

This supplement contains the following items:

1. Original protocol (V5.0 – previous versions were for ORIGIN 2b only), final protocol, and summary of changes.
2. Original statistical analyses plan, final statistical analysis plan (ex-US/US), summary of changes.



Clinical Study Protocol

Clinical Study Protocol Title:	A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)
Protocol Number:	VT-001-0050
Short Title:	Atacicept in Subjects with IgA Nephropathy (ORIGIN and ORIGIN 3)
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Vera Therapeutics Name and Contact Information:	
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Important Clinical Study Note

It is important to note to all study investigators, regulators, competent authorities, ethics committees, institutional review boards, scientific committees, site staff, clinical research organizations, and individuals involved in the review or conduct of this study that the design of this protocol is a multi-part study as described below. Some study sites and countries will be participating in the Phase 2b component only, the Phase 3 component only, or both components.

This is a multi-part study comprising of the original Phase 2b study (Parts A and B) and the addition of a separate Phase 3 study (Parts C and D). The Phase 3 study has been added as a separate component to the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from the Phase 2b study have been used to inform the Phase 3 study design including selection of dose and determination of sample size.

The Phase 2b study is referred to as ORIGIN and the Phase 3 study is referred to as ORIGIN 3.

To ensure clarity, this protocol is organized by study phase, as outlined below. The study phase-specific background information and procedures are kept distinctly within these sections.

1) Phase 2b:

- a) Synopsis: Pages [12](#) through [24](#)
- b) Protocol: Sections [1](#) through [9](#)

2) Phase 3:

- a) Synopsis: Pages [95](#) through [109](#)
- b) Protocol: Sections [11](#) through [19](#)

Key differences between the Phase 2b and Phase 3 studies are summarized in Section [10](#) and [Appendix 4](#).

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Phase 2b Study (ORIGIN)

- 1) Synopsis: Pages 12 through 24
- 2) Protocol: Sections 1 through 9

Ph2b (ORIGIN) Protocol Synopsis

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Rationale: Atacicept (also known as VT-001) targets B-cells by inhibiting B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), and has been studied in a pilot Phase 2a clinical study for immunoglobulin A (IgA) Nephropathy (IgAN). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and galactose-deficient IgA1 (Gd-IgA1), and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. Based on the available clinical data, the targeted population for this Phase 2b study component is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of renin-angiotensin-aldosterone system inhibition (RAASi) with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). The objectives of the study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN. An additional objective of the Phase 2b study is to determine the appropriate dose(s) for further clinical development.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 24
Secondary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	UPCR ^a	Week 36
Exploratory		
Evaluate the effect of atacicept on change in proteinuria in adult subjects with IgAN	UPCR ^a	Weeks 12, 48 and 96
Evaluate the effect of atacicept on rate of change in estimated glomerular filtration rate (eGFR)	Rate of change in eGFR ^b	Weeks 12, 24, 36, 48 and 96
Evaluate the effect of atacicept on change in serum immunoglobulin levels, complement levels and on serum Gd-IgA1 levels	IgA, IgG, IgM levels, C3 and C4 levels Gd-IgA1 levels	Weeks 12, 24, 36, 48, 96 and Follow Up Weeks 12 and 26
Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, adverse events	Entire study
Evaluate serum PK of atacicept	Serum concentration of atacicept	Entire study

AEs=adverse events; eGFR=estimated glomerular filtration rate; Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin; IgAN=immunoglobulin A Nephropathy; PK=pharmacokinetic; UPCR=urine protein to creatinine ratio.

^a Based on 24-hour urine sample

^b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults

Overall Design: This Phase IIb study is a multicenter, randomized, double-blind, placebo-controlled study. Subjects will be randomized 2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 75 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 25 mg once weekly subcutaneous (SC) injections (N=15)
- Placebo-to-match once weekly subcutaneous (SC) injections (N=30)

The study is composed of a (up to) 4-week Screening Period, a 36-week Blinded Treatment Period (Part A), followed by a 60-week Open-Label Extension (OLE) Period (Part B), and a 26-week Safety Follow-up (FU) Period. Upon completion of the 36-Week Blinded Treatment Period,

including attendance at Weeks 24 and 36 Visits for key study assessments, all subjects will be offered open-label atacicept 150 mg for an additional 60 weeks. At the Week 36 Visit after completion of all study visit assessments, subjects will switch from double-blinded treatment to open-label treatment. Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination (ET) Visit and have a 26-week follow-up period. After the last subject completes the Week 36 Visit or completes an Early Termination Visit, the study will be unblinded. The study will be conducted on an outpatient basis.

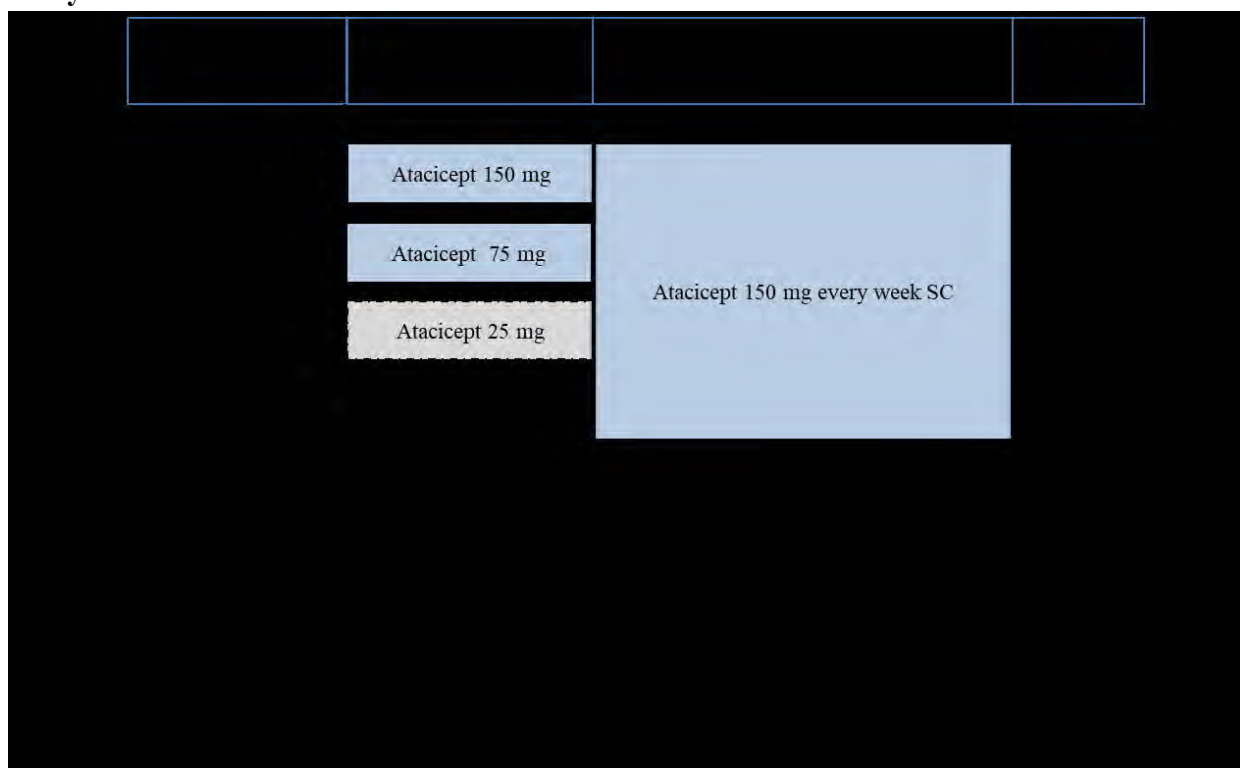
At selected sites, a subgroup of subjects (approximately 32 subjects, with 8 subjects per each Part A treatment arm) enrolled will have additional PK sampling visits that will be done at Day 2 and/or Day 3, approximately 24 and 48 hours after the first dose, respectively.

Number of Study Sites: Approximately 90 sites globally

Number of Subjects: Approximately 105 randomized

Involvement of Special Committee(s): An independent Data Monitoring Committee (iDMC) will review safety data on an ongoing basis.

Study Schema*



*For Czech Republic only, additional visits were conducted at Week 1 and Week 37.

*For Germany only, additional visits were added at Week 1 and Week 3.

Target Population: Male or female with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose.

Duration of Study Drug Treatment: Up to 96 weeks (36 weeks blinded + 60 weeks OLE)

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

- 1 Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
- 2 Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
 - For the Czech Republic an age limit of ≤ 70 also applies
- 3 Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit
- 4 Total urine protein excretion $>0.75\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCR) $>0.75\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
- 5 $\text{eGFR} \geq 30\text{ mL/min/1.73 m}^2$ at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- 6 On a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose at screening
 - The subject is eligible if they do not tolerate RAASi, provided their management of IgAN is standard of care (SoC) according to local guidelines. This must be documented by the Investigator.
- 7 Systolic blood pressure $\leq 150\text{ mmHg}$ and diastolic blood pressure $\leq 90\text{ mmHg}$ at screening
- 8 A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

Exclusion Criteria:

- 1 IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis
- 2 Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
- 3 Evidence of nephrotic syndrome within 6 months of screening (serum albumin $<30\text{g/L}$ in association with UPCR $>3.5\text{ mg/mg}$)
- 4 Total urine protein excretion $\geq 5\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCR) $\geq 5\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
- 5 Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants
- 6 Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
- 7 Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $>7.5\%$ at screening
- 8 History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

9 Prohibited medications:

- Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.

- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 3 months prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for > 1 week or 0.5 mg/kg/day prednisolone or equivalent
 - Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time
 - Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics
- 10 Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:
- serum IgG below 7 g/L
 - aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN
 - i. If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
 - For The Czech Republic only, the following criteria also apply:
 - hemoglobin <10 g/100 mL in men and hemoglobin <9 g/100 mL in women
 - platelets <100,000/L mm
- 11 Administration of live and live-attenuated vaccinations within 30 days prior to randomization
- 12 History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
- 13 Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
- 14 Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
- 15 Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.

- For Germany only, the following criteria also apply:
Specifically for COVID-19: Evidence of positive test for SARS-CoV-2, by PCR, at the Screening Visit; Subjects with a previous COVID-19 infection may be included provided the PCR test is negative for SARS-CoV-2 and they do not have chronic symptoms as a result of COVID-19. COVID-19 testing may be performed at local lab, per site/local guidelines.
- 16 History of acute or chronic infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus.
- Positive hepatitis B surface antigen (HBsAg): Subjects who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow-up
- 17 History of splenectomy
- 18 History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix
- For Germany only the following criteria apply:
History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).
- 19 Known hypersensitivity to atacicept or any component of the formulated atacicept
- 20 Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)
- Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)
- 21 Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
- 22 Unwillingness or lack of capacity to follow all study procedures
- 23 Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

Study Procedures/Frequency: Study visits will occur at Screening, Day 1, Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to

phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

There will be a 26-week follow up period after subject's end of treatment visit (EOT, Week 96). Subjects discontinuing study intervention early will require an Early Termination Visit within 10 days of the last dose and continue safety follow up for 26 Weeks from the ET visit. Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 1](#)).

Test Product, Dose, Mode of Administration, and Reference Therapy: In a blinded fashion, 150 mg atacicept, 75 mg atacicept, 25 mg atacicept or placebo to match, given as once-weekly subcutaneous (SC) injections for 36 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept, given as once-weekly SC injections for 60 weeks by prefilled syringe. Subject must also be on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose. It is recommended that changes in RAASi medication be avoided for the duration of the study.

Statistical Methods: The Statistical Analysis Plan (SAP) will be developed and finalized before the database lock for the first interim analysis and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Any deviations from this plan will be noted in the final clinical study report.

All endpoints will be summarized using descriptive statistics. Statistical testing will be conducted for primary and secondary efficacy endpoints with no adjustments for multiple comparisons. For the purposes of this trial, a significance level of 0.05 will be utilized.

Sample size and power calculations

Sample size and power are estimated for the primary efficacy endpoint, change from baseline to Week 24 in natural log transformed UPCR. It is assumed that the absolute difference (placebo – active) in the mean ratio of Week 24 UPCR to baseline UPCR is 0.28. The geometric mean ratio of Week 24 UPCR to baseline for placebo is expected to be 0.88. The coefficient of variation is estimated as 0.594 (i.e., pooled log standard deviation [SD] of 0.55). The expected placebo response and study intervention effect size are based on the analysis of the phase 2 study for atacicept and placebo in IgAN and placebo responses seen in other large IgAN studies. Based on these assumptions, 25 subjects in the placebo group and a combined total of 50 subjects in the atacicept 75 mg and 150 mg groups sufficient to provide at least 80% power to detect a ratio of 1.47 when the ratio under the null hypothesis is 1 [PASS 2008: two-sided two Sample t-test for ratios, $\alpha=0.05$, coefficient of variation on the original scale is 0.594]. Adjusting for a 15% dropout rate, 30 subjects should be enrolled in each of the placebo, atacicept 75 mg, and atacicept 150 mg groups to ensure 25 subjects complete Week 24 in each of these groups. The sample size of 15 for the atacicept 25 mg group is chosen to provide preliminary safety and efficacy information and is not based on statistical considerations.

Planned Analyses

The primary analysis of UPCR will be performed after all subjects complete the Week 24 visit or prematurely discontinue from the study. An End of Part A analysis will be performed when all subjects complete the double-blind portion of the study or prematurely discontinue from the study. A final analysis will be conducted once all subjects complete the OLE or discontinue from the trial. Additional analyses may be conducted at the discretion of the Sponsor to plan future trials. The details of these analyses will be provided in SAP.

Analysis Sets

All randomized subjects receiving at least one dose of study intervention will be included in the Safety Analysis Set. Subjects in the Safety Analysis Set who have at least one post-baseline evaluation of UPCR will be included in the Full Analysis Set (FAS). Subjects in the FAS will be analyzed according to randomized treatment assignment and all efficacy analyses will be based on the FAS. Safety analyses will be based upon treatment actually received.

Primary and key secondary efficacy endpoint analysis

The primary analysis of proteinuria will assess UPCR data via a mixed-model repeated measures analysis. Change from baseline in natural log transformed UPCR will be the dependent variable. Effects for randomized treatment, natural log transformed baseline value, time, and treatment-by-time interaction will be included as independent fixed effects, and subject will be included as a random effect. The primary comparison will test the mean difference between the combined 75 mg and 150 mg atacicept groups versus the placebo group at Week 24. This statistical comparison will be based on linear contrasts of the Least Squares Means (LSMeans) estimated from this model. LSMean differences will be exponentiated to obtain the mean ratio. The key secondary endpoint comparison at Week 36 will be assessed similarly.

Other efficacy endpoint analyses

A mixed-model random coefficients analysis will be used to analyze the rate of change in eGFR. Estimated glomerular filtration rate (eGFR) will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for randomized treatment, baseline eGFR, time, and the treatment-by-time interaction.

A mixed-model repeated measures analysis (as described for the primary endpoint) will be used to analyze the mean change from baseline over time for IgA, IgG, IgM, C3, C4, and Gd-IgA1 levels using appropriate data transformations. Differences between the treatment groups at each study visit will be presented.

Safety endpoint analyses

All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

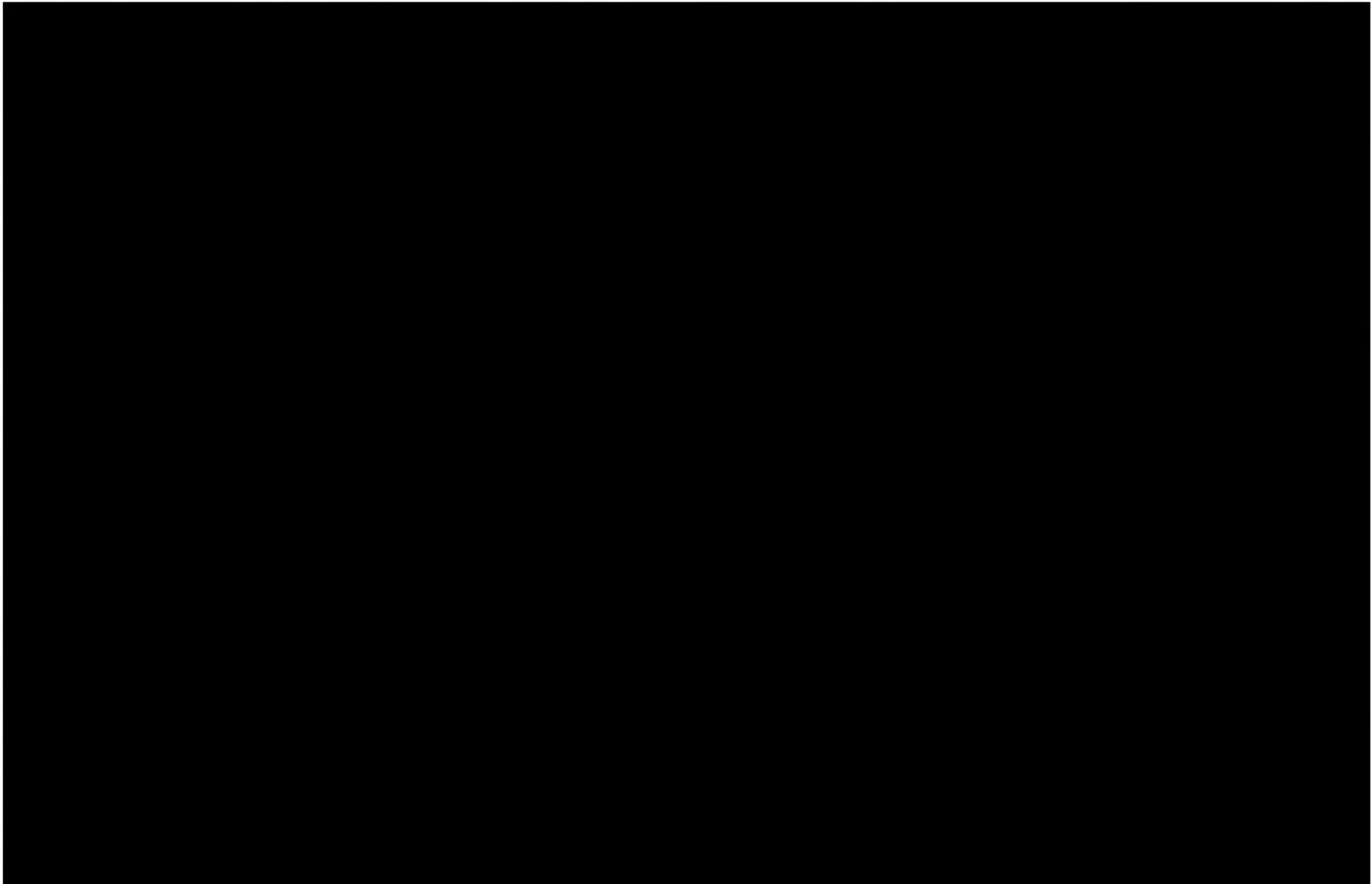
Blinding and unblinding considerations

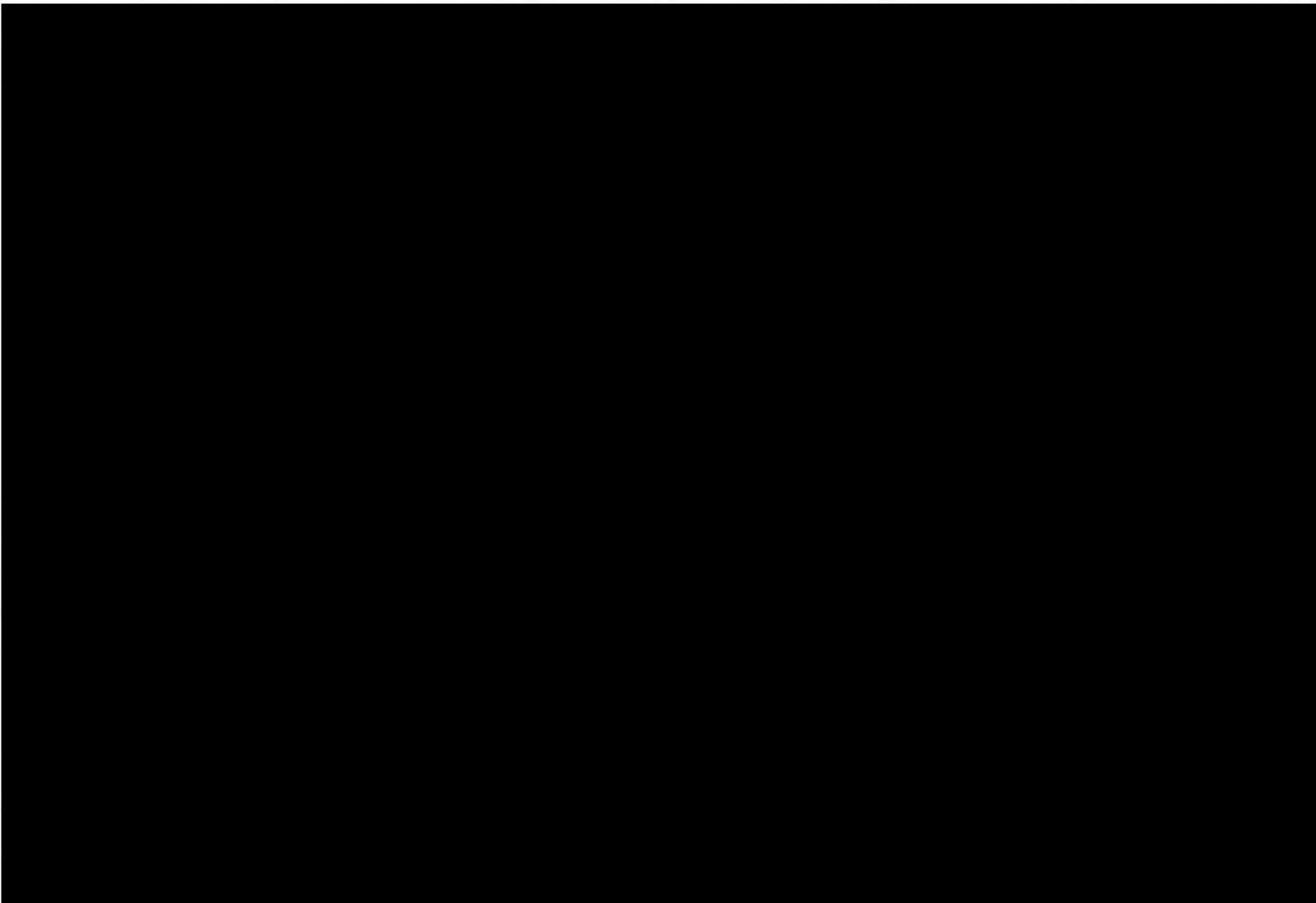
Subjects will be randomly assigned based on a predefined randomization code via the interactive web response system (IWRS) at the Day 1/Randomization visit. The site staff, Sponsor, and contract research organization (CRO) will be blinded to the subject's treatment allocation, with the exception of the selected study drug supply, and serious adverse event (SAE) reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of analysis of the primary endpoint. For emergency unblinding only, corresponding treatment assignments will be made available to the Investigator through the IWRS.

