	35
	16	Week 12	84	56 - < 126	70
	17	Week 24	168	126 - < 210	84
	18	Week 36	252	210 - < 294	84
	19	Week 48	336	294 - < 378	84
	…	…	…	….	84

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 is 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 Dates Information for Prior or Concomitant Medications

For the purposes of determining prior and concomitant medications, if a partial date is recorded, the following convention will be used to assign the medication dates:

- If a start date is missing the day information and month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing the month and the year is the same as first dose date then use first dose date, else January will be used for the start month.
- If a stop date is missing the day information and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the month and year is the same as last study date then use last study date, else December will be used for the stop month.

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 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.
- 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 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.

- 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 the first dose of investigational product, then a severity of "Mild" will be assigned.
- If the severity is missing for an AE starting on or after the date of the first dose of investigational product, 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 the first dose of investigational product, a causality of "Related" will be assigned.

13.6.6. Detectable Limits of Clinical Laboratory Variables

Lab results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics. Original values will be listed.

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 ANALYSES

15.1. Changes to Analyses Specified in the Protocol

Not applicable.

15.2. Changes from Analyses Specified in the Previous Version of the SAP

Statistical Analysis Plan Version 1.0 was used to produce results for the Part A (Core Study Phase). This SAP is used to present the safety and efficacy results for Part B (Long-Term Extension Phase). Since there were no specified objectives and endpoints defined in the protocol for Part B, modified endpoints from the Part A are used for Part B analysis.

16. REFERENCES

Not applicable.