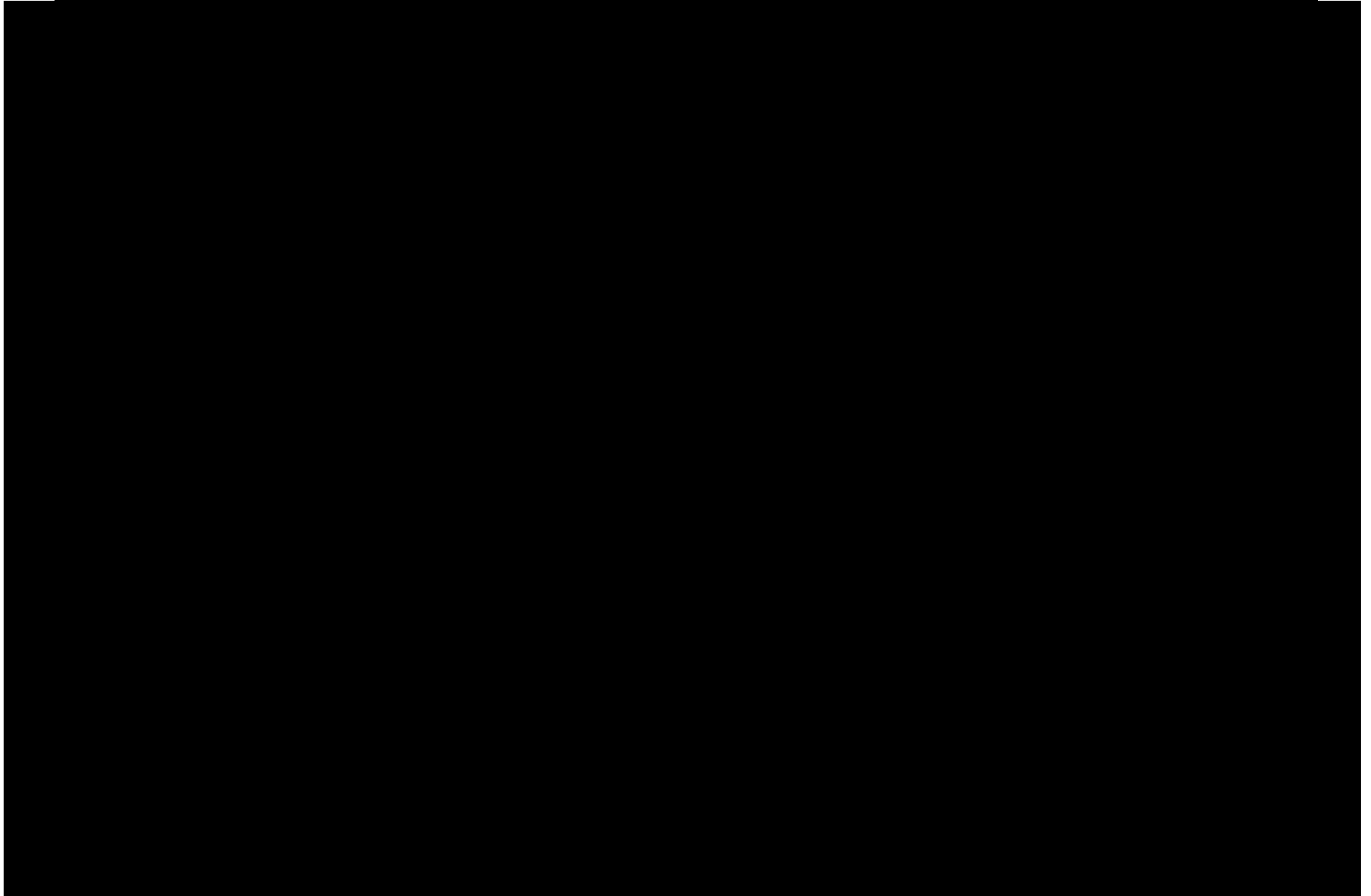
Compliance

The study will be conducted with the guidelines of Good Clinical Practice (GCP).

Table 1 **Phase 2b: Schedule of Assessments**







1 Phase 2b: Introduction

Atacicept (also known as VT-001) is a novel immunomodulator, administered by subcutaneous (SC) injections, dual-blocking the activity of B lymphocyte stimulator (BLyS, also known as B-cell activating factor) and a proliferation-inducing ligand (APRIL). Inhibition of BLyS and APRIL leads to a decrease in the maturation, differentiation, and effector function of B cells and plasma cells (Dillon 2006, Dillon 2010, Moore 1999, Ramanujam 2004, Schneider 1999). Atacicept is being developed for the treatment of patients with IgA Nephropathy (IgAN).

Complete information on the atacicept nonclinical and clinical program, and summaries of key chemistry, pharmacology, efficacy, and safety data of atacicept are provided in the Investigator's Brochure (IB).

1.1 Background

Immunoglobulin (Ig) A nephropathy (IgAN) or Berger's disease, is the most frequent biopsy-proven primary glomerular disease, but with widely variable geographic distribution (Lai 2016, Schena 2018). The prevalence of IgAN can be difficult to ascertain because of regional variability in screening and renal biopsy practices, however; a 15-year retrospective study of the United States (US) Renal Data System found that of over 84,000 end stage renal disease (ESRD) patients with glomerulonephritis (GN) etiology, around 15% were attributed to IgAN (O'Shaughnessy 2015). The global incidence of primary GN ranges from 2 to 25 per million people (pmp) per year, with a worldwide IgAN incidence of at least 25 pmp per year in adults (McGrogan 2011), and an age adjusted US incidence of approximately 21 pmp per year (Swaminathan 2006). Consistent with differences in incidence based on ethnicity and genetic predisposition, biopsy data from autopsy and donor registries support a higher prevalence of IgAN in East and Pacific Asian countries (Rodrigues 2017), as compared to Southern Europe and Africa (Kirylyuk 2012).

Immunoglobulin A nephropathy (IgAN) is highly variable, both clinically and pathologically. The classic presentation of IgAN is visible hematuria following an infection, but, more typically, IgAN presents as asymptomatic non-visible hematuria, with or without proteinuria. Renal impairment and hypertension are often present in subjects with older age at presentation (Barratt 2005). Up to 40% of all subjects with IgAN will progress to ESRD over 30 years (D'Amico 2000). In the US, IgAN accounted for 1.8% (10,557) of all prevalent subjects on dialysis at the end of 2011 (US Renal Data System 2013), with 5,044 incident subjects during the 5-year period from 2007 to 2011, or approximately 1000 subjects per year (US Renal Data System 2013). The annual incidence of ESRD due to IgAN can be estimated as 0.32/100,000 using the US population estimate from the US Census of 309 million people undertaken in 2010 (Mackun 2010).

A histopathological hallmark of IgAN is accumulation of poorly *O*-galactosylated IgA1 (Gd-IgA1) in the glomerular mesangium, either alone or in combination with IgG and/or IgM (Wyatt 2013). Sampling of the serum and plasma of subjects with IgAN has confirmed the presence of elevated levels of IgA-containing immune complexes containing Gd-IgA1 (Czerkinsky 1986). Circulating Gd-IgA1 containing immune complexes were later shown to be the target antigens for IgG antibodies with specificity for the *O*-glycans of the IgA1 hinge region (Suzuki 2009). Hence, IgAN is a unique autoimmune disease whereby the pathogenesis is driven by an autoantigen (Gd-IgA1) eliciting an autoantibody (IgG anti-glycan) response.

1.1.1 Medical Need in IgA Nephropathy

The level of 24-hour protein excretion is a risk indicator for morbidity and mortality in patients with renal disease. Patients with IgAN with persistent proteinuria > 1 g/day are at increased risk of progression to ESRD ($> 60\%$ over 20 years) (Berthoux 2011, Lee 2012, Moriyama 2014, Reich 2007). They are also at increased risk of cardiovascular mortality; up to 50% experience a cardiovascular event prior to reaching ESRD and their mortality risk is 43% higher compared with age/sex-matched controls in the general public (Lee 2012). By contrast, subjects with IgAN with proteinuria < 1 g/day have mortality rates similar to those of the general public. Furthermore, in the STOP-IgAN study which recruited IgAN patients with proteinuria (urine protein to creatinine ratio [UPCR] ≥ 0.75 mg/mg), $>50\%$ of patients progressed to death, ESRD, or eGFR decline of over 40% after 7.4 years, and use of immunosuppression, including corticosteroids, made no difference to outcome (Rauen 2020).

Since first being described in 1968, there have been limited advances in the treatment for IgAN. The central component of supportive care consists of appropriate blood pressure (BP) control and proteinuria management using Angiotensin Converting Enzyme Inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis (International Society of Nephrology 2012). The use of renin-angiotensin-aldosterone system inhibitor (RAASi) has been shown in randomized controlled studies to decrease proteinuria and correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day (Descamps-Latscha 2004).

Other treatments, such as corticosteroids (CS) and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is cautiously suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate blood pressure control and treatment with ACEis (International Society of Nephrology 2012), a recent review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist particularly in light of the prematurely halted TESTING study (Lv 2012, Lv 2017).

There is a significant unmet medical need for the treatment of IgAN, as there are currently no therapies proven effective in large randomized controlled trials. Current management includes BP control, renin-angiotensin system (RAS) blockade (with ACEi/ARB) and in rare instances combination immunosuppression with cyclophosphamide and corticosteroids for rapidly progressive IgAN (International Society of Nephrology 2012). In Japan, tonsillectomy is sometimes performed (Liu 2015). There are insufficient data supporting the use of most of the above listed therapies for IgAN, with the exception of RAASi. Reviews of randomized controlled trials suggest benefit from RAS blockade in reducing proteinuria and improving renal outcomes, but it is unclear whether this latter outcome is beyond the benefit expected from the control of hypertension alone (Cheng 2009, Hotta 2013, Reid 2011). The benefits of corticosteroid therapy and tonsillectomy for IgAN remain unclear (Lv 2012, Zhou 2011).

Thus, available treatments for IgAN are currently inadequate. Given that outcomes in subjects with IgAN remain poor, particularly with respect to development of ESRD and overall mortality, IgAN cannot be considered an indolent disease and better treatments are required.

1.2 Scientific Rationale for Study Design

This Phase IIb study will evaluate the efficacy and dose-response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria despite being on a maximally tolerated dose (MTD) of a RAASi. High risk of progression in IgAN is currently defined as a minimum of proteinuria >0.75 g/d despite optimized supportive care.

Atacicept is capable of binding to all known conformations of BLyS and APRIL and is thus expected to inhibit the maturation, differentiation, and effector function of B cells. These mechanisms are consistent with the known pharmacological effects of atacicept, which include depletion of peripheral B cell subsets, naïve follicular, marginal zone and long lived plasma cell B cell subsets, impeded germinal center reaction, and reduced immunoglobulins, while leaving immature B cells and memory B cells intact ([Dillon 2006](#), [Dillon 2010](#), [Gross 2001](#), [Moore 1999](#), [Schneider 1999](#), [Schneider 2005](#)). These effects are predicted to reduce the production and subsequent deposition of Gd-IgA1-containing immune complexes in kidney glomeruli, and thus reduce the extent of kidney injury in IgAN patients.

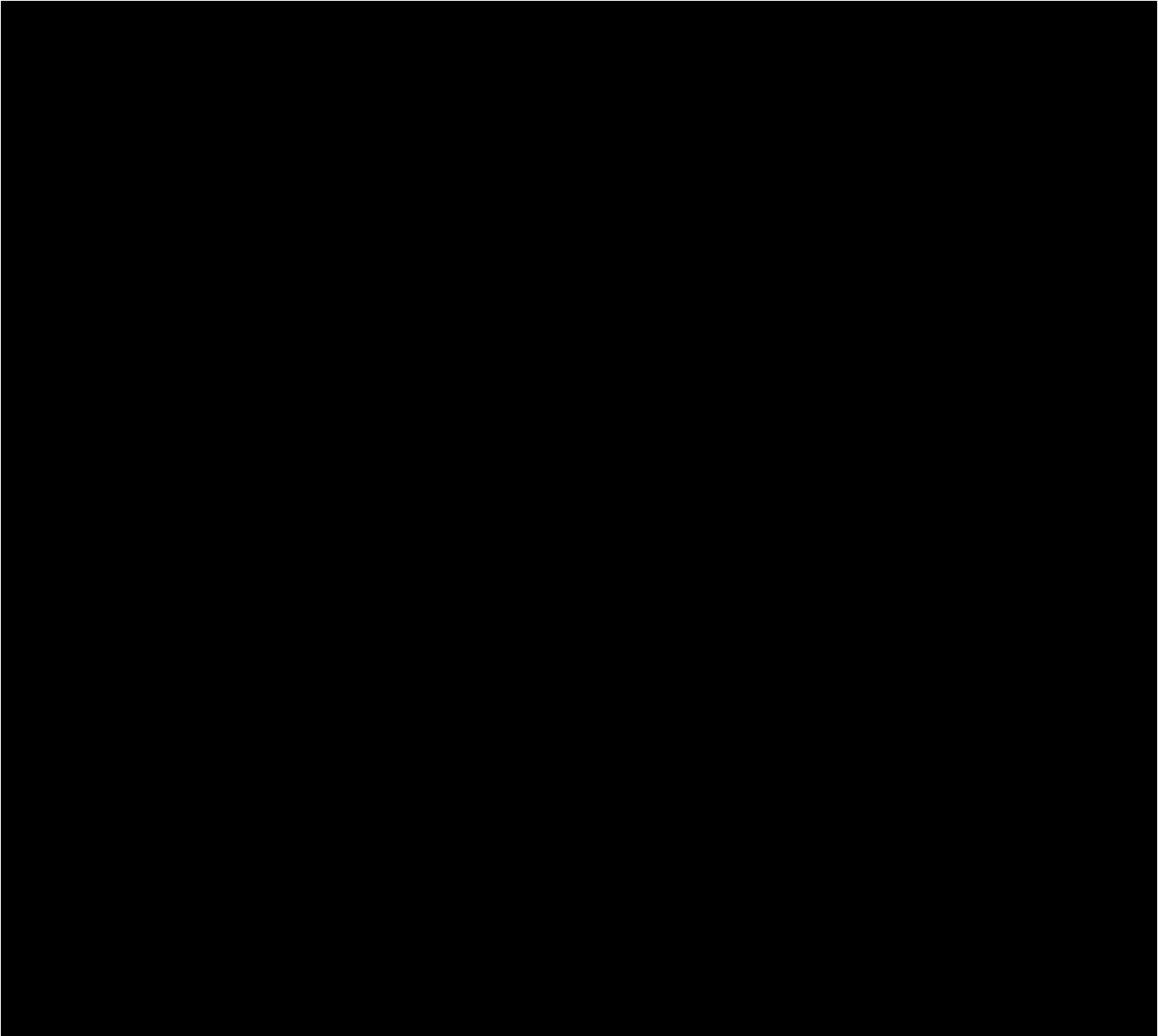
Atacicept has been studied in a pilot Phase IIa clinical study for IgAN (MS700461-0035). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and Gd-IgA1, and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. Based on the available clinical data, the targeted population for this Phase IIb study is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable and maximal supportive care regimen. The objectives of the study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN and determine the appropriate dose(s) for further clinical development.

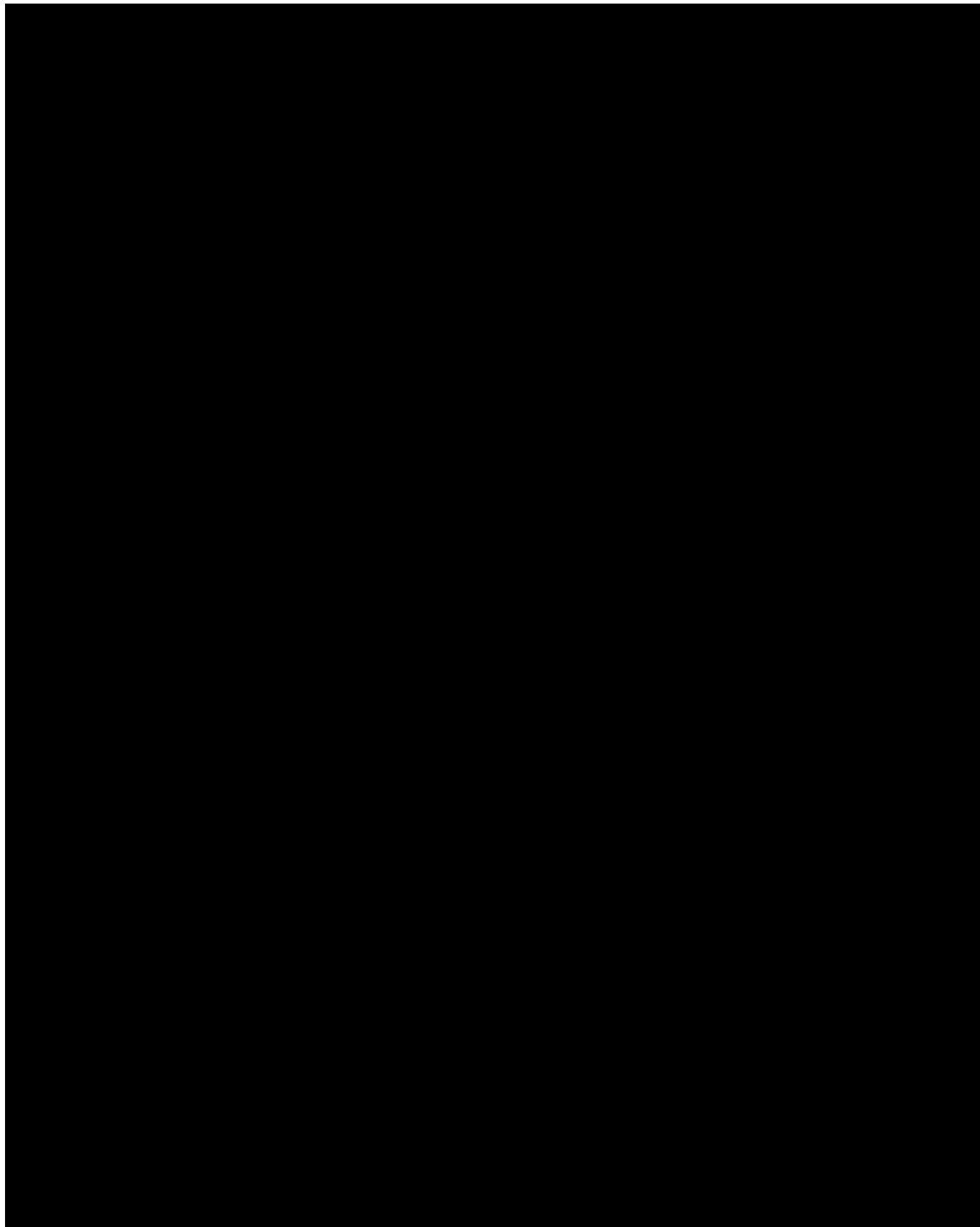
Use of ACEis and ARBs:

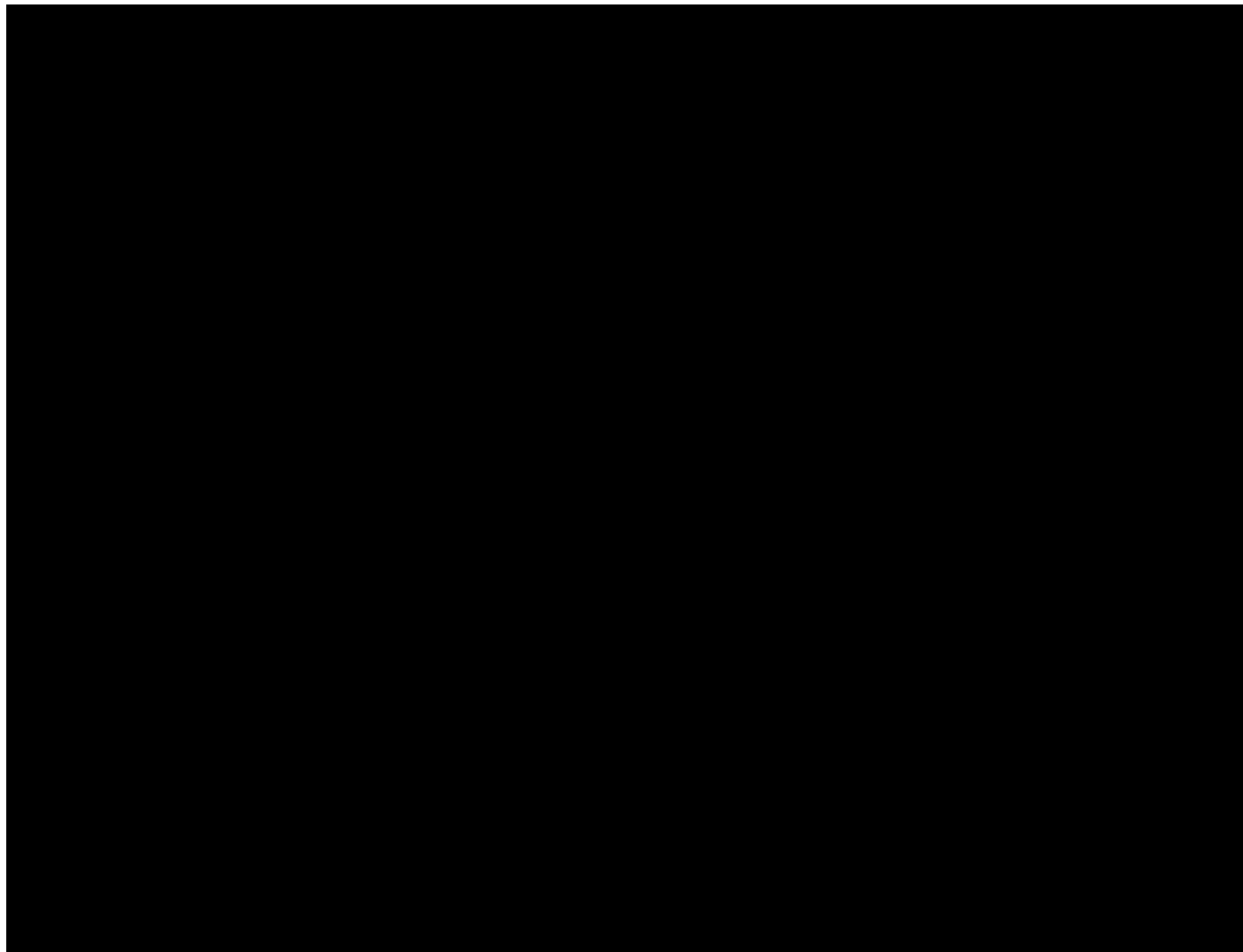
The central component of supportive care in IgAN consists of appropriate BP control and proteinuria management using RAASi as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis ([International Society of Nephrology 2012](#)). The use of ACEis has been shown in randomized controlled studies to decrease proteinuria, and this correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day ([Descamps-Latscha 2004](#)). Therefore, in this study, subjects at the Screening Visit will be required to be on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose (as determined by the Investigator), according to standard of care (SoC). Stable SoC background of RAASi medication is likely to decrease potential confounding of the study results and may help to better capture the effect of atacicept in this population. Therefore, subjects in all treatment groups will receive optimized, unchanged RAASi therapy 12 weeks prior to screening and throughout the duration of the study, thus providing a stable background SoC during this trial. Subjects who are unable to tolerate either RAASi medication may be eligible for participation in the study provided their management of IgAN is SoC according to applicable guidelines.

Use of Placebo:

Subjects in atacicept and placebo groups will continue to receive stable background SoC during this trial. Other treatments, such as CS and immunosuppressants, have not been shown to definitively improve renal outcomes ([Floege 2011](#)). Although a short course of CS is suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate BP control and treatment with ACEis ([International Society of Nephrology 2012](#)), a review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist ([Lv 2012](#), [Lv 2017](#)). Therefore, in this trial, the inclusion of a placebo group will allow differentiation of the effect of atacicept treatment from the effect of SoC therapy alone, without potential confounding by other immunosuppressant use.







1.4 Risk Benefit Assessment

The limited safety data available for atacicept in patients with IgAN are consistent with those reported in the much larger studies of atacicept in SLE. Data from 2 Phase II double-blind, randomized, placebo-controlled (DBPC) studies in SLE (APRIL-SLE and ADDRESS II) evaluated the efficacy and safety of atacicept 75 mg and atacicept 150 mg as compared to placebo for the treatment of SLE. These studies had different study designs, yet both studies were consistent in showing that atacicept 150 mg weekly SC injections were associated with efficacy and an acceptable safety profile, and thus a positive benefit:risk balance ([Isenberg 2015](#), [Merrill 2018](#), [Morand 2020](#)).

COVID Pandemic Risk/Benefit

Atacicept is an immune-modulator which may impact a patient's innate immune response to infection. In a patient receiving an immune-modulator, there may be a potential for limited or compromised immune response leading to more severe/serious complications of the SARS-CoV-2 infection. However, in an integrated safety analysis (Gordon et al 2019) of over 1500 patients in

previous atacicept clinical studies, serious infection rates were similar for atacicept and placebo. In addition, in the ADDRESS II study of SLE patients treated with atacicept 75 mg and 150 mg, titer status for both tetanus toxoid and diphtheria vaccinations remained protective from Day 1 to Week 72 (Wallace et al 2021). Risk mitigation includes excluding patients with active infection from study participation and recommendation to have up-to-date vaccinations as per local guidelines within 30 days of screening and to remain up to date with all non-live vaccination as per local guidelines during the study. Live and live-attenuated vaccines are not permitted during the study. In the setting of a pandemic or epidemic, the investigator should evaluate the best option of care for the patient including the screening for active infections prior to and during study participation according to the protocol, should this study be considered as an option.

IgAN patients continue to have too few approved therapies with a high unmet need given the risk for progression to end stage renal disease. Atacicept has promising potential to have clinical benefit for IgAN patients, while being supported with an acceptable safety profile.

2 Phase 2b: Objectives and Endpoints

The Phase 2b study objectives, endpoints and endpoint timelines are defined in the table below.

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 24
Secondary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	UPCR ^a	Week 36
Exploratory		
Evaluate the effect of atacicept on change in proteinuria in adult subjects with IgAN	UPCR ^a	Weeks 12, 48 and 96
Evaluate the effect of atacicept on rate of change in estimated glomerular filtration rate (eGFR)	Rate of change in eGFR ^b	Weeks 12, 24, 36, 48 and 96
Evaluate the effect of atacicept on change in serum immunoglobulin levels, complement levels and on serum Gd-IgA1 levels	IgA, IgG, IgM levels, C3 and C4 levels Gd-IgA1 levels	Weeks 12, 24, 36, 48, 96 and Follow Up Weeks 12 and 26
Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, adverse events	Entire study
Evaluate serum PK of atacicept	Serum concentration of atacicept	Entire study

AEs=adverse events; eGFR=estimated glomerular filtration rate; Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin; IgAN=immunoglobulin A Nephropathy; PK=pharmacokinetic; UPCR=urine protein to creatinine ratio.

^a Based on 24-hour urine sample

^b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults,

3 Phase 2b: Study Design

3.1 Overall Design

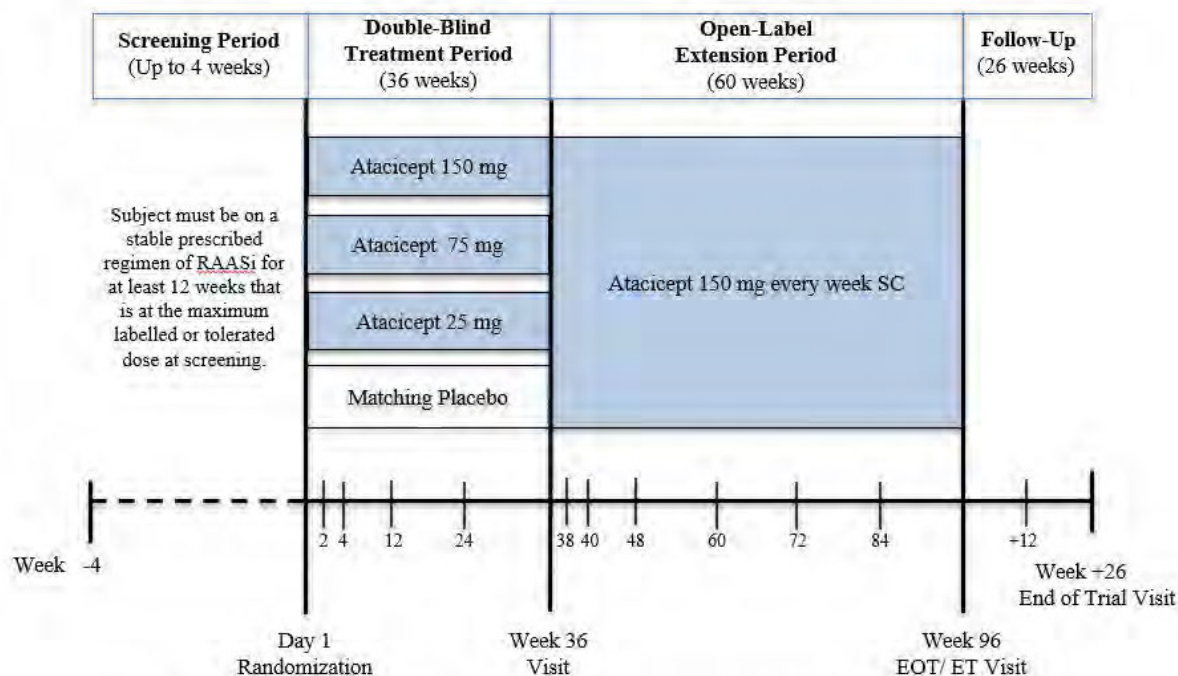
This Phase IIb study is a multicenter, randomized, double-blinded, placebo-controlled study. Approximately 105 subjects will be randomized 2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo.

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 75 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 25 mg once weekly subcutaneous (SC) injections (N=15)
- Placebo-to-match once weekly subcutaneous (SC) injections (N=30)

The study is composed of a (up to) 4-week Screening Period, a 36-week Blinded Treatment Period (Part A), followed by a 60-week Open-Label Extension (OLE) Period (Part B), and a 26-week Safety Follow-up (FU) Period. Upon completion of the 36-Week blinded period, including attendance at Weeks 24 and 36 Visits for key study assessments, all subjects will be offered open-label atacicept 150 mg for an additional 60 weeks. At the Week 36 Visit following completion of all study visit assessments, subjects will switch from double-blinded treatment to open-label treatment. Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination Visit and have a 26-week follow-up period. After the last subject completes the Week 36 Visit, the study will be unblinded. The study will be conducted on an outpatient basis.

The target study population includes male or female subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen for at least 12 weeks with a RAASi that is at the maximum labeled or tolerated dose.

Figure 1 Phase 2b: Study Schema



Note: Subject's stable dose of ACEi and/or ARB must be maintained for the duration of the study.

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; EOT=end of treatment; ET=early termination; RAASi= renin-angiotensin-aldosterone system inhibitor; SC=subcutaneous.

*For Czech Republic only, additional visits were conducted at Week 1 and Week 37.

*For Germany only, additional visits were added at Week 1 and Week 3.

Study visits will occur at Screening, Day 1, Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

There will be a 26-week follow up after subject's end of treatment visit (EOT, Week 96). Subjects discontinuing study intervention early will require an Early Termination Visit within 10 days of the last dose and safety follow up for 26 Weeks from the ET visit. Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 1](#)).

A subject has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in the Schedule of Assessments ([Table 1](#)).

The end of the study is defined as the date of last contact with the last subject who participates in the study (i.e., last subject's last visit); see Section 9.4 for details on study and site closures.

3.2 Independent Data Monitoring Committee

An independent data monitoring committee (iDMC) will monitor the safety and welfare of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority on all aspects. Details regarding the role, responsibilities and data review requirements of the iDMC will be outlined in a separate iDMC charter.

4 Phase 2b: Study Population

The Phase 2b study eligibility criteria in Sections 4.1 (Inclusion Criteria) and 4.2 (Exclusion Criteria) are designed to enroll only subjects who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a subject is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the subject's routine medical care, the Investigator will confirm that the subject has provided written informed consent, as indicated in Section 9.1.3.

Subject eligibility (based on Screening Visit assessments of the inclusion and exclusion criteria) must be reviewed again by the Investigator on Day 1 prior to randomization. Eligible subjects will be randomized to treatment with atacicept or placebo through a central randomization process by an interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility.

4.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
 - For the Czech Republic an age limit of ≤ 70 also applies.
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit
4. Total urine protein excretion >0.75 g per 24-hour or UPCR >0.75 mg/mg based on a 24-hour urine sample during the Screening Period
5. GFR ≥ 30 mL/min/1.73 m² at screening as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
6. On a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose at screening.
 - The subject is eligible if they do not tolerate RAASi, provided their management of IgAN is SoC according to local guidelines. This must be documented by the Investigator.
7. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening

8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
- Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).
- OR
- Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

4.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), SLE, dermatitis herpetiformis, ankylosing spondylitis
2. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
3. Evidence of nephrotic syndrome within 6 months of screening (serum albumin $< 30\text{g/L}$ in association with UPCr $> 3.5\text{ mg/mg}$)
4. Total urine protein excretion $\geq 5\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCr) $\geq 5\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
5. Renal or other organ transplantation prior to, or expected during, the study with the exception of corneal transplants
6. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
7. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $> 7.5\%$ at screening
8. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

9. Prohibited medications:

- Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc):
 - Within 3 months prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for > 1 week or 0.5 mg/kg/day prednisolone or equivalent
- Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics

10. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:

- serum IgG below 7 g/L
- aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN.
 - i. If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
- For The Czech Republic only, the following criteria also apply:
 - i. hemoglobin <10 g/100 mL in men and hemoglobin <9 g/100 mL in women
 - ii. platelets <100,000/L mm

11. Administration of a live and live-attenuated vaccinations within 30 days prior to randomization

12. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)

13. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.

14. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation

15. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks

prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.

- For Germany only, the following criteria also apply:

Specifically for COVID-19: Evidence of positive test for SARS-CoV-2, by PCR, at the Screening Visit; Subjects with a previous COVID-19 infection may be included provided the PCR test is negative for SARS-CoV-2 and they do not have chronic symptoms as a result of COVID-19. COVID-19 testing may be performed at local lab, per site/local guidelines.

16. History of acute or chronic infection with human immunodeficiency virus or hepatitis B virus.

- Positive hepatitis B surface antigen (HBsAg) Subjects who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow-up

17. History of splenectomy

18. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix

- For Germany only the following criteria also apply:

History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).

19. Known hypersensitivity to atacicept or any component of the formulated atacicept

20. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)

- Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)

21. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion

22. Unwillingness or lack of capacity to follow all study procedures

23. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

4.3 Screen Failures

Repeat testing: Aside from the TB testing as delineated above, tests that do not meet the above inclusion/exclusion criteria may be repeated once within the 28-day Screening Period if the results are thought to represent a laboratory error or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values. If eligibility criteria are not met at the end of the 28-day Screening Period, the subject should be considered a screen failure and not be enrolled in the study.

Re-Screening: Subjects who do not meet the above eligibility criteria (in Sections 4.1, 4.2) within the screening period and screen fail may undergo re-screening upon approval by the Medical Monitor. If the subject is re-screened, then the subject will receive a new subject identification number (Subject ID). The second screening is a new 28-day screening episode.

5 Phase 2b: Investigational Medicinal Product(s)

Investigational Medicinal Product (IMP) or study drug is atacicept or placebo intended to be administered to a study subject per the study protocol.

5.1 Randomization, Blinding, and Measures to Minimize Bias

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, is confirmed, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessments ([Table 1](#)).

Before the study is initiated, the login information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study drug administration for each subject.

5.1.1 Blinding of Investigational Medicinal Product

This study will be double-blinded for all subjects and investigators through Part A. Investigational Medicinal Product (IMP) packaging and labeling will be prepared to protect the blinded nature of the study. Study drugs will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part B of the study will be conducted in an open-label fashion.

5.1.2 Procedures for Breaking the Treatment Codes

If, at any time during Part A of this study, any site personnel are unblinded to the treatment code for any reason, the circumstances and reason must be documented. The Sponsor and clinical research organization (CRO) study staff will be blinded to the study group assignment with the exception of the selected study drug supply vendor, IDMC (if applicable) and SAE reporting contact personnel.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study drug discontinued.

In a medical emergency, the Investigator is solely responsible for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted in cases of suspected serious infection or where breaking the blind is required to provide medical care, the Investigator should contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study drug, except to the designated drug

safety representative, as appropriate. The date of and reason for unblinding must be recorded in the source documents. Contact information for unblinding in an emergency is given on the subject emergency card provided to each subject, as noted in Section 9.2.2 (Emergency Medical Support).

The Sponsor (or delegate) will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

In the case of emergency unblinding, the subject must be discontinued from the study drug and complete all assessments and procedures specified for the Early Termination (ET) Visit and should remain in the study and continue the study visits completion of follow-up assessments.

Causality assessments if emergency unblinding is for an AE/SAE should be documented for the AE/SAE prior to unblinding. Further details on expedited reporting and SAEs are in Section 7.

5.1.3 Other Blinding Parameters

Laboratory results:

After Day 1, certain laboratory results can reveal the PD effects of atacicept. These laboratory/analyte results (serum IgG, IgA, and IgM) that could be indicative of treatment allocation will not be reported to investigative sites or other blinded personnel.

Serum IgG level is one of the blinded laboratory tests which will be monitored by the central laboratory. If serum IgG is < 3 g/L on two consecutive timepoints at least 28 days apart, representing severe hypogammaglobulinemia, the study drug will be discontinued. The central laboratory will notify the Medical Monitor that the study subject meets the treatment discontinuation criteria. The site will receive notification from the Medical Monitor to discontinue the treatment of study drug for this study subject. This event will likely unblind the treatment assignment for this subject.

Lymphocyte counts as assessed by routine complete blood counts will not be blinded; these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5% to 20%).

Independent Data Monitoring Committee (iDMC):

The iDMC will review available safety data in a blinded manner with the capability to review unblinded data in case of a safety concern. See Section 3.2 for further information on the iDMC.

Unblinding Clinical Studies for Sample Analysis of Special Data:

Bioanalysis and PK scientists may be unblinded to study treatment information in order to perform sample analysis and preliminary PK and PK /PD analysis activities. Anyone who will be unblinded prior to database lock will be named with clear instruction on how to ensure the integrity of the clinical study.

5.2 Investigational Medicinal Product(s)

The atacicept protein is a soluble glycoprotein containing [REDACTED] amino acids, resulting from the fusion of human IgG1-Fc and the extracellular domain of the BLYS and APRIL receptor TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor), with a predicted mass of [REDACTED] kilodaltons. The product conformation is dimeric, and thus atacicept has a predicted mass of [REDACTED] kilodaltons. [REDACTED]

5.2.1 Formulation

Atacicept is the active ingredient in the drug product. [REDACTED]

5.3 Packaging and Labeling

The drug product/placebo is manufactured, packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released under Good Manufacturing Practice conditions. The active dosage form and placebo will be supplied by the Sponsor as a ready-to-use, prefilled syringe with 1.0 mL or drug product/placebo.

Atacicept and placebo will be packed in kits containing pre-filled syringes (one syringe is needed for 1 administration). Each pre-filled syringe will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. The labeling configuration of the pre-filled syringes results in the active and placebo being identical in appearance. Full re-traceability is provided from the unique medication number on the labels together with the packaging documentation, according to the current Good Manufacturing Practice guidelines.

5.4 IMP Administration

Study drug dosing is a single injection of 1.0 mL, once weekly from Day 1 to Week 96, subcutaneous (SC) administration by pre-filled syringe. Subjects will contact the Investigator any time they have any injection administration (pre-filled syringe) complaint.

Participants or family members/caregivers who receive appropriate training will be permitted to administer medication in this study. Participants and any caregivers who may give the injection will be trained at the investigational site on the appropriate use of the pre-filled syringe and storage of the IMP. The initial training will occur on the day of randomization. The first injection will be performed under supervision. After the first injection on Day 1 and Week 36, the participant will remain at the site for observation for 2 hours in case of hypersensitivity reaction.

- For the Czech Republic only, the injections at Week 1, Week 2, Week 37 and Week 38 are performed on site with a 2-hour observation period.

It is recommended that the weekly dose of IMP be taken on the same day of the week as the original dose. For missed dose(s) of study drug, subjects should be instructed to take the missed dose(s) as soon as possible. If necessary, a dose can be given ± 3 days from the scheduled dose day as long as there is an interval of at least 4 days from the previous injection, with subsequent doses resumed to be taken on the original day of the week.

At the Week 36 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 36 will be the first OLE dose.

5.5 IMP Preparation, Handling, Storage, and Accountability

All study drug (atacicept and matching placebo) is provided in prefilled single-use syringe to the site via cooled transport. No additional preparation will be required at the site.

Storage

All study drug supplied to each site must be stored in their original containers carefully, safely, and temperature controlled. The storage facility at the study site must be locked and accessible only to authorized site personnel. The study drug must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light. The study drug temperature will be monitored and documented per the site's standard process for refrigerated medication. Atacicept and placebo must NOT be frozen.

To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the study drug back home and instructed not to leave their medicine unattended or in a place that might get too hot, e.g., inside a car, or exposed to light. Subjects should have access to refrigeration to store the study drug.

Handling

Each study drug syringe should be removed from the refrigerator and kept at room temperature for at least 30 minutes prior to SC injection. The syringe should not be left out at room temperature for more than 60 minutes. Additional details on the instructions for handling and storage will be provided to subjects as required for home injection.

Accountability

Information on the time, date, and location of each dose will be recorded by the subject for at-home administration and by the study staff for on-site dosing. Appropriate information from the Injection Diary and assessment worksheets will be entered into the eCRF.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study drug(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Only subjects enrolled in the study may receive study drug(s) and only authorized site staff may supply it.
- Study drug(s) accountability records at the study site will include the following:
 - Confirmation of receipt, in good condition and in the defined temperature range
 - The dose(s) each subject used during the study
 - The disposition (including return, if applicable) of any unused study drug(s)
 - Dates, quantities, study drug number, expiry dates, and the subject numbers
- The Investigator site will maintain records which adequately document that subjects were provided the doses specified in this protocol and all study drug(s) provided were fully reconciled
- Unused study drug(s) must not be discarded or used for any purpose other than the present study. No study drug that is dispensed to a subject may be re-dispensed to a different subject.
- A Study Monitor will periodically collect the study drug(s) accountability forms
- Further guidance and information for the final disposition of unused study drug(s) are provided in the Pharmacy Manual.

Pre-filled Syringe Disposal:

Pre-filled syringes will be disposed of according to the Pharmacy Manual (including the use of sharps containers).

Subjects will be instructed to dispose of used syringes in sharps containers at home, and to return the sharps containers to the site once full, at Week 36 and again at Week 96), or Early Termination Visit. Investigators will instruct subjects to store any syringes associated with an injection administration complaint separately and return them to the site in a separate container.

Destruction of used and unused study drug(s) should be performed at site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible.

5.6 Study Drug Compliance

The study drug will be administered by the subject under supervision as defined in the Schedule of Assessments. All other dosing will be done by the subject, subject's caregiver, or home health nurse (if available) at home throughout the rest of the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient study drug for at-home dosing until the next scheduled visit.

Compliance will be determined based on the Injection Diary entries. Acceptable compliance for the study is defined as 80%-100% (inclusive) of study drug compliance based on drug

accountability calculated for the blinded period and open-label extension period. If dosing is interrupted for any reason, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures. The Medical Monitor should be contacted if a subject misses 2 consecutive doses or 2 doses within a month period.

Subjects will be instructed to return their subject recorded Injection Diary at each clinic visit, in order to allow the assessment of compliance with study treatment, see Section 5.4 for details.

Consequences of noncompliance will lead to retraining and/or discontinuation of study drug as described in Section 6.10.1. In case of overdose see Section 7.10.

5.7 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines) used from the time the subject signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, date(s) administered, and dosing information (as applicable).

Contact the Medical Monitor for any questions on concomitant or prior therapy.

5.7.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study drug may be given at the Investigator's discretion.

Permitted medications are any medications that are required by the subject during the course of the study and which are not specifically prohibited by the protocol (see Section 5.7.2). Any such medications prescribed or used should be recorded in the eCRF.

All subjects who tolerate RAASi medication will have begun treatment with RAASi at least 12 weeks prior to Screening and will have been on a stable prescribed regimen for at least 12 weeks with an RAASi that is at the maximum labeled or tolerated dose. For subjects who are unable to tolerate either RAASi medication, management of IgAN will be SoC according to local practice. Changes in RAASi medication including dose changes should be avoided for the duration of the study. Changes in RASi medication including dose changes are specifically prohibited up to Week 36 and every effort should be made to maintain the same dose of RASi throughout the treatment period. In the case of ACEI specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non RASi medications should have been considered before these drug classes. In certain instances (i.e. hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].

All other antihypertensive medications, including diuretics, calcium channel blockers and β -blockers, can be used at any timepoint during the study per the Investigator and following current guidelines.

Statins and dihydropyridines are permitted, but it is recommended to keep doses stable. In subjects receiving SGLT2 inhibitors at the time of enrollment, the dose must be stable for at least 8 weeks prior to screening and is expected to be at a stable dose over the study period. If deemed indicated by the Investigator, SGLT2 inhibitors may be initiated during the study after week 36, but it is expected that the doses will remain stable over the study period. The Investigator should discuss planned use of an SGLT2 inhibitor with the Medical Monitor prior to initiation for their awareness.

Use of these additional treatments commonly given to subjects with IgAN outside of above dose recommendations will incur protocol deviations but does not require IMP discontinuation. Any medications (other than those excluded by the protocol) that are considered necessary for the subjects' welfare and will not interfere with the study drug may be given at the Investigator's discretion.

- For the Czech Republic. The Investigator may initiate use of an SGLT-2 inhibitor prior to discussion with the Medical Monitor and will inform the Medical Monitor about any use of an SGLT2 inhibitor.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

For the Czech Republic only.

Rescue Medications

Should the Investigator consider that medication (steroids and/or immunosuppressive treatment) be needed, such treatment can be initiated by the Investigator. However, in consideration of current guidelines (2021 KDIGO guidelines), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

- Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] (although treatment toxicity must be considered in those with eGFR < 50); and/or
- Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., > 3.5 g/day] and hypoalbuminemia [albumin < 3.0 g/dL])

Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. Although the Investigator is responsible for the decision to implement new treatment, the Medical Monitor must be notified prior to initiation to discuss potential discontinuation of study treatment which will affect eligibility of the open-label extension.

Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of

the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 5.7.1.

5.7.2 Prohibited Medicines

The following treatments are not permitted during the study:

- Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For GCS, “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Use of systemic GCS is prohibited except for a maximum of 3 periods of 2 weeks duration with the equivalent of 0.5 mg/kg/day prednisolone or less
- Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics

Note: Intravenous (IV) hydrocortisone is permitted for stress dosing in emergency situations only, e.g., traumatic event requiring hospitalization. If administered, the event should be discussed with the Medical Monitor to ensure IMP does not need to be discontinued.

If the Investigator believes that treatment with a medication within the categories described above is required, and the potential benefits outweigh the possible risks, the Medical Monitor must be notified, as continued dosing with IMP may, in this circumstance, be discontinued (see Section 6.10.1).

Refer to the inclusion and exclusion criteria (Sections 4.1 and 4.2) for prohibited medications before and during the study.

5.7.3 Other Interventions

Treatment with a stable dose of over-the-counter supplements (herbal or non-herbal) is allowed if herbal supplements are initiated before the Screening Visit.

Planned/expected major surgery during the entire study period is exclusionary. Unplanned major surgeries should be discussed in advance with the Medical Monitor with respect to whether the subject may continue in the study.

5.7.3.1 Vaccinations

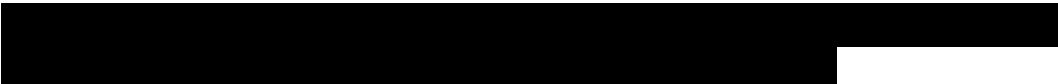
It is recommended that subjects have up-to-date vaccinations, as per local guidelines, within 30 days of screening and during the study. Investigators should review the subject's vaccine status, and ensure they remain up to date with all non-live vaccinations as per local guidelines. Live and live-attenuated vaccinations will not be permitted during the study period.

5.8 Special Precautions

- Women of childbearing potential must be willing to use a form of highly effective contraception at least 7 days prior to randomization through 175 days after the last dose of study drug ([Appendix 2](#))
- Male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the highly effective methods of contraception as well. ([Appendix 2](#)) Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.
- Caution should be exercised when administering atacicept to subjects with underlying conditions that may predispose them to infections (see [Section 7.7.2](#))
- **Good hygiene practice should be employed:** Subjects should be consistently reminded of the importance of good hygiene practices such as hand washing for their care providers and/or social contacts, especially if they are suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. It is recommended they be vaccinated according to local recommendations for individuals with a chronic disease and/or immunosuppression. They should be advised to promptly report to the Investigator any signs or symptoms suggestive of an infection.

6 Phase 2b: Study Assessments and Procedures

The following assessments will be conducted during screening and at selected timepoints specified in the Schedule of Assessments (Table 1). Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the Investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate eCRF. General considerations for study visits include, but are not limited to:

- No protocol waivers or exemptions are allowed
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the subject's routine medical care, the Investigator will obtain written informed consent as specified in Section 9.1.3 (Informed Consent Process). Upon subject's agreement, their primary health care provider should be informed about the subject's enrollment in the study.
- Order of Procedures:
 - Vital signs should be collected prior to blood draws.
 - 
 - Pharmacokinetics and immunogenicity sampling (if scheduled) and laboratory samples must be collected prior to dosing.
 - All other study assessments should also be performed, according to the Schedule of Assessments (Table 1).
- **Unscheduled visits:** may occur at any time during the study; assessments to be performed according to the Investigator's judgment.

6.1 Screening Period and Confirmation of Eligibility

The subject's eligibility will be assessed at the Screening Visit that will occur up to, at most, 4 weeks (28 days) before the Randomization Visit (Day 1). Demographic data will be collected at screening.

Subjects will arrive at the site and the following procedures will be done to determine the subject's eligibility to participate in the study:

- Obtain written informed consent prior to screening procedures
- The physical examination will be performed at the discretion of the site investigator if deemed necessary as per SoC.
- Obtain additional written informed consent if participating in the PK sub-study, as necessary
- Review inclusion and exclusion criteria
- Collect demographic data
- Complete medical and disease history
- Document the criteria for IgAN diagnosis for eligibility
- Assess vital signs: seated systolic and diastolic BP, pulse rate, temperature (oral or body – with same method to be used throughout the study), height and weight measurements (see Section 6.6.2 for details)
- Perform standard, single, 12-lead electrocardiogram (ECG) (see Section 6.6.3)
- Complete physical examination as specified in the schedule of events
- Collect blood and fresh clean catch urine samples for routine laboratory tests (see Table 2).

The laboratory tests will include:

- Clinical chemistry and hematology
- HbA1c
- Thyroid stimulating hormone (TSH)
- Follicle stimulating hormone (FSH) for woman only
- Immunoglobulins (IgG, IgA, IgM)
- Gd-IgA1
- Serum virology
 - For Germany only - COVID-19 PCR test (tested locally)
- Quantiferon test for TB assessment
- Urinalysis and urine sediment from fresh, clean-catch, mid-stream specimen obtained in the clinic
- Dispense:
 - Two 24-hour urine collection containers (one for Screening and one for the Day 1 Visit)

- Serum pregnancy test (β -hCG) required only for WOCBP. Any woman with a positive pregnancy test will be ineligible for the study. [NOTE: It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 12 months or who are surgically sterile]
- If an archival kidney biopsy (within 10 years of Screening Visit) is unavailable, a pre-treatment kidney biopsy is required to confirm subject eligibility but is to be performed at the discretion of the Investigator.
- Safety
 - Record AEs beginning after the informed consent form (ICF) has been signed.
 - Review/record prior and concomitant medications
 - Review/record vaccinations. Administration of a vaccine is acceptable within 30 days of screening or planned during the study.

Subjects who meet the screening criteria and are to be randomized will be given instructions as to the date and time they are due back at the site for Day 1 (randomization/first day of dosing).

Subjects who do not meet the screening criteria can be re-screened upon approval of the Medical Monitor. In specific circumstances, repeat testing of screening testing may be allowed. See Section 4.3 for further details.

6.2 Randomization/First Administration IMP (Day 1)

The following assessments will be conducted on Day 1. All subjects will return to the site in the morning up to at most 4 weeks (28 days) after the Screening Visit. At this visit, subjects or caregivers will be provided with training to properly store and perform self-injection of IMP at home from Week 1 onwards. Retraining can be provided by the site at the Week 2 Visit as required.

- For Czech Republic only, subjects will be dosed in clinic on Day 1 and Weeks 1, 2, 36, 37, and 38.

These dosing instructions will be reviewed with the subject/caregiver before leaving the site. At each of these visits, site staff will contact the IWRS to obtain appropriate kit numbers and the specified kit will be dispensed.

Predose Assessments

Predose assessments on Day 1 are considered baseline measurements prior to first dose of study drug. The results of all assessments and procedures performed at the Screening Visit will be reviewed to assess the subject's eligibility. All eligible subjects will undergo the following procedures before IMP administration (unless stated otherwise):

- Review inclusion and exclusion criteria
- Record archival kidney biopsy (if obtained)

- Vital signs: BP, pulse rate, temperature (oral or body – with same method to be used throughout the study) (see Section 6.6.2 for details)
- Standard, single, 12-lead ECG (see Section 6.6.3)
- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Table 2).
- Urine:
 - 24-hour collection for UPCR, [REDACTED]

Urine sample at study visit for routine urinalysis

PK (see Section 6.7.1)

- Blood samples will be collected per schedule of assessments. The exact time and date of the last dose of study drug and of blood sampling should be recorded.
- Anti-drug antibodies (binding and neutralizing)

Other analyses (see Section 6.8)

- Blood samples will be collected to assess serum BLyS and APRIL **prior to the first dose** of IMP (predose).
- Serum immunoglobulins: IgG, IgA, and IgM
- Serum Gd-IgA1
- Blood sample for storage and future testing

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Randomization

Eligible subjects will be randomized in a 2:2:1:2 ratio to 1 of 4 treatment groups by the IWRS.

Treatment with IMP (first dose)

- The study staff will instruct the subject (or caregiver) in proper technique of SC administration and demonstrate it by administering the allocated IMP to the subject via SC injection.
- The first dose (on Day 1 and Week 36) will be given at the study site. After the first dose, subjects or caregivers will be permitted to administer the medication following instruction in injection technique and verification of satisfactory technique.

- On Day 1 and Week 36, the study staff will record the exact time and location of dosing and monitor the following:
 - Injection site reactions (ISRs) (local tolerability) (see Section 6.6.5).
 - Pulse and BP will be recorded for 2 hours at approximately the following timepoints post administration: 5 ± 2 minutes, 15 ± 5 minutes and 30 ± 5 minutes, 1 hour ± 10 minutes, 1.5 hours ± 10 minutes and 2 hours ± 10 minutes.
- If suspected hypersensitivity reaction occurs at any time, the subject will be treated symptomatically (see Section 7.7.1).
- At the Week 36, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 36 will be the first OLE dose.

PK sampling (post-first dose)

- On Day 1 only, following ISR monitoring, a blood sample will be collected 2-4 hours after the first study dose.
- After Day 1, at PK timepoints, a blood sample for PK analysis will be collected to assess levels of serum atacicept.
- If participating in the PK substudy (see Section 6.7.1), additional blood samples will be collected only for PK analysis at the following timepoints after dosing: Day 2 and/or Day 3 post-first dose. The subject can be registered to this subgroup analysis through the IWRS (this will be done during the randomization process).

Completion of Day 1

Following completion of all Day 1 procedures described above, the following additional procedure should be completed before the subject leaves the site:

- Provide subjects with emergency contact numbers (see Section 9.2.2).

6.3 Post-Randomization Visits

Assessments to be performed for each visit are outlined in the Schedule of Assessments (Table 1).

6.3.1 Treatment Periods

Following completion of Randomization (Day 1), study visits will occur at Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE period with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

For the Czech Republic and Germany only: If in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted on Day 1 and at Weeks 1, 2, 36, 37, and 38. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

6.3.2 End of Treatment or Early Termination

End of treatment is defined as subjects who complete Part A and B for a total of 96 weeks of study drug.

Criteria for discontinuation are provided in Section 6.10. Subjects who are discontinued from IMP will complete the Early Termination (ET) visit as soon as possible (within 10 days) after IMP discontinuation. These subjects should receive a 24-hour urine collection container in advance (e.g., at the prior visit), but no later than 2 days before the scheduled ET visit.

End of treatment is defined as subjects who complete Part A and B for a total of 96 weeks of study drug. The ET Visit follows the same schedule of assessments as Week 96.

6.3.3 Safety Follow-up Period

After the last dose of the IMP, all subjects are required to enter a Safety FU period. For subjects who completed the 96-week total treatment (36 weeks for Part A plus 60 weeks for Part B), or for subjects who are discontinued from IMP, the Safety FU period is 26 weeks, with visits at Weeks 12 and 26.

6.4 Demographic and Other Baseline Characteristics

Demographic data such as date of birth, self-reported race and ethnic origin, gender, weight, height, and body mass index (to be calculated by CRO/Sponsor) will be assessed at screening. Information about previous and concomitant medications will also be recorded.

Complete medical and disease history will be recorded. This includes history of disease treatments, including but not limited to conditions that may affect eligibility (herpes zoster, cytomegalovirus, Epstein Barr virus, TB, cancer, infections [current active infections, recent serious infections, opportunistic infections, chronic or recurrent infections], congestive heart failure, hypersensitivity to drugs and other significant illnesses, smoking history, alcohol or drug abuse). In addition, a history and status of medications will be recorded, including surgeries and other procedures, with particular attention to current and previous treatments for IgAN.

Other baseline measurements such as physical examination, safety laboratory parameters, ECG, and vital signs will be assessed as specified below.

6.5 Efficacy Assessments and Procedures

Assessments for the endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 1).

Clinical renal disease assessments:

- UPCR, 24-hour total protein excretion, [REDACTED]
- Active urinary sediments by urinalysis.
- Renal function by eGFR will be calculated by the central lab as follows: (Levey 2011)
CKD-EPI: $eGFR = 141 \times \min (Scr / \kappa, 1)^\alpha \times \max (Scr / \kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.159$ (if black)
Scr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicated the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

Blood assessments:

- Ig levels (i.e., IgG, IgA, and IgM), Gd-IgA1.
- Baseline (predose) levels of free BLyS and free APRIL.

6.6 Safety Assessments and Procedures

Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, and evaluation of AE/SAEs, with attention given to infections (serious), cardiovascular events, local tolerability (ISRs) and hypersensitivity reactions.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

Adverse events of special interest (AESIs) are opportunistic infections, hypersensitivity reactions, demyelinating disorders and cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease).

6.6.1 Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A complete physical examination will include, at a minimum assessment of the General Appearance, Skin, Lymph Nodes (Cervical), Head, Ears, Eyes, Nose, Throat (HEENT), Neck, Thorax/Lungs, Cardiovascular, Abdomen, Musculoskeletal, and Neurological systems. Height (at Screening Visit) and Weight will also be measured and recorded.

At selected visits, a symptom-driven physical examination will be performed, and will include assessment of any new subject complaints or changes from baseline.

6.6.2 Vital Signs

Vital sign measurements (BP, pulse, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, at the visits specified in the Schedule of Assessments (Table 1).

- Temperature, pulse rate, respiratory rate
- Blood pressure and pulse measurements will be assessed with the subject seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
 - During the Screening Period, blood pressure will be measured up to 3 times with each measurement separated by up to 2 minutes (the lowest value will be recorded on the eCRF).
 - After first dose of study drug at randomization and at Week 36 during ISR monitoring, pulse and BP recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes
- Vital signs to be taken before blood collection for laboratory tests
- Height will be measured at Day 1 only. Body weight will be measured with a balance beam scale if possible.

6.6.3 Resting Electrocardiogram (ECG)

Digital ECGs for all subjects will be recorded at the site using an appropriate ECG machine.

- A standard, single, digital 12-lead ECG will be obtained as outlined in the Schedule of Assessments after the subject has been resting in the supine position for 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals

All digital ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The Investigator will judge the overall interpretation as normal or abnormal. Clinical significance and the reason for the abnormality will be recorded on the eCRF.

Any changes in ECG values that are abnormal that are determined to be clinically significant by the Investigator will be recorded as AEs.

6.6.4 Clinical Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in the following table, at the timepoints listed in the Schedule of Assessments.

- All samples should be clearly identified.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations
- The tests will be performed by the central laboratory
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- Non-fasting blood samples are acceptable for this study.
- Repeat laboratory testing may be required during the study for various reasons, e.g., loss of sample en route to the central laboratory. Any testing which is required to be repeated should be repeated as soon as possible after a visit.

For information on blinded laboratory results see Section 5.1.3. Approximately 14 – 46 mL of blood will be collected per subject for each study visit. Approximately 552 mL of blood will be collected per subject for the entire study. Routine hematology, chemistry, PK serum atacicept, PK anti-drug antibodies, PD immunoglobulins, PD Gd-IgA1, PD serum BLYS & APRIL, and exploratory biomarkers will be assessed from the blood samples for each subject visit as per the schedule of assessments and description in Table 2.

6.6.4.1 Clinical Safety and Screening Evaluations

Table 2 Phase 2b: Clinical Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	██████████ Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range)	Calcium Serum creatinine (eGFR will be calculated from serum creatinine using the CKD-EPI equation)	Glucose Potassium Sodium Total protein Uric acid
Urine Sediment Analysis	Urine red blood cells and white blood cells/high powered field Casts Organisms Crystals		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick		

Laboratory Assessments	Parameters
	Microscopic examination (if blood or protein is abnormal).
Quantitative Analysis (24 -hour Urine Collection)	Total volume Total protein [REDACTED] Total creatinine UPCR [REDACTED]
Other Tests	Serum IgG, IgA, IgM Gd-IgA1 Complement (C3, C4) Serum BLYS and APRIL level (if assay is available) HBsAg, anti-HBc [total and IgM] (hepatitis B) <ul style="list-style-type: none"> If HBsAg negative and hepatitis B core antibody is positive, HBV-DNA will be performed and monitored monthly through safety follow up Anti-atacicept antibody titers (binding and neutralizing) anti-HCV (if anti-HCV positive with reflex testing for HCV RNA by PCR) anti-HIV 1 and 2 HbA1c TSH FSH (for women only) Serum pregnancy test (β -hCG) required only for WOCBP at Screening. Local urine testing will be standard all other visits unless serum testing is required by local regulation or IRB/IEC. Positive urine pregnancy test results will be confirmed by serum pregnancy testing. Quantiferon test for TB Urine drug screen for amphetamines, cocaine, methadone, and opiates

β -hCG= beta human chorionic gonadotropin; antiHBc=anti-hepatitis B core; anti-HCV = anti-hepatitis C virus; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin-A1c; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; Ig=immunoglobulin; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid; TB=tuberculosis; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=woman of childbearing potential.

6.6.4.2 Urine Sampling and Testing

Urine samples need to be collected in different ways for different tests:

Quantitative proteinuria assessments: A 24-hour urine collection will be used to determine 24-hour total protein excretion, UPCR, [REDACTED]. Total volume of the 24-hour collection will be measured and an aliquot taken for determining protein, [REDACTED] and creatinine concentration to calculate the proteinuria and [REDACTED]. Subjects will be provided with the materials for conducting their 24-hour urine collections and will have to bring the collection to the clinic; for remote study visits, transport of the sample will need to be arranged. At the Screening Visit, the subject will receive the collection materials and the 24-hour collection should be conducted and brought into the clinic as soon as complete within the Screening Period. At other visits requiring a 24-hour urine collection, the subject is advised to collect the urine starting the day prior to the visit and bring it to the visit.

24-hour urine collection: The 24-hour urine collection should begin 1 day before the study visit and should start with discarding the first morning void, and collecting all urine produced thereafter (through the day and night) up to 24 hours later (including the first morning void of the second morning).

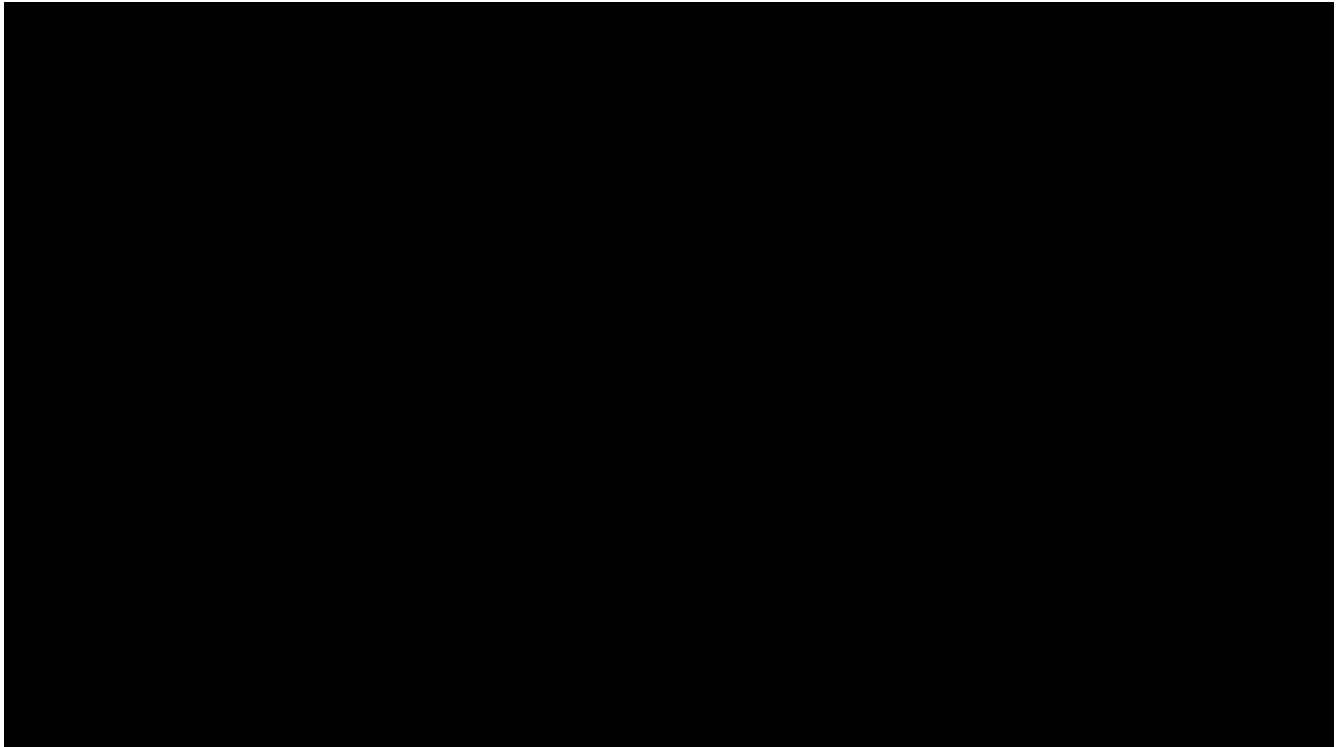
Urine collection: A urine sample from “fresh” urine will be collected during the scheduled clinic visit. Subjects will be provided a urine cup and instructions for a midstream collection to provide a clean catch specimen. The urine collection will be used for routine urinalysis and urine sediment analysis, and at specified visits, for sample storage for future exploratory biomarker analysis (see Section 6.8.1).

6.6.5 Local Tolerability (Injection Site Assessment)

Any local ISRs will be assessed by the Investigator or his/her designee and recorded as AEs in the eCRF, starting after first study drug administration and continuing through Part A and B or Early Termination (see Table 1).

Severity of the ISR reported on the AE form should reflect the highest severity of the manifestation (see below). For example, if the swelling is mild and the redness is moderate, then the AE should be reported as moderate.

The definition of ISR severity is the following:



If the subject experiences one or more of the above injection site symptoms, these should be reported with the AE verbatim term “injection site reaction”. These events will be captured on the AE page of the eCRF.

If the subject has any other injection site symptoms not included in the list above (e.g., injection site necrosis, injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (e.g., injection site necrosis, injection site abscess, injection site cellulitis) rather than the term “injection site reaction”.

Subjects who complete their last study visit with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required.

6.7 Pharmacokinetics

On Day 1, following first monitoring of ISR, a blood sample will be collected between 2-4 hours after first dose.

After Day 1 at PK timepoints in the Schedule of Assessments ([Table 1](#)) a blood sample will be collected prior to administration of study drug. Blood samples for PK analysis to assess trough levels of serum atacicept will be collected from all subjects. Instructions for collection, preparation and shipping these samples will be provided in a Laboratory Manual. Serum concentrations of atacicept will be assessed at trough as noted in the Schedule of Assessments. The actual date and time (24-hour clock time) of each sample will be recorded.

Blood samples for assessment of anti-drug antibodies, binding and/or neutralizing, will be collected at the visits specified in the Schedule of Assessments ([Table 1](#)). Samples will be tested first for binding activity, and those found to be positive will be tested for neutralizing activity when an assay is available.

6.7.1 Pharmacokinetic Sub-Study

At selected sites, a subgroup of subjects (approximately 32 subjects with 8 subjects per each Part A treatment arm) enrolled will have additional PK sampling visits that will be done at Day 2 and/or Day 3, approximately 24 and 48 hours after the first dose, respectively, in order to capture the drug's T_{max} . The exact time and date of blood sampling should be recorded.

6.8 Other Assessments

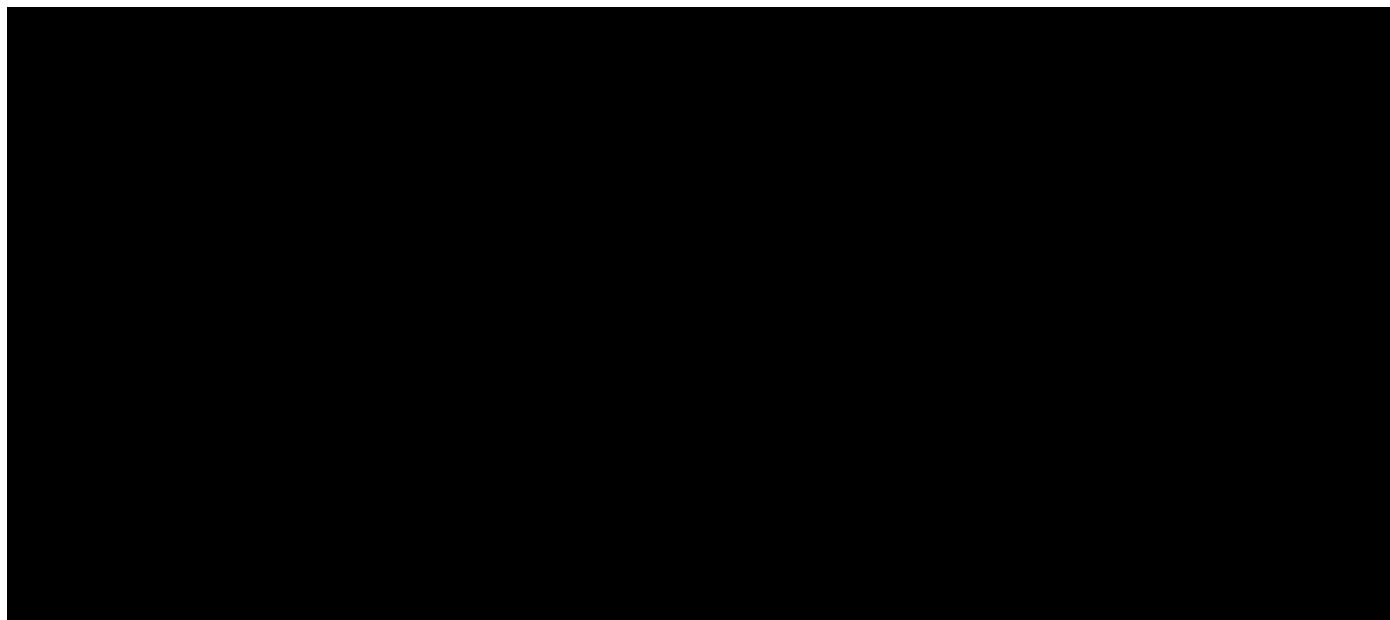
6.8.1 Biomarkers

Storage and analyses of samples will be handled according to the study Laboratory Manual, and described in the appropriate Informed Consent Form.

Serum Biomarkers

The following markers may be evaluated: predose serum BLYS and serum APRIL, and serum IgG, IgA, and IgM, serum Gd-IgA1.

Exploratory Biomarkers



Pharmacodynamic Assessments

Blood samples will be collected at the timepoints specified in the Schedule of Assessments ([Table 1](#)). Immunoglobulin levels may be integrated into the Population PK, PD and exposure-response modeling and simulation analysis, including assessment of the influence of renal function (e.g., eGFR).

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

6.9 Considerations for Coronavirus Outbreaks

The global coronavirus pandemic or outbreaks may impose difficulties with study conduct which may inhibit the subjects' ability of entering the study site. In cases of coronavirus limitations, it is the Investigator's responsibility to assure the safety of study subjects which should include phone or video contact to assess the subject's well-being including any adverse events, collection of study samples and clinical data as best as possible, and direct shipment of study drug to study subjects if necessary. These assessments can be performed at a scheduled or unscheduled study visit(s). Where available and appropriate, home health care may be considered to facilitate monitoring of subject safety and study continuity. Documentation of these cases and the site's management of subjects should be recorded in the Investigator study files.

6.10 Discontinuation of Study Drug and Subject Discontinuation/Withdrawal

6.10.1 Discontinuation of Study Drug

Study drug may be stopped at any time at the Investigator's discretion.

Subjects who withdraw from, or are withdrawn from study drug early should remain in the study, completing an early termination visit and continuing in the 26-week Safety Follow-up Period (see Table 1).

For such subjects who permanently discontinue study drug but remain in the study, the ET visit must be completed within 10 days of discontinuation, followed by the Safety Follow-up visits as described in Section 6.3.3.

For subjects who withdraw consent or are lost to follow-up or death, Safety Follow-up visits will not be possible. In such cases, the appropriate eCRF section must be completed.

If a subject is unblinded (Part A), the subject must be discontinued from the study drug and complete all assessments and procedures specified for the ET visit and complete the Safety Follow-up period.

The subject must be withdrawn from study drug in the event of any of the following:

- Enrollment despite violation of an exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the subject necessary.
For Germany only – ineligible patients will not be enrolled and thus not discontinued
- Occurrence of an AE/SAE that makes discontinuation of study drug desired or considered necessary by the Investigator and/or the subject.
- Participation in any other interventional study during the duration of this study for which the Investigator considers discontinuation of the IMP necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to Section 7.9).
- If disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes (Section 5.7) is warranted in the view of the Investigator. Discussion with the Medical Monitor should occur prior to discontinuing IMP for this reason.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on Investigator judgment.
- Use of a nonpermitted medicine, as defined in Section 5.7.2. This should first be confirmed with the Medical Monitor before discontinuation of study drug.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance to the required study considerations, as defined in Section 5.6.
- Discontinuation of LTBI therapy before completion if present at the Screening Visit.
- If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart.
- Surgery considered by the Investigator or Sponsor to be major (see Section 4.2).
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Atacicept is contraindicated in subjects with a history of MS, ON, or any other demyelinating disease. Any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as, but not limited to, MS, ON, or transverse myelitis) should stop dosing of IMP.

The Schedule of Assessments specifies the data to collect at study drug discontinuation and follow-up, and any additional evaluations that need to be completed.

6.10.2 Study Drug Interruption

The Medical Monitor must be notified if the subject has missed 2 consecutive doses or 2 doses within a month period. If treatment has been interrupted for ≥ 4 consecutive weeks, the Investigator should discuss with the Medical Monitor whether to restart or discontinue treatment.

If the subject is unable to resume study drug, see Section 6.10.

6.11 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent). Investigator or designee should make reasonable effort to obtain explanation for subject withdrawal and ask about the occurrence of any AEs. The subject will be asked to return for an ET visit per Schedule of Assessments (Table 1).

- The subject may be withdrawn by the Investigator due to participation in another clinical study
- The subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed
- A subject is considered withdrawn from the study due to death
- A subject must be withdrawn from the study in the event the subject is lost to follow-up.
- Discontinuation of the study at the request of the sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC).

When a subject must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor.

If a subject is withdrawn from the study, the samples will be kept, and the subject may be asked to return for Safety Follow-up assessments. If the subject withdraws consent, the Sponsor may retain and continue to use any data collected prior to such withdrawal of consent; however, all samples not tested will be destroyed.

If there is a medical reason for withdrawal from the study, the subject will remain under the supervision of the Investigator until satisfactory health has returned or health has stabilized. The Investigator will inform the subject's primary health care provider as applicable and as agreed by the subject if the subject withdraws from the study, to ensure the subject receives the appropriate follow up and care.

Subjects who are withdrawn from the study for any reason after receipt of the study drug on or after Day 1 will not be replaced.

6.12 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the

Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). The Investigator reserves the right to discontinue the study should his/her judgment so dictate and should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

6.13 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study
- Before a subject is deemed “lost to follow-up”, the Investigator or designee must make every effort to regain contact with the subject:
 - 1 where possible, make 3 telephone calls, AND
 - 2 if necessary, send a certified letter (or an equivalent local method) to the subject’s last known mailing address.

These contact attempts should be documented in the subject’s medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

6.14 Medical Care of Subjects after End of Study

After a subject has completed the study including the Safety Follow- Up Period, or has withdrawn early, standard treatment should be administered, if required, in accordance with the study site’s SoC and generally accepted medical practice and depending on the subject’s individual medical needs.

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for patients with IgAN.

7 Phase 2b: Adverse Events and Toxicity Management

7.1 Definitions of Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated and does not interfere with everyday activities.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out his or her usual activities. An AE that is assessed as severe should not be confused with an SAE. An event is defined as “serious” when it meets at least one of the predefined outcomes in the definition of SAE, and not when it is rated as severe.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study drug include, but may not be limited to, temporal relationship between the AE and the study drug, known side effects of study drug, medical history, concomitant medication, course of the underlying disease, and study procedures.

Investigators must also assess the causal relationship of AEs to the pre-filled syringe.

- Unrelated:** Not reasonably related to the study drug. AE could not medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol. A reasonable alternative explanation must be available.
- Related:** Reasonably related to the study drug. AE could medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Clinically significant abnormal laboratory or other examination (e.g., electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., electrocardiogram abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

The severity of abnormal laboratory values should be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) and recorded per the Qualitative Toxicity Scale, as follows:

Mild: CTCAE Grade 1

Moderate: CTCAE Grade 2

Severe: CTCAE Grade 3 and 4

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition(s); this may or may not be in agreement with the grading of the laboratory abnormality.

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization

Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment

of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are baseline conditions (e.g., pre-existing) and are not to be considered AEs. Situations where an untoward medical occurrence has not occurred are not to be considered AEs (e.g., hospitalization for elective surgery, social and/or convenience admissions).

Adverse Events of Special Interest

Adverse events of special interest must be reported on the SAE/AESI Report Form and will follow the procedure described below for reporting SAEs and AESIs.

Categories of AESIs include:

- Opportunistic infections considered to be medically significant by the Investigator, but do not meet at least one of the criteria for an SAE (infections meeting one or more of the seriousness criteria should be reported as SAEs)
- Hypersensitivity reactions
- Demyelinating disorders
- Cardiac events (cardiac failure, cardiac arrhythmias, and ischemic heart disease)

7.2 Time Period and Frequency for Collecting Adverse Event, Adverse Event of Special Interest and Serious Adverse Event Information

The AE/AESI/SAE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Safety FU Visit After informed consent, but prior to initiation of study drug, all SAEs and adverse events related to protocol-mandated procedures should be collected.

- Following initiation of study drug, collect all AEs, regardless of cause or relationship.

Any SAE assessed as related to study drug must be recorded and reported, whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Section 7.5.

7.3 Method of Detecting Adverse Events, Adverse Events of Special Interest and Serious Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, regardless if reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and AESIs must be additionally documented and reported using the appropriate report form as specified in Section 7.5.

7.4 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 7.2, and are assessed for their outcome at the last Safety FU Visit. All SAEs ongoing at the last Safety FU Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.5 Investigator Requirement and Instructions for Reporting Adverse Events, Serious Adverse Events, Adverse Events of Special Interest

Recording and Follow-Up of AEs

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study drug administration time), its severity, its causal relationship with the study drug, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All reports should be transmitted using the AE page and indicating the AE meets criteria for an SAE in eDC. Required information in eDC must be completed by the Investigator following specific completion instructions.

In exceptional circumstances (e.g., eDC is down), an SAE (or follow-up information) may be reported by fax or email; in these cases, a written report using the back-up paper SAE Reporting Form must be sent immediately by fax or email contacts listed below by any study site. Once eDC becomes accessible, the SAE needs to be entered into the system immediately.

IQVIA Safety (Back Up Contact Information):

Email (preferred): PhV_TZA74011_SO@IQVIA.com

Fax: refer to country specific fax numbers provide with paper forms

Additional documents will be provided by the Investigator, if requested by the Sponsor or its designee (e.g., laboratory results, hospital report, autopsy report) depending on the availability of the document.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports, by updating the (S)AE form in the eDC system and submitting any supporting documentation (e.g., subject discharge summary or autopsy report) to IQVIA via e-mail (preferred) or fax. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited

safety reporting obligations. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE information in the eDC and submit any supporting documentation as requested (e.g., subject discharge summary or autopsy report) to IQVIA Safety via e-mail (preferred) or fax. If it is not possible to access the eDC system, refer to the procedures outlined above for initial reporting of SAEs.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will enter the AE into eDC and indicate the AE is an AESI in eDC in a timely manner. AESIs that meet the definition of an SAE must be reported in the same timely manner and process as SAEs as outlined above.

7.6 Regulatory Reporting Requirements for Serious Adverse Events

Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For atacicept, the reference safety information is included in the Investigator’s Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report where possible.

Regulatory Reporting

The Sponsor or designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the Independent Ethics Committee / Institutional Review Board (IEC/IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC’s/IRB’s approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.7 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are hypersensitivity reactions, opportunistic infections, cardiac disease/disorders (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and demyelination disorders.

7.7.1 Hypersensitivity Reactions

Atacicept is contraindicated in subjects with known hypersensitivity to the drug substance or to any of the excipients. If allergic angioedema or other serious hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions occur, administration of IMP should be discontinued immediately, and appropriate therapy initiated. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for resumption of IMP or permanent discontinuation.

Local ISRs may be treated as per Section 6.6.5.

7.7.2 Opportunistic Infections

Opportunistic infections are those due to bacteria, fungi, viruses, or parasites that normally do not cause a disease, but become pathogenic when the body's defense system is impaired.

Treatment of infections must be prompt and done in accordance with local SoC depending on considerations such as the nature and severity of the infection, patient's overall health status, etc.

- Subjects must be carefully examined for signs of infection and questioned about recent infective illnesses and recent vaccination(s)
- If laboratory findings raise concern, in the opinion of the Investigator, that there may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section 4.2, and may lead to study drug discontinuation
- Subjects will be instructed by study site personnel to monitor for early signs of infection, such as upper respiratory symptoms, fever, painful urination, productive cough, breathlessness, constitutional symptoms, etc. Subjects should inform the study site if any of these symptoms or signs are present and should be evaluated and treated in a timely manner according to the local SoC. At each study visit, monitoring for subject's symptoms and signs should also be

done. Standard medical care will be provided at the study sites for all AEs occurring during the study. Any subject who experiences a chronic or recurrent significant infection, or opportunistic infection, should be re-evaluated (as per Investigator's clinical judgment and discussion with Medical Monitor) as to whether or not continued treatment with atacicept is appropriate. Serious infections will be reported as described in Section 7.5.

For infections associated with severe hypogammaglobulinemia (serum IgG < 3 g/L), consideration can be given to administration of Ig and discontinuation of study drug. If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart, then the subject will be discontinued from study drug (see Section 6.10.1).

7.7.3 Cardiac Disease/Disorders

Treatment with atacicept must be temporarily discontinued in subjects who develop new onset or worsening of clinically significant symptomatic arrhythmias that require medical intervention (such as paroxysmal atrial tachycardia, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia, ventricular fibrillation or tachycardia), cardiac failure, or cardiac ischemic symptoms. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for discontinuation or resumption of study drug.

7.7.4 Demyelination Disorders

Based on the clinical trial results, MS patients who received atacicept developed significantly more relapses than patients in the placebo group. Therefore, any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as but not limited to MS, optic neuritis or transverse myelitis) should discontinue the study drug.

7.8 Management of Adverse Events Associated with Abnormal Laboratory Findings

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

Grades 1 (Mild) and 2 (Moderate) Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

Grade 3 (Severe) Laboratory Abnormality or Clinical Event

Study drug may be continued if the event is considered to be unrelated to study drug.

For clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to $\geq$ Grade 3 following re-starting of study drug and is considered related to study drug and medically important by Investigator and/or Sponsor/designee, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

Grade 4 (Severe) Laboratory Abnormality or Clinical Event

For clinical event or Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug and medically important by Investigator and/or Sponsor/designee, study drug should be permanently discontinued and the subject managed according to local clinical practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to the study drug.

All subjects experiencing AEs must be monitored until symptoms subside and any abnormal laboratory values have resolved, returned to baseline levels, are considered irreversible, or have a reasonable explanation for the changes observed.

7.9 Pregnancy

Pregnancy should not be captured as an AE. However, pregnancies with an estimated conception date during the period defined in Section 7.2 must be recorded in the eCRF for both pregnancies in female subjects and pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Section 7.5.

Investigators must actively follow up, document and report on the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Reporting Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 7.2, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the study, the subject must be discontinued from study drug. The Sponsor/designee must be notified without delay and the subject must be followed as indicated above.

7.10 Special Situation Reports

Special situation reports include site-reported instances of overdose, misuse, abuse, medication error, and adverse reactions associated with product complaints.

- **Overdose:** For this study, any instance when IMP is given 3 times or more per week is considered an overdose. Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).

Note: The Sponsor does not recommend specific treatment for an overdose. The effects of an overdose of atacicept are unknown and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and appropriate supportive treatment should be given as needed per Investigator's clinical judgment.

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events should be reported as a protocol deviation and any associated events reported as an AE. Special Situations that are considered to meet SAE criteria will be managed per the same process as SAEs in Section 7.5.

8 Phase 2b: Statistical Considerations

The Phase 2b Statistical Analysis Plan (SAP) will be developed and finalized before the database lock for the first interim analysis and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary efficacy and safety endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Stratification factors will be described in the SAP.

All endpoints will be summarized using descriptive statistics. Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number. Statistical testing will be conducted for primary and secondary efficacy endpoints with no adjustments for multiple comparisons. For the purposes of this trial, a significance level of 0.05 will be utilized.

All statistical analyses will be conducted by the Sponsor or its agent using SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA 27513).

8.1 Stratification

[REDACTED]

8.2 Statistical Hypotheses

[REDACTED]

8.3 Sample Size Determination

Sample size and power are estimated for the primary efficacy endpoint, change from baseline to Week 24 in natural log transformed UPCR. It is assumed that the absolute difference (placebo – active) in the mean ratio of Week 24 UPCR to baseline UPCR is 0.28. The geometric mean ratio of Week 24 UPCR to baseline for placebo is expected to be 0.88. The coefficient of variation is estimated as 0.594 [i.e., pooled log SD of 0.55]. The expected placebo response and study intervention effect size are based on the analysis of the phase 2 study for atacicept and placebo in

IgAN and placebo responses seen in other large IgAN studies. Based on these assumptions, 25 subjects in the placebo group and a combined total of 50 subjects in the atacicept 75 mg and 150 mg groups are considered sufficient to provide at least 80% power to detect a ratio of 1.47 when the ratio under the null hypothesis is 1 [PASS 2008: two-sided two Sample t-test for ratios, $\alpha=0.05$, coefficient of variation on the original scale is 0.594]. Adjusting for a 15% dropout rate, 30 subjects should be enrolled in each of the placebo, atacicept 75 mg, and atacicept 150 mg groups to ensure 25 subjects complete Week 24 in each of these groups. The sample size of 15 for the atacicept 25 mg group is chosen to provide preliminary safety and efficacy information and is not based on statistical considerations.

8.4 Populations for Analyses

The analysis populations are specified below. The final decision to exclude subjects from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Population	Description
Screening	All subjects who sign informed consent.
Intent-to-treat (ITT)	The ITT Population consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.
Full Analysis Set (FAS)	The FAS Population consists of all randomized subjects who have received at least 1 dose of treatment and have at least 1 post-baseline measurement of UPCR. Subjects will be analyzed according to randomized treatment.
Per-Protocol (PP)	The PP population consists of all subjects in the FAS who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the SAP, including exclusion of subjects who take prohibited medications. The PP Population will be used for supportive analyses on the primary and selected efficacy endpoints. Subjects will be analyzed according to treatment received.
Safety	The Safety Population consists of all randomized subjects who receive at least 1 dose of treatment. The Safety Population is the analysis population for the safety endpoints. Subjects will be analyzed according to treatment received.
Pharmacokinetics	The PK population consists of all randomized subjects who were administered at least 1 dose of treatment and have at least 1 evaluable PK sample. All PK evaluations will be based on this analysis set. Subjects will be analyzed according to treatment received.

Unless otherwise indicated, the Full Analysis Set (FAS) is the primary analysis population for efficacy endpoints and the Safety Analysis Set is the primary analysis population for safety endpoints.

8.5 Statistical Analysis

8.5.1 Efficacy Analyses

The primary analysis of proteinuria will assess UPCR data via a mixed-model repeated measures analysis. Change from baseline in natural log transformed UPCR will be the dependent variable.

Safety Analyses

Safety analyses will include the examination of vital signs, physical exam, 12-lead ECG, routine clinical laboratory tests (including hematology, blood chemistries, urinalysis), and AEs. All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

8.5.2 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent adverse events (TEAEs) will be summarized using descriptive statistics by treatment group. Treatment-emergent adverse events are defined as AEs with onset dates occurring during the study period (i.e., from the first dose until the subject's last study visit) and will be assigned to the most recently received treatment at the start of the AE. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each MedDRA System Organ Class and MedDRA Preferred Term, by treatment group. Treatment-emergent adverse events will also be summarized by relationship to treatment and by severity within each treatment group, and by predefined AESIs.

8.5.3 Other Analyses

Laboratory data, vital sign data, and ECG data will be summarized by timepoint and treatment group with descriptive statistics.

8.5.4 Pharmacokinetic and Pharmacodynamic Analyses

Analyses of the PK substudy, serum BLyS, APRIL, Gd-IgA1, and other exploratory biomarkers will be summarized using descriptive statistics. Additional analyses may be detailed in the SAP.

9 Phase 2b: Responsibilities

9.1 Investigator Responsibilities

9.1.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2 Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

9.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions on the study.
- Subjects must be informed that their participation is voluntary.
- Subjects or their legal representative under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, subjects must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the subject.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

9.1.4 Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected.

- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study subject. The file must identify each subject, contain the following demographic and medical information for the subject, and should be as complete as possible:

Subject's full name, date of birth, sex, height, and weight

Medical history and concomitant diseases

Prior and concomitant therapies (including changes during the study)

Study identifier (i.e., the Sponsor's study number) and subject's study number

Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site

Any medical examinations and clinical findings predefined in the protocol

All AEs

Date that the subject left the study, including any reason for early withdrawal from the study or study drug, if applicable

- All source data must be filed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] scan images, ECG recordings, and laboratory results). Each document must clearly identify the subject and the procedure date, ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. Investigators must notify Sponsor in advance if source documents are to be moved to another location, such as for archiving.

9.1.5 Data Protection

- The Sponsor will assign a unique identifier to subjects after obtaining their informed consent. All subject records or datasets transferred to the Sponsor will contain the identifier only; subject names or any identifiable information will not be transferred.
- The Sponsor must inform subjects that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain subjects' confidentiality.
- The Investigator will complete the subject registration using the IWRS (Section 5.1). If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the

subject will be registered by IWRS. If the subject is ineligible for the study, a subject number will be allocated and documented.

9.2 Sponsor Responsibilities

This clinical study will be Sponsored by: Vera Therapeutics, Inc.

The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

An iDMC will be formed in this study (see Section 3.2).

9.2.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
 - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study subjects. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
 - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
 - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

9.2.2 Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to subjects for use during the study. These provide the means for subjects to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical

treatment for the subject. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the subject. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician (or designee). This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician (or designee) to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.2.3 Clinical Study Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

9.2.4 Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator.

9.2.5 Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.2.6 Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

9.3 Data Quality Assurance

- All subject study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of subjects are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

9.4 Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
 - Inadequate recruitment of subjects by the Investigator
 - Discontinuation of further development of the Sponsor's compound

Phase 3 Study (ORIGIN 3)

10 Important Clinical Study Note

It is important to note to all study investigators, regulators, competent authorities, ethics committees, institutional review boards, scientific committees, site staff, clinical research organizations, and individuals involved in the review or conduct of this study that the design of this protocol is a multi-part study as described below. Some study sites and countries will be participating in the Phase 2b component only, the Phase 3 component only, or both components.

This is a multi-part study comprising of the original Phase 2b study (Parts A and B) and the addition of a separate Phase 3 study (Parts C and D). The Phase 3 study has been added as a separate component to the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from the Phase 2b study have been used to inform the Phase 3 study design including selection of dose and determination of sample size.

The Phase 2b study is referred to as ORIGIN and the Phase 3 study is referred to as ORIGIN 3.

Phase 3:

- a) Synopsis: Pages [95](#) through [109](#)
- b) Protocol: Sections [11](#) through [19](#)

Key differences between the Phase 2b and Phase 3 studies are summarized in the table below and in [Appendix 4](#).

Key Differences Between Phase 2b and Phase 3 Studies

	Phase 2b	Phase 3
Objectives and Endpoints		
Primary endpoint	UPCR at Week 24	UPCR at Week 36
Secondary endpoint	UPCR at Week 36	Key: Annualized rate of change in eGFR at Week 104 Other: <ul style="list-style-type: none"> GdIgA1 at Weeks 36, 52, and 104 [REDACTED] Composite kidney failure endpoint
Exploratory endpoints	<ul style="list-style-type: none"> UPCR at Week 12 [REDACTED] eGFR at Week 12, 24, and 36 IgA, IgG, IgM levels, C3, C4, and Gd-IgA1 levels at Weeks 12, 24, and 36 PK of atacicept 	[REDACTED]
Study Design		
Randomization and treatment	2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo	1:1 to atacicept 150 mg or matching placebo
Stratification	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (≥ 30 to < 45 mL/min/1.73 m² and ≥ 45 mL/min/1.73 m² by CKD-EPI) 	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (< 45 mL/min/1.73 m², or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI) Screening total urine protein excretion (< 2 g/24h or ≥ 2 g/24h) Region (Asia or Other) SGLT2 inhibitor use at screening (Yes or No)

	Phase 2b	Phase 3
Double-blind period duration	36 weeks	104 weeks
Study visits and assessments after premature study drug discontinuation in the double-blind period	Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination (ET) Visit and have a 26-week follow-up period.	Subjects who prematurely discontinue study drug prior to completion of the 104-week treatment period should continue with study visits and assessments per protocol through the end of the double-blind period.
Open-label extension duration	60 weeks	52 weeks
Duration of treatment	Up to 96 weeks	Up to 156 weeks
Number of sites / subjects	90 / 105	200 / 376
Eligibility Criteria – Inclusion criteria		
Upper age limit	Not defined	≤70 years
Screening proteinuria allowed	Total urine protein excretion >0.75g or UPCR >0.75 mg/mg based on a 24-hour urine sample	Total urine protein excretion ≥1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥1.0 mg/mg based on a 24-hour urine sample
Criteria for RAASi use during Screening	On a stable prescribed regimen of RAASi (ACEi, ARB or MRA) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening.	On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1.
Eligibility Criteria – Exclusion criteria		
Systemic corticosteroids	Corticosteroids for the treatment of IgAN within 3 months prior to screening.	Corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening.
Criteria for clinically significant or predefined abnormalities	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN. <p>If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver</p>	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN. <p>- If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase</p>

	Phase 2b	Phase 3
	transaminases), contact the Medical Monitor for further discussion.	<p>in liver transaminases), contact the Medical Monitor for further discussion.</p> <ul style="list-style-type: none"> hemoglobin <10 g/100 ml in men and hemoglobin <9 g/100 ml in women platelets <100 000/1 mm³
Hepatitis C virus (HCV)	Subjects with any hepatitis C virus (HCV) are excluded	Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
History of malignancy	History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix	History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ), with no evidence of recurrence
Permitted Medications		
Use of SGLT2 inhibitors and mineralocorticoid receptor antagonists	In subjects receiving SGLT2 inhibitors at the time of enrollment, the dose must be stable for at least 8 weeks prior to screening and is expected to be at a stable dose over the study period. The Investigator should discuss planned use of an SGLT2 inhibitor with the Medical Monitor prior to initiation for their awareness.	As with RASi medications, subjects prescribed SGLT2 inhibitors and/or mineralocorticoid receptor antagonists (MRAs; e.g. aldactone, eplerenone or finerenone) are required to be on a stable dosing regimen for at least 12 weeks prior to screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes or the introduction of SGLT2 inhibitors and/or MRAs. If, in the opinion of the Investigator, intervention is warranted, it is strongly recommended that the Investigator the Medical Monitor must be notified within 48 hours of such intervention. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the introduction of SGLT2

	Phase 2b	Phase 3
		inhibitors and/or MRAs, but this at the investigator's discretion if feasible.
RAAS inhibitor changes during treatment period	It is recommended that changes in RASi medication be avoided for the duration of the study.	To be eligible for randomization, all subjects who tolerate RASi (ACEi or ARB) medication are required to be on stable RASi treatment for at least 12 weeks prior to Screening that is at the maximum labeled or tolerated dose, which must be maintained through the screening period to Day 1. For subjects who are unable to tolerate RASi medication, management of IgAN will be SoC according to local practice. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes and changes in type of RASi medication; every effort should be made to maintain subjects on their stable RASi dose, unless required for safety reasons. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non RASi medications should have been considered before these specific drug classes. In certain instances (i.e. hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].
Rescue medications	Not defined	Defined as: Should the Investigator consider that rescue medication (steroids and/or immunosuppressive treatment) be needed, such treatment can be initiated by the Investigator. However, in consideration of current guidelines (2021 KDIGO guidelines), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

	Phase 2b	Phase 3
		<ul style="list-style-type: none"> • Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] (although treatment toxicity must be considered in those with eGFR < 50); and/or • Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., >3.5 g/day] and hypoalbuminemia [albumin < 3.0 g/dL]) <p>Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. If rescue medication is required, it is the Investigator's decision to implement new treatment. In this case, the Medical Monitor must be notified within 48 hours after the initiation of rescue therapy, as continued dosing with IMP may, in this circumstance, be discontinued. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of rescue medication, but this at the investigator's discretion if feasible.</p> <p>Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 15.7.1.</p>

	Phase 2b	Phase 3
Prohibited Medications		
Systemic corticosteroids	No specific corticosteroid given	Includes oral budesonide
Schedule of Assessments		
Additional site visits not included in SOA table	N/A	Additional visits can be conducted at Weeks 1, 3, and 105.
Treatment with IMP		
Pulse and BP monitoring on Study Day 1	Pulse and BP will be recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes	Pulse and BP will be recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
Local Tolerability (Injection Site Assessment)		
Grading scales for severity of manifestations	Any local injection site reactions (ISRs) will be assessed by the Investigator and recorded as AEs. Severity of the ISR reported on the AE form should reflect the highest severity of the manifestation.	Any clinically significant ISR as per Investigator judgement will be reported as an AE. Severity of the ISR reported on the AE form based on grading scale provided in protocol Section 16.6.5.
Clinical Laboratory Assessments		
Amount of blood collected per subject per visit / total	14-16 mL / 552 mL	15-43 mL / 757.5 mL
Abnormal lab values	Adverse events related to abnormal lab values are graded based on CTCAE scale.	Adverse events related to abnormal lab values are graded based on the Toxicity Scale used for all other adverse events.

	Phase 2b	Phase 3
Adverse Events of Special Interest (AESI)		
Definition of AESI of infection	Defined as opportunistic infections considered to be medically significant but not meeting definition of serious adverse events (SAE) of infection	Defined as serious adverse event (SAE) of infection
<i>Contraception</i>		
Female subjects	Not defined	Invasive Methods defined as user-independent invasive contraceptive methods herein mentioned in this appendix is provided as a guidance. Women of childbearing potential who are already using one of these highly effective invasive contraceptive methods prior to inclusion OR who will begin using any of these highly effective contraceptive methods by their own decision will be eligible for inclusion.
Male subjects	Not included	It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

	Phase 2b	Phase 3
<i>Statistical Methods</i>		
Statistical testing	Statistical testing will be conducted for the primary and secondary efficacy endpoints with no adjustments for multiple comparisons with a significance level of 0.05.	To control type 1 error in the evaluation of the primary and key secondary efficacy endpoints, the hypothesis testing will be performed in sequential order. The primary efficacy endpoint will be tested first at a significance level of 0.05. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at a significance level of 0.05. If the statistical significance is not met for the primary endpoint, the key secondary efficacy endpoint cannot be deemed statistically significant, although nominal p-values and 95% CIs may be reported and considered descriptive. Similarly, the sequential testing approach will be used to test other selected secondary endpoints.

Phase 3 (ORIGIN 3) Protocol Synopsis

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Rationale: Atacicept (also known as VT-001) targets B-cells by inhibiting B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), and has been studied in a pilot Phase 2a clinical study for immunoglobulin A (IgA) Nephropathy (IgAN). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and galactose-deficient IgA1 (Gd-IgA1), and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. The Phase 2b clinical study results at week 24 support clinical efficacy and safety as well as best dose regimen for further evaluation. Based on the available clinical data, the targeted population for this Phase 3 study is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). The objectives of the Phase 3 study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 36 (MMRM)
Key Secondary		
Evaluate the effect of atacicept on annualized rate of change in estimated glomerular filtration rate (eGFR)	Annualized Rate of change in eGFR ^b	Through Week 104
Secondary		
Evaluate the effect of atacicept compared to placebo on change in Gd-IgA1	Gd-IgA1	Weeks 36, 52, and 104
Evaluate the effect of atacicept on annualized rate of change in eGFR	Annualized Rate of change in eGFR ^b	Through Week 52
Time from randomization to first occurrence of composite kidney failure endpoint event	<p>Composite kidney failure endpoint defined as experiencing at least one of the following during the study:</p> <ul style="list-style-type: none"> At least a 30% reduction in eGFR sustained for at least 30 days eGFR <15 mL/min/1.73m², sustained for at least 30 days Chronic dialysis ≥30 days Kidney transplantation Death from kidney failure. 	Through the end of double-blinded period.
Exploratory		

ADA=anti-drug antibodies; eGFR=estimated glomerular filtration rate; [REDACTED]
[REDACTED] Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin;
IgAN=immunoglobulin A Nephropathy; MMRM = mixed-effect model with repeated measurement; [REDACTED]
[REDACTED]

- a. Based on 24-hour urine sample
b. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults

Overall Design:

This is a multi-part study comprising of the original Phase 2b study and the addition of a separate Phase 3 study. A Phase 3 study (i.e., Parts C and D) has been added as a separate component of the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from the Phase 2b parts have been used to determine the dose selection and sample size for the Phase 3 study design.

The Phase 3 study is a multicenter, randomized, double-blind, placebo-controlled trial. In Part C, subjects will be randomized 1:1 to atacicept 150 mg or placebo for 104 weeks:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly subcutaneous (SC) injections (N=188)

Followed by a 52-week open-label extension (Part D) in which subjects will be given 150 mg atacicept once weekly subcutaneous (SC) injections.

Subjects who have participated in Part A or B may not participate in Part C or D.

Subjects participating the study will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/ 1.73 m², or ≥ 45 to <90 mL/min/ 1.73 m², or ≥ 90 mL/min/ 1.73 m²), total urine protein excretion (<2 g/24h or ≥ 2 g/24h), SGLT2i use at screening (yes or no), and Region (Asia or Other). The use of SGLT2 inhibitors could impact the evaluation of clinical efficacy of the IMP. The Sponsor may cap the enrollment of these subjects.

The Phase 3 study is composed of a (up to) 4-week Screening Period, a 104-week Double-Blind Treatment Period (Part C), a 52-week Open-Label Extension (Part D) and 26 weeks of follow-up. Subjects who complete the 104-week Double-Blind Period on treatment will be eligible for open-label atacicept 150 mg for an additional 52 weeks (Open-Label Extension). Subjects who prematurely discontinue study drug prior to completion of the 104-week treatment period should continue with study visits and assessments per protocol through the end of the double-blind period. After the last subject completes the 104-week double-blind period or completes an Early Termination Visit, the study will be unblinded.

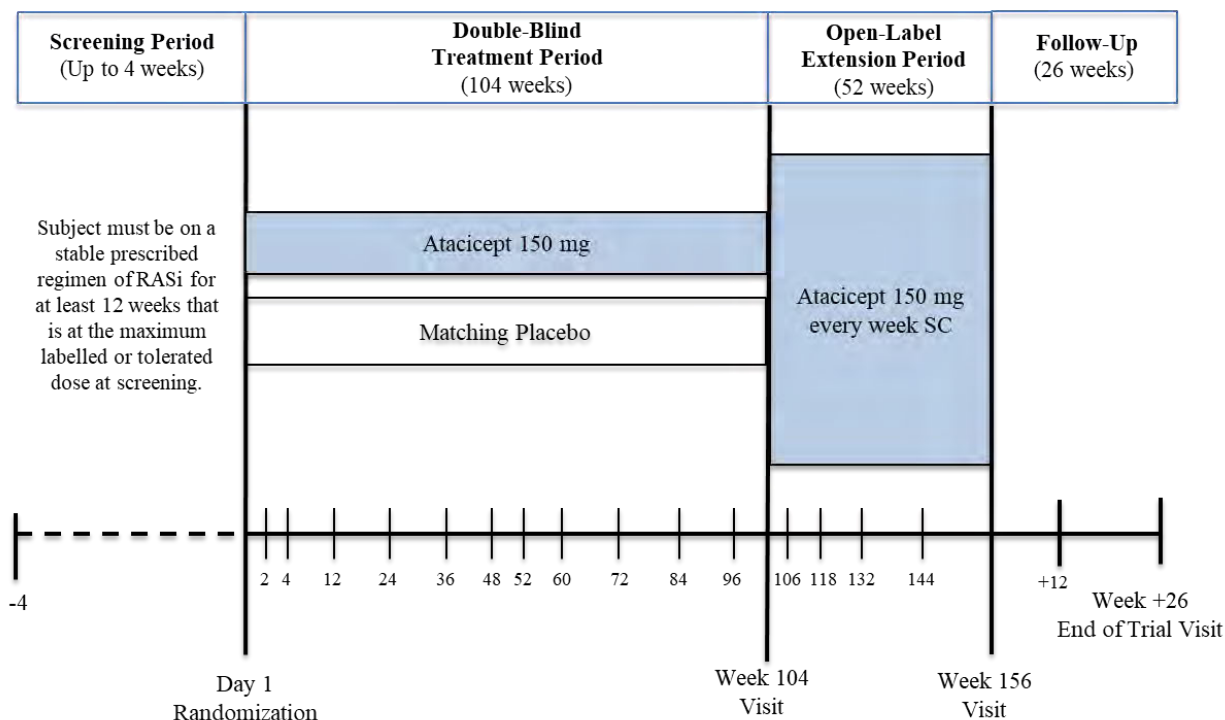
The study will be conducted on an outpatient basis.

Number of Study Sites: Approximately 200

Number of Subjects: Approximately 376 randomized

Involvement of Special Committee(s): An independent Data Monitoring Committee (iDMC) will review safety data on an ongoing basis.

Study Schema



Note: Subject's stable dose of ACEi and/or ARB must be maintained for the duration of the study.

Target Population: Male or female patients with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of RASi for at least 12 weeks that is at the maximum labeled or tolerated dose.

Duration of Study Drug Treatment: Up to 156 weeks (104 weeks blinded + 52 weeks OLE)

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age and ≤ 70 years, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit.
4. Total urine protein excretion ≥ 1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 1.0 mg/mg based on a 24-hour urine sample during the Screening Period
5. eGFR ≥ 30 mL/min/1.73 m² at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

- 6 On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1
 - The subject is eligible if they do not tolerate RASi, provided their management of IgAN is standard of care (SoC) per local practice. This must be discussed with the medical monitor and documented by the Investigator
- 7 Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening
- 8 A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details

Exclusion Criteria:

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. Participation in the Phase 2b (Parts A and B) study or any previous treatment with atacicept.
2. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis
3. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
4. Evidence of nephrotic syndrome within 6 months of screening (serum albumin < 30 g/L in association with UPCR > 3.5 mg/mg)
5. Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants
6. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
7. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $> 7.5\%$ at screening
8. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive QuantiFERON test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without

evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

9. Prohibited medications:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 12 weeks prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for >1 week or average dose >0.5 mg/kg/day prednisolone or equivalent
- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or expected use during the study.
- Use of traditional Chinese medications and/or Ayurvedic medications within 12 weeks prior to screening or from screening to Day 1.
- Use of B-cell-directed biologic therapies including but not limited to belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time
- Use of endothelin receptor antagonists (ERAs) for any period of time

10. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:

- serum IgG below 7 g/L
- aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN.
 - i. If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.

- hemoglobin <10 g/100 mL in men and hemoglobin <9 g/100 mL in women
 - platelets <100,000/L mm³
11. Administration of live and live-attenuated vaccinations within 30 days prior to randomization
 12. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
 13. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
 14. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
 15. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.
 16. History of acute or chronic infection with human immunodeficiency virus, or hepatitis B virus.
 - Positive hepatitis B surface antigen (HBsAg) are excluded
 - Subjects who are HBsAg negative, hepatitis B core antibody (HBcAb) positive, hepatitis B surface antibody (HBsAb) positive, and with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow-up
 17. Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
 18. History of splenectomy
 19. History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).
 20. Known hypersensitivity to atacicept or any component of the formulated atacicept
 21. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)

22. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
23. Unwillingness or lack of capacity to follow all study procedures
24. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

Study Procedures/Frequency:

Study visits will occur at Screening, Day 1, Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, 96, and Week 104 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 106, 118, 132, 144, and 156. Note that for Weeks 4, 48, 84, 106, and 132, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP and home health care (if available). For the Phase 3 study, facilitation of optional remote visit(s) is the responsibility of the Investigator and site staff.

If, in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted at Weeks 1, 3, and 105. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

There will be a 26-week follow up period after the subject's end study visit (Week 156). Subjects discontinuing study medication prior to Week 104 should continue with study visits and assessments per protocol through the end of the double-blinded period. If the subject discontinued study drug more than 26 weeks before week 104, the subject does not need to complete a further 26 weeks of follow-up after the Week 104 visit. If discontinued less than 26 weeks before Week 104, the subject should complete all visits up to Week 104 and continue into the 26-week safety follow-up period for the appropriate amount of time to ensure 26 weeks of safety follow-up data are collected after the last dose of study drug. Subjects who discontinue after Week 104 will require a 26-week follow-up period.

Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 3](#)).

Test Product, Dose, Mode of Administration, and Reference Therapy:

In a blinded fashion, 150 mg atacicept or placebo, given as once-weekly subcutaneous (SC) injections for 104 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept, given as once-weekly SC injections for 52 weeks by prefilled syringe. It is strongly recommended that changes in RASi medication be avoided for the duration of the double-blind study.

Statistical Methods: The Phase 3 Statistical Analysis Plan (SAP) will be developed and finalized before the database lock for the first analysis. The SAP will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary

endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Any deviations from this plan will be noted in the final clinical study report.

To control the overall type 1 error in the evaluation of the primary and key secondary efficacy endpoint at a two-sided alpha of 0.05, the hypothesis testing will be performed in sequential order by fallback procedure. The primary efficacy endpoint will be tested first at a two-sided significant level of 0.04. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at two-sided significant level of 0.05. If statistical significance is not met for the primary endpoint, the key secondary efficacy endpoint will be tested at a two-sided significant level of 0.01. If statistical significances are met for both primary and key secondary endpoints, the sequential testing approach will be used to test other secondary endpoints at a two-sided significant level of 0.05. More details regarding the order of sequential testing will be pre-specified in Phase 3 statistical analysis plan.

Sample size and power calculations

The primary efficacy endpoint is the change from baseline at Week 36 in natural log transformed UPCR (i.e., $\log(\text{UPCR})$). A two-sample t-test for ratios was used to determine the sample size for UPCR. It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo groups is expected to be 0.67 and the standard deviation (SD) for the mean change of $\log(\text{UPCR})$ from baseline is assumed to be 0.7 in both groups (based on ORIGIN Phase 2b Week 24 Primary Endpoint Analysis). Based on these assumptions, 85 subjects per group will provide 95% power to detect a ratio of 0.67 with a two-sided alpha of 0.04 when the ratio under the null hypothesis is 1 [PASS 2021: two-sided two Sample t-test for ratios]. Adjusting for a dropout rate of approximately 15%, 200 subjects in total (100 subjects per group) will be needed to support the primary endpoint analysis at Week 36.

For the key secondary endpoint, a meta-analyses for the association of treatment effects on early change in UPCR and treatment effect on eGFR annualized slope in IgAN patients by [Inker et al \(2021\)](#) is referenced to estimate the expected treatment effect on eGFR annualized slope. The mixed-effects model with random intercept and random slope for comparing the 2 slopes was used to determine the sample size for eGFR ([Ahn 2014](#)). It is assumed that the ratio of geometric mean ratio of week 36 UPCR to baseline between atacicept and placebo is 0.67. According to the established association between UPCR change at 9 months and eGFR annualized slope by Inker et al, the expected difference in annualized slope in eGFR is 2 mL/min/1.73m²/year using linear extrapolation. The variance of random slope is 27 and the variance of residuals is 32 based on an internal Phase 2a study (JANUS trial). The follow-up period is approximately 2 years (ie., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between atacicept and placebo groups. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) should be enrolled.

Planned Analyses

The primary analysis of UPCR will be performed after the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study. An End of Part C analysis will be performed when

all subjects complete the double-blind portion of the study (i.e., Week 104) or prematurely discontinue from the study. A final analysis will be conducted once all subjects complete the OLE and safety follow-up visits or discontinue from the study. Additional analyses may be conducted at the discretion of the Sponsor to plan future studies. The details of these analyses will be provided in the SAP.

Analysis Population

All randomized subjects receiving at least one dose of study intervention will be included in the Safety Analysis Set and Full Analysis Set (FAS). Subjects in the FAS who do not have any clinically important protocol deviations will be included in the Per-Protocol (PP) Analysis Set. Subjects in the FAS will be analyzed according to randomized treatment assignment. The primary analyses for all efficacy endpoints will be based on the FAS and the supplemental analyses for the primary and selected efficacy endpoints will be based on the PP Set. Safety analyses will be based upon treatment actually received and include all subjects in Safety Analysis Set.

Primary and key secondary efficacy endpoint analysis

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR at Week 36. A mixed-effects model with repeated measurement will be used to analyze the change from baseline in natural-log transformed UPCR. Effects for natural-log transformed baseline value, stratification factor(s), randomized treatment, visit, and treatment-by-visit interaction will be included as independent fixed effects, and subject will be included as a random effect. The primary comparison will test the mean difference between the atacicept and the placebo at Week 36. This statistical comparison will be based on linear contrasts of the Least Squares Means (LSMeans) estimated from this model. LSMeans differences will be exponentiated to obtain the mean ratio.

Other efficacy endpoint analyses

All other efficacy endpoints will be evaluated based on the FAS and include all available data following the treatment-policy strategy.

Continuous efficacy endpoints will be analyzed in a similar manner as for the primary efficacy endpoint of UPCR.

Binary efficacy endpoints will be presented as the number and percentage of responders by treatment group. The population-level summary measure is the odds ratio comparing the odds of being a responder in the atacicept vs. placebo group, which will be evaluated by a logistic regression model controlling for stratification factor(s), randomized treatment, and the appropriate baseline value. The odds ratio for the treatment effect, 95% CIs, and p-value will be estimated from the model.

Time-to-event efficacy endpoints will be displayed using Kaplan-Meier methodology. The population level summary measure is the ratio of the hazard rates of the atacicept vs. placebo group for the corresponding endpoint. The population-level study measure will be evaluated using the Cox proportional hazard model with effects for stratification factor(s), randomized treatment, and the appropriate baseline value. Subjects who do not have an endpoint of interest will be censored at the last assessment of the endpoint. The adjusted hazard ratio of the risk of the event between the atacicept and the placebo group, the corresponding 95% CIs, and p-value will be estimated from this model.

Safety endpoint analyses

All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

Blinding and unblinding considerations

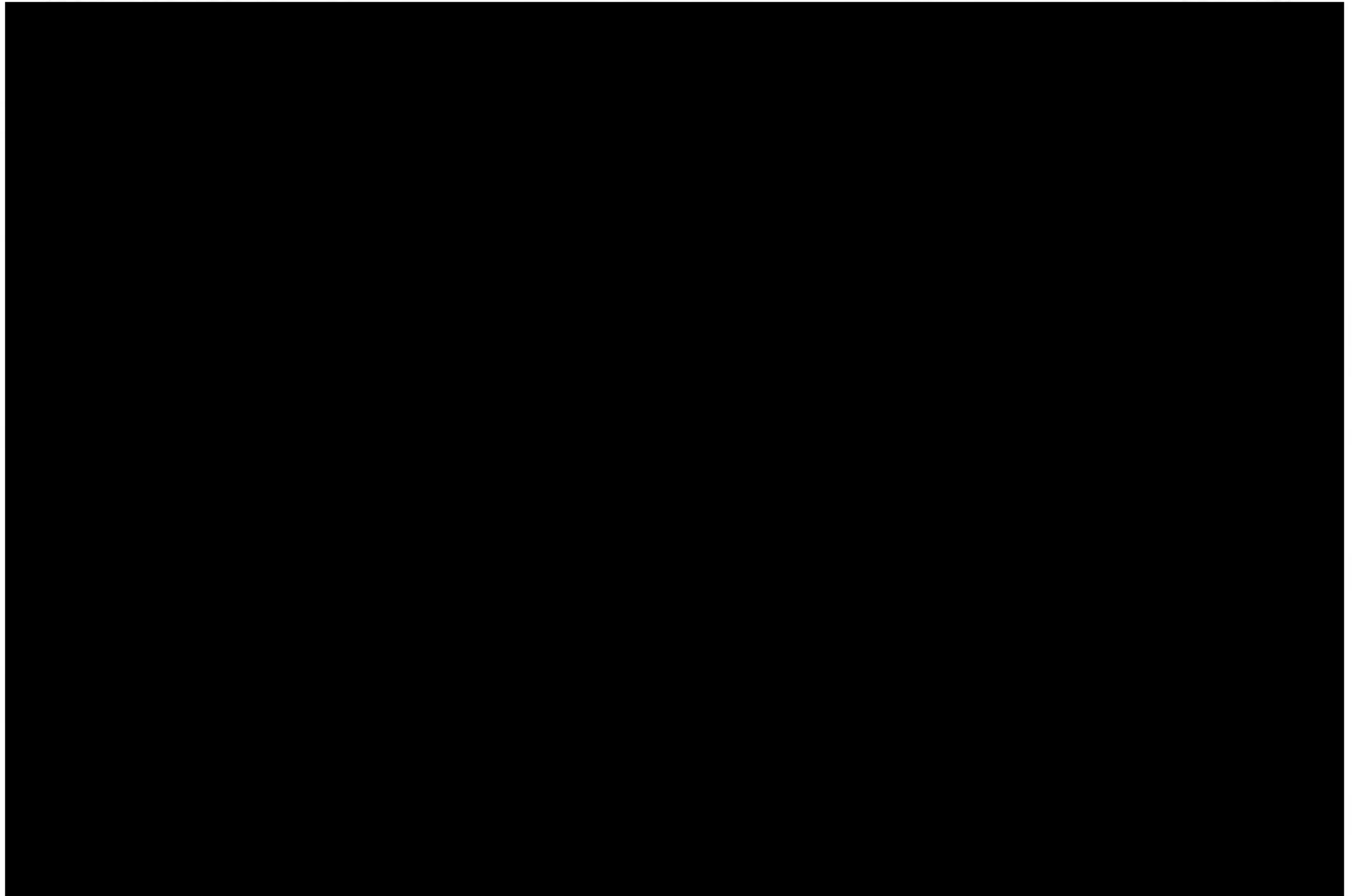
Subjects will be randomly assigned to a treatment group based on a predefined randomization code via the interactive web response system (IWRS) at the Day 1/Randomization visit. The site staff, Sponsor, and contract research organization (CRO) will be blinded to the subject's treatment allocation, with the exception of the selected study drug supply, iDMC, and serious adverse event (SAE) reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of analysis of the primary endpoint. A blinding plan will be developed to outline the study-specific approaches to protect the study blind and data integrity. For emergency unblinding only, corresponding treatment assignments will be made available to the Investigator through the IWRS.

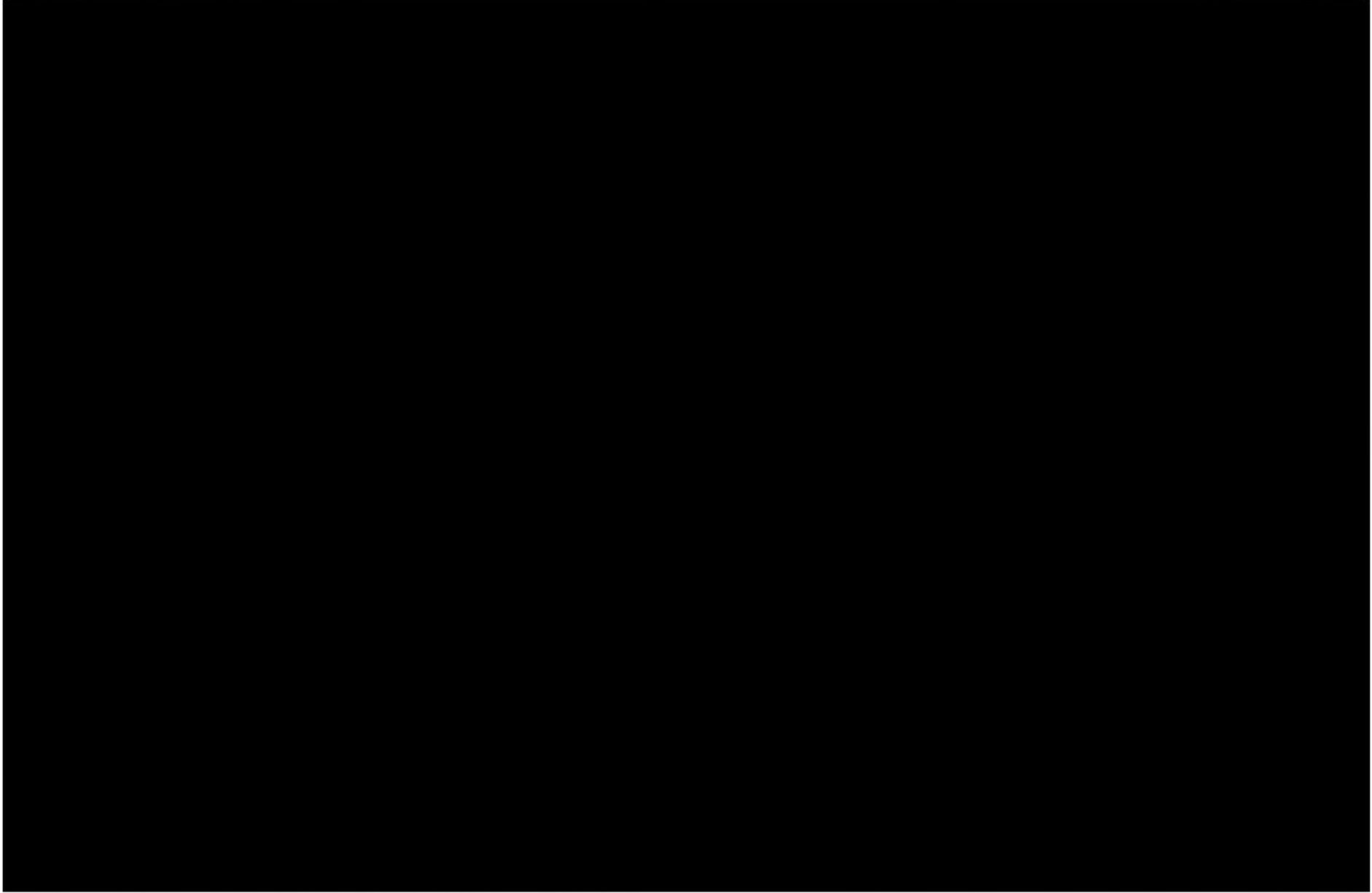
Compliance

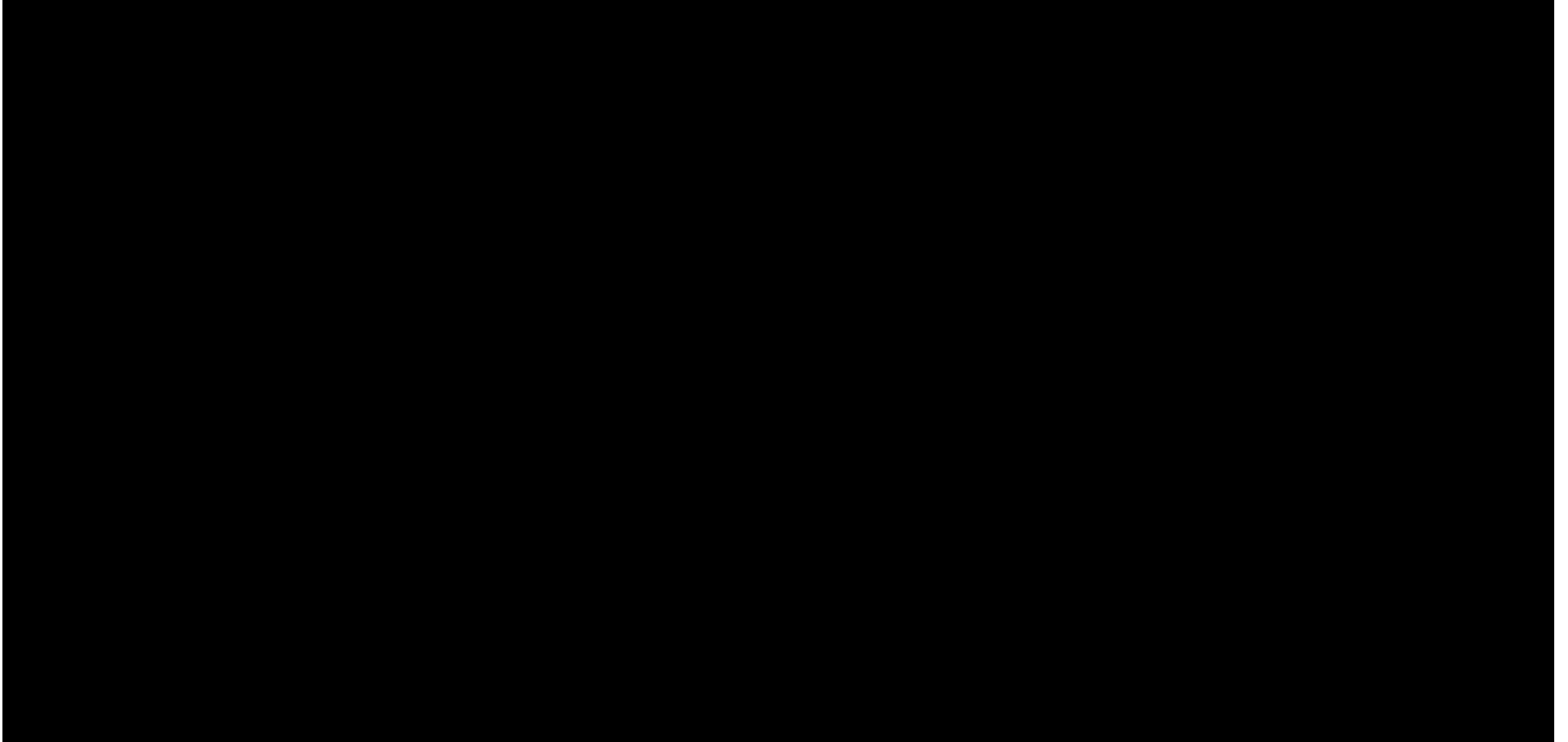
The study will be conducted with the guidelines of Good Clinical Practice (GCP).

Table 3 **Phase 3: Schedule of Assessments**









11 Phase 3: Introduction

Atacicept (also known as VT-001) is a novel immunomodulator, administered by subcutaneous (SC) injections, dual-blocking the activity of B lymphocyte stimulator (BLyS, also known as B-cell activating factor) and a proliferation-inducing ligand (APRIL). Inhibition of BLyS and APRIL leads to a decrease in the maturation, differentiation, and effector function of B cells and plasma cells (Dillon 2006, Dillon 2010, Moore 1999, Ramanujam 2004, Schneider 1999). Atacicept is being developed for the treatment of patients with IgA Nephropathy (IgAN).

Complete information on the atacicept nonclinical and clinical program, and summaries of key chemistry, pharmacology, efficacy, and safety data of atacicept are provided in the Investigator's Brochure (IB).

11.1 Background

Immunoglobulin (Ig) A nephropathy (IgAN) or Berger's disease, is the most frequent biopsy-proven primary glomerular disease, but with widely variable geographic distribution (Lai 2016, Schena 2018). The prevalence of IgAN can be difficult to ascertain because of regional variability in screening and renal biopsy practices, however; a 15-year retrospective study of the United States (US) Renal Data System found that of over 84,000 end stage renal disease (ESRD) patients with glomerulonephritis (GN) etiology, around 15% were attributed to IgAN (O'Shaughnessy 2015). The global incidence of primary GN ranges from 2 to 25 per million people (pmp) per year, with a worldwide IgAN incidence of at least 25 pmp per year in adults (McGrogan 2011), and an age adjusted US incidence of approximately 21 pmp per year (Swaminathan 2006). Consistent with differences in incidence based on ethnicity and genetic predisposition, biopsy data from autopsy and donor registries support a higher prevalence of IgAN in East and Pacific Asian countries (Rodrigues 2017), as compared to Southern Europe and Africa (Kiryluk 2012).

Immunoglobulin A nephropathy (IgAN) is highly variable, both clinically and pathologically. The classic presentation of IgAN is visible hematuria following an infection, but, more typically, IgAN presents as asymptomatic non-visible hematuria, with or without proteinuria. Renal impairment and hypertension are often present in subjects with older age at presentation (Barratt 2005). Up to 40% of all subjects with IgAN will progress to ESRD over 30 years (D'Amico 2000). In the US, IgAN accounted for 1.8% (10,557) of all prevalent subjects on dialysis at the end of 2011 (US Renal Data System 2013), with 5,044 incident subjects during the 5-year period from 2007 to 2011, or approximately 1000 subjects per year (US Renal Data System 2013). The annual incidence of ESRD due to IgAN can be estimated as 0.32/100,000 using the US population estimate from the US Census of 309 million people undertaken in 2010 (Mackun 2010).

A histopathological hallmark of IgAN is accumulation of poorly *O*-galactosylated IgA1 (Gd-IgA1) in the glomerular mesangium, either alone or in combination with IgG and/or IgM (Wyatt 2013). Sampling of the serum and plasma of subjects with IgAN has confirmed the presence of elevated levels of IgA-containing immune complexes containing Gd-IgA1 (Czerkinsky 1986). Circulating Gd-IgA1 containing immune complexes were later shown to be the target antigens for IgG antibodies with specificity for the *O*-glycans of the IgA1 hinge region (Suzuki 2009). Hence, IgAN is a unique autoimmune disease whereby the pathogenesis is driven by an autoantigen (Gd-IgA1) eliciting an autoantibody (IgG anti-glycan) response.

11.1.1 Medical Need in IgA Nephropathy

The level of 24-hour protein excretion is a risk indicator for morbidity and mortality in patients with renal disease. Patients with IgAN with persistent proteinuria > 1 g/day are at increased risk of progression to ESRD ($> 60\%$ over 20 years) (Berthoux 2011, Lee 2012, Moriyama 2014, Reich 2007). They are also at increased risk of cardiovascular mortality; up to 50% experience a cardiovascular event prior to reaching ESRD and their mortality risk is 43% higher compared with age/sex-matched controls in the general public (Lee 2012). By contrast, subjects with IgAN with proteinuria < 1 g/day have mortality rates similar to those of the general public. Furthermore, in the STOP-IgAN study which recruited IgAN patients with proteinuria (urine protein to creatinine ratio [UPCR] ≥ 0.75 mg/mg), $>50\%$ of patients progressed to death, ESRD, or eGFR decline of over 40% after 7.4 years, and use of immunosuppression, including corticosteroids, made no difference to outcome (Rauen 2020).

Since first being described in 1968, there have been limited advances in the treatment for IgAN. The central component of supportive care consists of appropriate blood pressure (BP) control and proteinuria management using Angiotensin Converting Enzyme Inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis (International Society of Nephrology 2012). The use of renin-angiotensin-aldosterone system inhibitor (RAASi) has been shown in randomized controlled studies to decrease proteinuria and correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day (Descamps-Latscha 2004).

Other treatments, such as corticosteroids (CS) and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is cautiously suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate blood pressure control and treatment with ACEis (International Society of Nephrology 2012), a recent review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist particularly in light of the prematurely halted TESTING study (Lv 2012, Lv 2017).

There is a significant unmet medical need for the treatment of IgAN, as there are currently no therapies proven effective in large randomized controlled trials. Current management includes BP control, renin-angiotensin system (RAS) blockade (with ACEi/ARB) and in rare instances combination immunosuppression with cyclophosphamide and corticosteroids for rapidly progressive IgAN (International Society of Nephrology 2012). In Japan, tonsillectomy is sometimes performed (Liu 2015). There are insufficient data supporting the use of most of the above listed therapies for IgAN, with the exception of RAASi. Reviews of randomized controlled trials suggest benefit from RAS blockade in reducing proteinuria and improving renal outcomes, but it is unclear whether this latter outcome is beyond the benefit expected from the control of hypertension alone (Cheng 2009, Hotta 2013, Reid 2011). The benefits of corticosteroid therapy and tonsillectomy for IgAN remain unclear (Lv 2012, Zhou 2011).

Thus, available treatments for IgAN are currently inadequate. Given that outcomes in subjects with IgAN remain poor, particularly with respect to development of ESRD and overall mortality, IgAN cannot be considered an indolent disease and better treatments are required.

11.2 Scientific Rationale for Study Design

This Phase 3 study will evaluate the efficacy and safety of the planned commercial dose of atacicept (150 mg) compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria despite being on a maximally tolerated dose (MTD) of a RASi. High risk of progression in IgAN is currently defined as proteinuria >0.75 -1 g/d despite optimized supportive care ([International Society of Nephrology 2021](#)).

Atacicept is capable of binding to all known conformations of BLyS and APRIL and is thus expected to inhibit the maturation, differentiation, and effector function of B cells. These mechanisms are consistent with the known pharmacological effects of atacicept, which include depletion of peripheral B cell subsets, naïve follicular, marginal zone and long lived plasma cell B cell subsets, impeded germinal center reaction, and reduced immunoglobulins, while leaving immature B cells and memory B cells intact ([Dillon 2006](#), [Dillon 2010](#), [Gross 2001](#), [Moore 1999](#), [Schneider 1999](#), [Schneider 2005](#)). These effects are predicted to reduce the production and subsequent deposition of Gd-IgA1-containing immune complexes in kidney glomeruli, and thus reduce the extent of kidney injury in IgAN patients.

Atacicept has been studied in a pilot Phase 2a clinical study for IgAN (MS700461-0035). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and Gd-IgA1, and stable estimated glomerular filtration rate (eGFR), which warranted further study of atacicept in this population. Further evaluation of atacicept was performed through 24 weeks of a dose-ranging Phase 2b study for IgAN (VT-001-0050). Results from this study showed a statistically significant difference in reduction of proteinuria with atacicept 150 mg compared with placebo at 24 weeks. Estimated GFR (eGFR) stabilization and reduction in galactose-deficient IgA1 (Gd-IgA1) were also seen in subjects on atacicept 150 mg while both parameters remained stable with placebo. Based on the available clinical data, the targeted population for this Phase 3 study is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable and maximal supportive care regimen. The objectives of the study will be to determine the effect of atacicept versus placebo on proteinuria and preservation of renal function in subjects with IgAN.

Use of ACEis and ARBs:

The central component of supportive care in IgAN consists of appropriate BP control and proteinuria management using RASi as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis ([International Society of Nephrology 2021](#)). The use of ACEis has been shown in randomized controlled studies to decrease proteinuria, and this correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day ([Descamps-Latscha 2004](#)). Therefore, in this study, subjects at the Screening Visit will be required to be on a stable prescribed regimen of RASi for at least 12 weeks that is at the maximum labeled or tolerated dose (as determined by the Investigator), according to standard of care (SoC). Stable SoC background of RASi medication is likely to decrease potential confounding of the study results and may help to better capture the effect of atacicept in this population. Therefore, subjects in all treatment groups will receive optimized, unchanged RASi therapy 12 weeks prior to screening and throughout the duration of the study, thus providing a stable background SoC during this trial. Subjects who are unable to

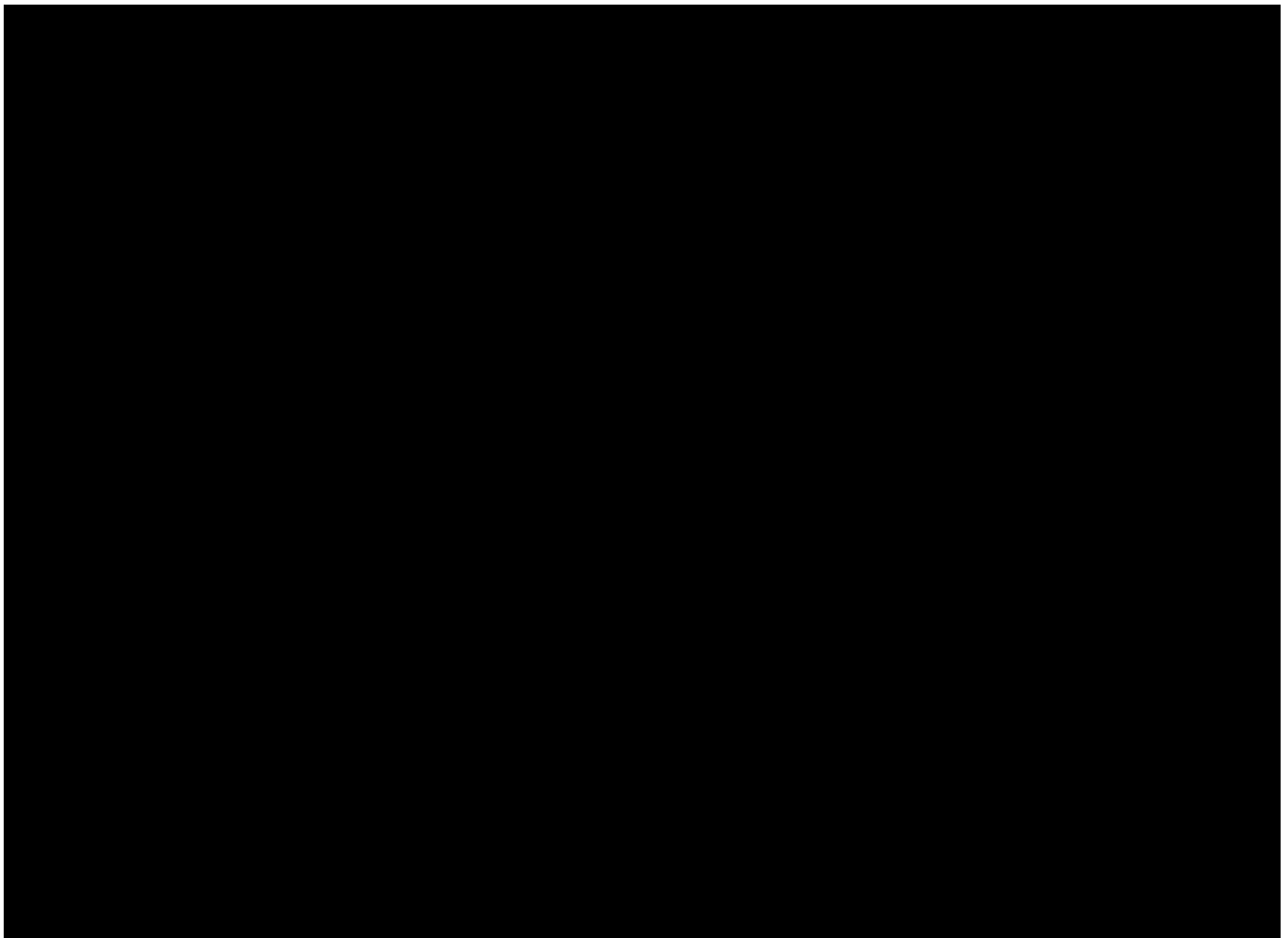
tolerate either RASi medication may be eligible for participation in the study provided their management of IgAN is SoC according to local practice.

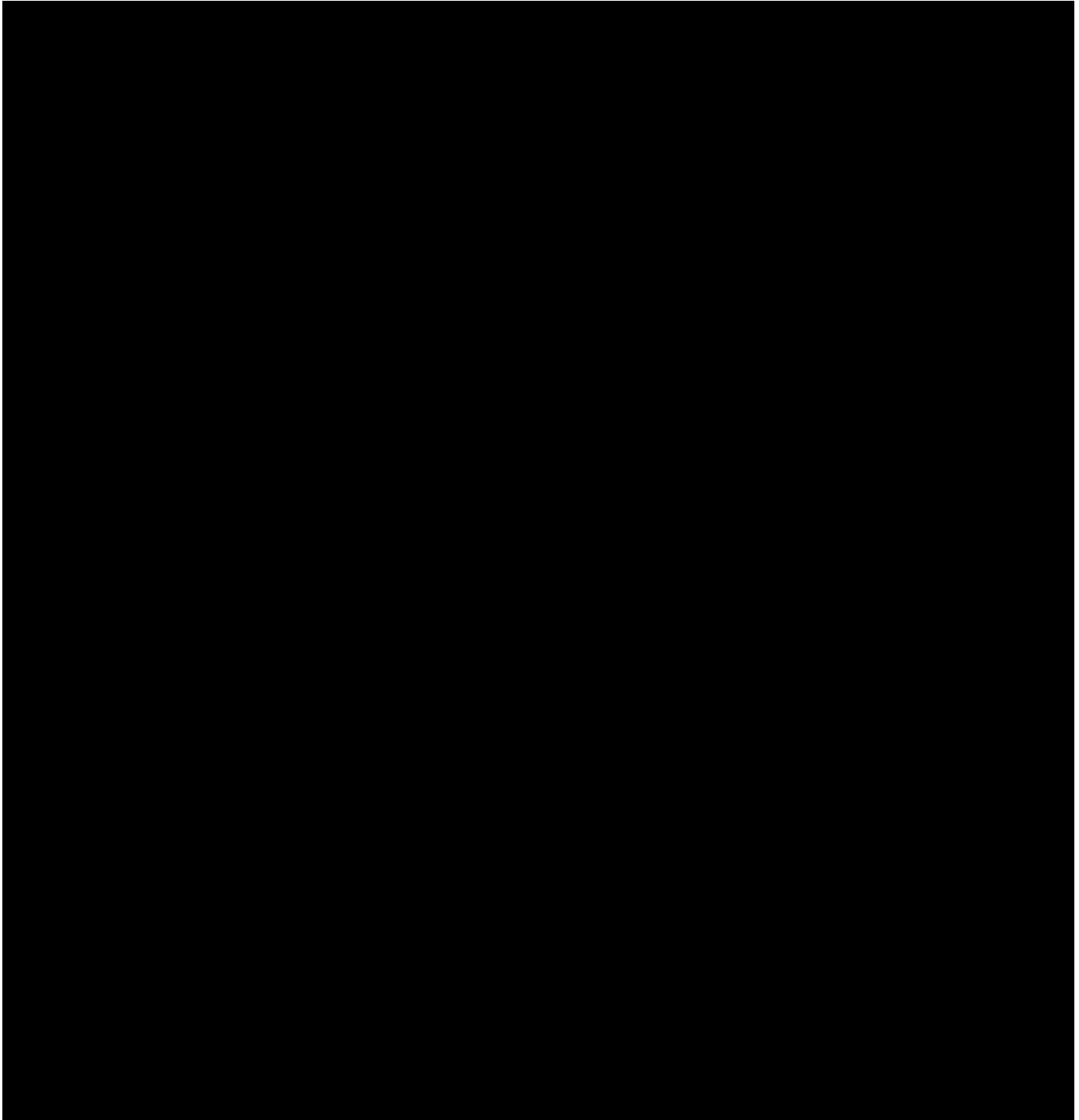
Use of Placebo:

Subjects in atacicept and placebo groups will continue to receive stable background SoC during this trial. Other treatments, such as CS and immunosuppressants, have not been shown to definitively improve renal outcomes ([Floege 2011](#)). Although a short course of CS is suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate BP control and treatment with ACEis ([International Society of Nephrology 2012](#)), a review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist ([Lv 2012](#), [Lv 2017](#)). Therefore, in this trial, the inclusion of a placebo group will allow differentiation of the effect of atacicept treatment from the effect of SoC therapy alone, without potential confounding by other immunosuppressant use.

In conclusion, based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

11.3 Justification for Dose Selection





11.4 Risk Benefit Assessment

The Week 24 results from the Phase 2b part of this study in addition to the Phase 2a JANUS study support that the safety data available for atacicept in patients with IgAN are consistent with those reported in the much larger studies of atacicept in SLE. Data from 2 Phase 2 double-blind, randomized, placebo-controlled (DBPC) studies in SLE (APRIL-SLE and ADDRESS II) evaluated the efficacy and safety of atacicept 150 mg and atacicept 75 mg as compared to placebo

for the treatment of SLE. These studies had different study designs, yet both studies were consistent in showing that atacicept 150 mg weekly SC injections were associated with efficacy and an acceptable safety profile, and thus a positive benefit:risk balance ([Isenberg 2015](#), [Merrill 2018](#), [Morand 2020](#)).

COVID Pandemic Risk/Benefit

Atacicept is an immune-modulator which may impact a patient's innate immune response to infection. In a patient receiving an immune-modulator, there may be a potential for limited or compromised immune response leading to more severe/serious complications of the SARS-CoV-2 infection. However, in an integrated safety analysis (Gordon et al 2019) of over 1500 patients in previous atacicept clinical studies, serious infection rates were similar for atacicept and placebo. In addition, in the ADDRESS II study of SLE patients treated with atacicept 150 mg and 75 mg, titer status for both tetanus toxoid and diphtheria vaccinations remained protective from Day 1 to Week 72 (Wallace et al 2021). Finally, the Week 24 results from the Phase 2b support that number of subjects with COVID-19 AEs was not disproportionate between arms (atacicept 22%, 18 subjects; placebo 18%, 6 subjects). Risk mitigation includes excluding patients with active infection from study participation and recommendation to have up-to-date vaccinations as per local guidelines within 30 days of screening and to remain up to date with all non-live vaccination as per local guidelines during the study. Live and live-attenuated vaccines are not permitted during the study. In the setting of a pandemic or epidemic, the Investigator should evaluate the best option of care for the patient including the screening for active infections prior to and during study participation according to the protocol, should this study be considered as an option.

IgAN patients continue to have too few approved therapies with a high unmet need given the risk for progression to end stage renal disease. Atacicept has promising potential to have clinical benefit for IgAN patients, while being supported with an acceptable safety profile.

12 Phase 3: Objectives and Endpoints

The objectives, endpoints, and endpoint timelines are defined in the table below.

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 36 (MMRM)
Key Secondary		
Evaluate the effect of atacicept on annualized rate of change in estimated glomerular filtration rate (eGFR)	Annualized Rate of change in eGFR ^b	Week 104 (MMRM)
Secondary		
Evaluate the effect of atacicept compared to placebo on change in Gd-IgA1	Gd-IgA1	Weeks 36, 52, and 104
Evaluate the effect of atacicept on annualized rate of change in eGFR	Annualized Rate of change in eGFR ^b	Week 52 (MMRM)
Time from randomization to first occurrence of composite kidney failure endpoint event	<p>Composite kidney failure endpoint defined as experiencing at least one of the following during the study:</p> <ul style="list-style-type: none"> At least a 30% reduction in eGFR sustained for at least 30 days eGFR <15 mL/min/1.73m², sustained for at least 30 days Chronic dialysis ≥30 days Kidney transplantation Death from kidney failure. 	Through the end of double-blinded period.

ADA=anti-drug antibodies; eGFR=estimated glomerular filtration rate;

Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin; IgAN=immunoglobulin A Nephropathy; MMRM = mixed-effect model with repeated measurement; UACR= Urine albumin to creatinine ratio; UPCR=urine protein to creatinine ratio.

a. Based on 24-hour urine sample

b. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults

13 Study Design

13.1 Overall Design

This Phase 3 study is a multicenter, randomized, double-blinded, placebo-controlled study.

The target study population includes male or female subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen for at least 12 weeks with a RASi that is at the maximum labeled or tolerated dose. The use of SGLT2 Inhibitors could impact the evaluation of clinical efficacy of the IMP. The sponsor may cap the enrollment of these subjects.

Approximately 376 subjects will be randomized 1:1 to atacicept 150 mg or placebo:

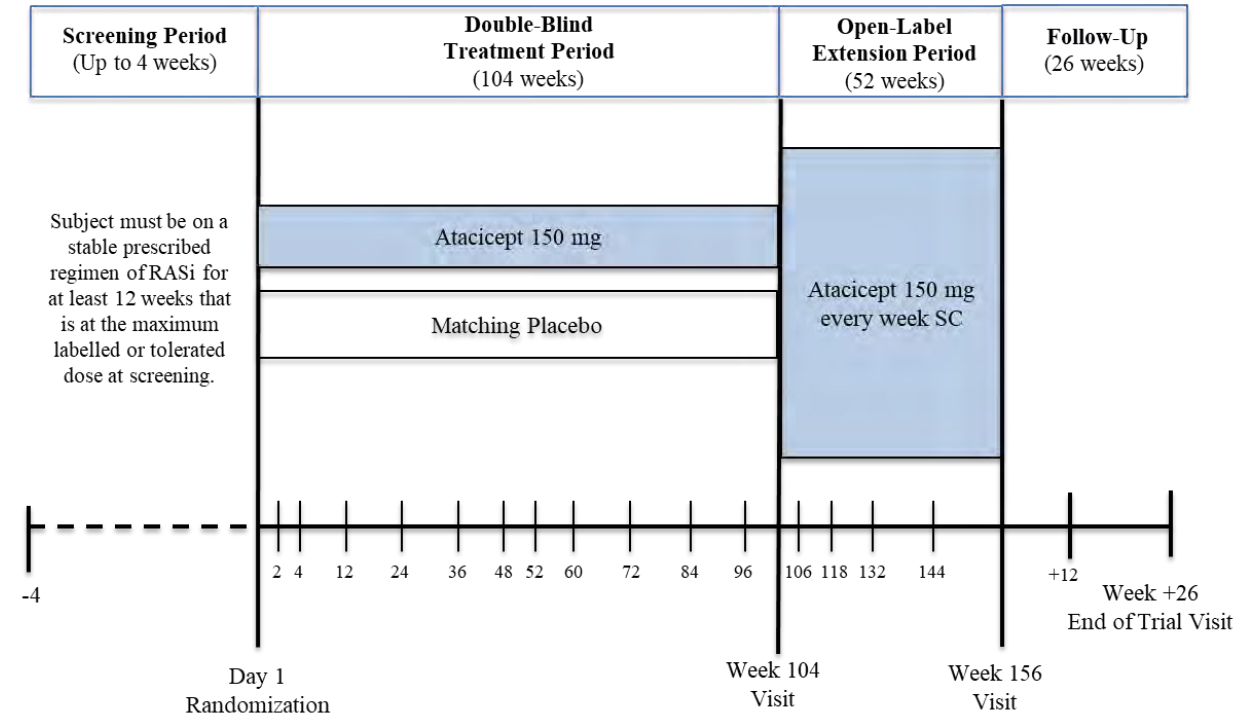
- Atacicept 150mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly subcutaneous (SC) injections (N=188)

The Phase 3 study is composed of a (up to) 4-week Screening Period, a 104-week Double Blind Treatment Period (Part C), a 52-week Open-Label Extension (Part D) and 26 weeks of follow-up. Subjects completing the 104-week Double-Blind Treatment Period on study drug will be offered open-label atacicept at 150 mg for an additional 52 weeks (Open-Label Extension). Subjects who prematurely discontinue study drug prior to completion of the 104-week treatment period should continue with study visits and assessments per protocol through the end of the double-blind period. After completion of the study, all patients will have a 26-week follow up period except if the subject discontinued study drug more than 26 weeks before week 104. After the last subject completes the 104-week double-blind period or completes an Early Termination Visit, the study will be unblinded.

The study will be conducted on an outpatient basis.

Subjects who participated in the Phase 2b portion may not participate in the Phase 3.

Figure 2 **Phase 3: Study Schema**



Note: Subject's stable dose of ACEi and/or ARB must be maintained for the duration of the study.

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; EOT=end of treatment; ET=early termination; RASi= renin-angiotensin system inhibitor; SC=subcutaneous.

13.2 **End of Study Definition**

A subject has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in the Schedule of Assessments (Table 3).

The end of the study is defined as the date of last contact with the last subject who participates in the study (i.e., last subject's last visit); see Section 19.4 for details on study and site closures.

13.3 **Independent Data Monitoring Committee**

An independent data monitoring committee (iDMC) will monitor the safety and welfare of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority on all aspects. Details regarding the role, responsibilities and data review requirements of the iDMC will be outlined in a separate iDMC charter.

14 Phase 3: Study Population

The eligibility criteria in Sections 14.1 (Inclusion Criteria) and 14.2 (Exclusion Criteria) are designed to enroll only subjects who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a subject is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the subject's routine medical care, the Investigator will confirm that the subject has provided written informed consent, as indicated in Section 19.1.3.

Subject eligibility (based on Screening Visit assessments of the inclusion and exclusion criteria) must be reviewed again by the Investigator on Day 1 prior to randomization. Once a subject meets eligibility requirements, the subjects will be randomized to treatment with atacicept or placebo through a central randomization process. The interactive web response system (IWRS) will be used to randomize a subject to study drug assignment.

14.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age and ≤ 70 years, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit.
4. Total urine protein excretion ≥ 1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 1.0 mg/mg based on a 24-hour urine sample during the Screening Period
5. eGFR ≥ 30 mL/min/1.73 m² at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
6. On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1.
 - The subject is eligible if they do not tolerate RASi, provided their management of IgAN is standard of care (SoC) per local practice. This intolerance must be documented by the Investigator and discussed with the medical monitor.
7. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening
8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).
- OR
- Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

14.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. Participation in the Phase 2b (Parts A and B) study or any previous treatment with atacicept
2. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis
3. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
4. Evidence of nephrotic syndrome within 6 months of screening (serum albumin $<30\text{g/L}$ in association with UPCR $>3.5\text{ mg/mg}$)
5. Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants
6. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
7. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $>7.5\%$ at screening
8. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

9. Prohibited medications:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or expected use during the study.
- For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal. For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 12 weeks prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for >1 week or average dose >0.5 mg/kg/day prednisolone or equivalent
- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or expected use during the study.
- Use of traditional Chinese medications and/or Ayurvedic medications within 12 weeks prior to screening or from screening to Day 1
- Use of B-cell-directed biologic therapies including but not limited to belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time
- Use of endothelin receptor antagonists (ERAs) for any period of time

10. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:

- serum IgG below 7 g/L
- aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level $>2.5 \times$ upper limit of normal (ULN) or total bilirubin $>1.5 \times$ ULN.
 - i. If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
- hemoglobin <10 g/100 mL in men and hemoglobin <9 g/100 mL in women
- platelets $<100,000/\text{L mm}^3$

11. Administration of live and live-attenuated vaccinations within 30 days prior to randomization
12. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
13. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
14. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
15. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.
16. History of acute or chronic infection with human immunodeficiency virus, or hepatitis B virus.
 - Subjects with positive hepatitis B surface antigen (HBsAg) are excluded
 - Subjects who are HBsAg negative, hepatitis B core antibody (HBcAb) positive, hepatitis B surface antibody (HBsAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow-up
17. Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
18. History of splenectomy
19. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix.
20. Known hypersensitivity to atacicept or any component of the formulated atacicept
21. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety Follow-up Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)

22. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
23. Unwillingness or lack of capacity to follow all study procedures
24. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

14.3 Screen Failures

Repeat testing: Aside from the TB testing as delineated above, tests that do not meet the above inclusion/exclusion criteria may be repeated once within the 28-day Screening Period if the results are thought to represent a laboratory error or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values. If eligibility criteria are not met at the end of the 28-day Screening Period, the subject should be considered a screen failure.

Re-Screening: Subjects who do not meet the above eligibility criteria (in Sections 14.1 and 14.2) within the screening period and screen fail may undergo re-screening upon approval by the Medical Monitor. If the subject is re-screened, then the subject will receive a new subject identification number (Subject ID). The second screening is a new 28-day screening episode.

15 Phase 3: Investigational Medicinal Product(s)

Investigational Medicinal Product (IMP) or study drug is atacicept or placebo intended to be administered to a study subject per the study protocol.

15.1 Randomization, Blinding, and Measures to Minimize Bias

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessments ([Table 3](#)).

Before the study is initiated, the login information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study drug administration for each subject.

15.1.1 Blinding of Investigational Medicinal Product

This study will be double-blinded for all subjects and Investigators through Part C. Investigational Medicinal Product (IMP) packaging and labeling will be prepared to protect the blinded nature of the study. Study drugs will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part D of the study will be conducted in an open-label fashion.

15.1.2 Procedures for Breaking the Treatment Codes

If, at any time during Part C of this study, any site personnel are unblinded to the treatment code for any reason, the circumstances and reason must be documented. The Sponsor and clinical research organization (CRO) study staff will be blinded to the study group assignment with the exception of the selected study drug supply vendor, iDMC (if applicable) and SAE reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of analysis of the primary endpoint. A blinding plan will be developed to outline the study-specific approaches to protect the study blind and data integrity.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study drug discontinued.

In a medical emergency, the Investigator is solely responsible for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted in cases of suspected serious infection or where breaking the blind is required to provide medical care, the Investigator should contact the Sponsor prior to the unblinding, unless this could delay emergency treatment.

The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study drug, except to the designated drug safety representative, as appropriate. The date of and reason for unblinding must be recorded in the source documents and electronic case report form (eCRF). Contact information for unblinding in an emergency is given on the subject emergency card provided to each subject, as noted in Section 19.2.2 (Emergency Medical Support).

The Sponsor (or delegate) will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

In the case of emergency unblinding, the subject must be discontinued from the study drug and complete all assessments and procedures specified for the Early Termination (ET) Visit and should remain in the study and continue the study visits through Week 104.

Causality assessments if emergency unblinding is for an AE/SAE should be documented for the AE/SAE prior to unblinding. Further details on expedited reporting and SAEs are in Section 17.

15.1.3 Other Blinding Parameters

Laboratory results:

After Day 1, certain laboratory results can reveal the PD effects of atacicept. These laboratory/analyte results (serum Gd-IgA1, IgG, IgA, and IgM) that could be indicative of treatment allocation will not be reported to investigative sites or other blinded personnel.

Serum IgG level is one of the blinded laboratory tests which will be monitored by the central laboratory. If serum IgG is < 3 g/L on two consecutive timepoints at least 28 days apart, representing severe hypogammaglobulinemia, the study drug will be discontinued. The central laboratory will notify the Medical Monitor that the study subject meets the treatment discontinuation criteria. The site will receive notification from the Medical Monitor to discontinue the treatment of study drug for this study subject. This event will likely unblind the treatment assignment for this subject.

Lymphocyte counts as assessed by routine complete blood counts will not be blinded; these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5% to 20%).

Independent Data Monitoring Committee (iDMC):

The iDMC will review available safety data in a blinded manner with the capability to review unblinded data in case of a safety concern. See Section 13.3 for further information on the iDMC.

Unblinding Clinical Studies for Sample Analysis of Special Data:

Bioanalysis and PK scientists may be unblinded to study treatment information in order to perform sample analysis and preliminary PK and PK /PD analysis activities. Anyone who will be unblinded

prior to database lock will be named with clear instruction on how to ensure the integrity of the clinical study.

15.2 Investigational Medicinal Product(s)

The atacicept protein is a soluble glycoprotein containing [REDACTED] amino acids, resulting from the fusion of human IgG1-Fc and the extracellular domain of the BLyS and APRIL receptor TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor), with a predicted mass of [REDACTED] kilodaltons. The product conformation is dimeric, and thus atacicept has a predicted mass of [REDACTED] kilodaltons. [REDACTED]

15.2.1 Formulation

Atacicept is the active ingredient in the drug product. The formulation contains the following excipients: trehalose as a stabilizing agent and sodium acetate buffer (pH 5.0). Unit dosage strength for atacicept (per 1.0 mL) will be 150 mg/mL. The placebo-to-match formulation contains trehalose and sodium acetate buffer (pH 5.0).

15.3 Packaging and Labeling

The drug product/placebo is manufactured, packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released under Good Manufacturing Practice conditions. The active dosage form and placebo will be supplied by the Sponsor as a ready-to-use, prefilled syringe with 1.0 mL or drug product/placebo.

Atacicept and placebo will be packed in kits containing four pre-filled syringes (one syringe is needed for 1 administration). Each pre-filled syringe will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. The labeling configuration of the pre-filled syringes results in the active and placebo being identical in appearance. Full re-traceability is provided from the unique medication number on the labels together with the packaging documentation, according to the current Good Manufacturing Practice guidelines.

15.4 IMP Administration

Study drug dosing is a single injection of 1.0 mL, once weekly from Day 1 to Week 156, subcutaneous (SC) administration by pre-filled syringe. Subjects will contact the Investigator any time they have any injection administration (pre-filled syringe) complaint.

Participants or family members/caregivers who receive appropriate training will be permitted to administer medication in this study and will be trained at the investigational site on the appropriate use of the pre-filled syringe and storage of the IMP. The initial training will occur on the day of

randomization. The first injection will be performed under supervision. The Day 1 visit should be performed no later than 3 days after randomization. For the injection on Day 1 and Week 104, pulse and BP will be recorded before the dosing and will be recorded as clinically indicated. The study staff monitor for injection site reactions (ISRs) (local tolerability) (see Section 16.6.5).

It is recommended that the weekly dose of IMP be taken on the same day of the week as the original dose. For missed dose(s) of study drug, subjects should be instructed to take the missed dose(s) as soon as possible. If necessary, a dose can be given ± 3 days from the scheduled dose day as long as there is an interval of at least 4 days from the previous injection, with subsequent doses resumed to be taken on the original day of the week.

At the Week 104 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 104 will be the first OLE dose.

15.5 IMP Preparation, Handling, Storage, and Accountability

All study drug (atacicept and placebo) is provided in prefilled single-use syringe to the site via cooled transport. No additional preparation will be required at the site.

Storage

All study drug supplied to each site must be stored in their original containers carefully, safely, and temperature controlled. The storage facility at the study site must be locked and accessible only to authorized site personnel. The study drug must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light. The study drug temperature will be monitored and documented per the site's standard process for refrigerated medication. Atacicept and placebo must NOT be frozen.

To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the study drug back home and instructed not to leave their medicine unattended or in a place that might get too hot, e.g., inside a car, or exposed to light. Subjects should have access to refrigeration to store the study drug.

Dispensation

Site staff will dispense kits as per the kit number assigned by IWRS. At randomization, drug should be administered no later than 3 days after a subject is randomized.

During the study, if needed, an extra drug kit may be provided in order to allow subjects to have back up study drug in the event a syringe is left out for over 60 minutes, or a visit is conducted late in the visit window.

Handling

Each study drug syringe should be removed from the refrigerator and kept at room temperature for at least 30 minutes prior to SC injection. The syringe should not be left out at room temperature

for more than 60 minutes. Additional details on the instructions for handling and storage will be provided to subjects as required for home injection.

Accountability

Information on the time of each dose will be recorded by the subject or by the study staff and collected in the eDC system. At visits where new drug kits are dispensed, subjects should return all cartons and any unused syringes.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study drug(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Only subjects enrolled in the study may receive study drug(s) and only authorized site staff may supply it.
- Study drug(s) accountability records at the study site will include the following:
 - Confirmation of receipt, in good condition and in the defined temperature range
 - The number of dose(s) each subject used during the study
 - The disposition (including return, if applicable) of any unused study drug(s)
 - Dates, quantities, study drug number, expiry dates, and the subject numbers
- The Investigator site will maintain records which adequately document that subjects were provided the doses specified in this protocol and all study drug(s) provided were fully reconciled
- Unused study drug(s) must not be discarded or used for any purpose other than the present study. No study drug that is dispensed to a subject may be re-dispensed to a different subject.
- A Study Monitor will periodically collect the study drug(s) accountability forms
- Further guidance and information for the final disposition of unused study drug(s) are provided in the Pharmacy Manual.

Pre-filled Syringe Disposal:

Pre-filled syringes will be disposed of according to the Pharmacy Manual (including the use of sharps containers).

Subjects will be instructed to dispose of used syringes in sharps containers at home, and to return the sharps containers to the site once full, at Week 52, Week 104 and again at Week 156, or Early Termination Visit. Investigators will instruct subjects to store any syringes associated with an injection administration complaint separately and return them to the site in a separate container.

Destruction of used and unused study drug(s) should be performed at site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible.

15.6 Study Drug Compliance

The study drug will be administered by the subject under supervision as defined in the Schedule of Assessments. All other dosing will be done by the subject, subject's caregiver, or home health nurse (if available) at home throughout the rest of the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient study drug for at-home dosing until the next scheduled visit. Subjects will be provided with an Injection Diary to enter information regarding administration of each dose.

Compliance will be determined based on the Injection Diary entries. Acceptable compliance for the study is defined as 80%-100% (inclusive) of study drug compliance based on drug accountability calculated for the blinded period and open-label extension period. If dosing is interrupted for any reason, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures.

Consequences of noncompliance will lead to retraining and/or discontinuation of study drug as described in Section 16.10.1. In case of overdose see Section 17.9.

15.7 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines) used from the time the subject signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, date(s) administered, and dosing information (as applicable).

Contact the Medical Monitor for any questions on concomitant or prior therapy.

15.7.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study drug may be given at the Investigator's discretion.

Permitted medications are any medications that are required by the subject during the course of the study and which are not specifically prohibited by the protocol (see Section 15.7.2). Any such medications prescribed or used should be recorded in the eCRF.

Use of RASi and anti-hypertensive medications

To be eligible for randomization, all subjects who tolerate RASi (ACEi or ARB) medication are required to be on stable RASi treatment for at least 12 weeks prior to Screening that is at the maximum labeled or tolerated dose, which must be maintained through the screening period to Day 1. For subjects who are unable to tolerate RASi medication, management of IgAN will be SoC according to local practice. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes and changes in type of RASi

medication; every effort should be made to maintain subjects on their stable RASi dose, unless required for safety reasons. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non-RASi medications should have been considered before these specific drug classes. In certain instances (i.e., hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases Investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].

All other antihypertensive medications, including diuretics, calcium channel blockers and β -blockers, can be used at any timepoint during the study per the Investigator and following current guidelines.

Use of SGLT2 inhibitors and mineralocorticoid receptor antagonists

As with RASi medications, subjects prescribed SGLT2 inhibitors and/or mineralocorticoid receptor antagonists (MRAs; e.g. aldactone, eplerenone or finerenone) are required to be on a stable dosing regimen for at least 12 weeks prior to screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes or the introduction of SGLT2 inhibitors and/or MRAs. If, in the opinion of the Investigator, intervention is warranted, the Medical Monitor must be notified within 48 hours of such intervention. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the introduction of SGLT2 inhibitors and/or MRAs, but this at the Investigator's discretion if feasible.

Use of statins and dipyridamoles

Statins and dipyridamoles are permitted, but it is recommended to keep doses stable.

15.7.1.1 Rescue Medications

Should the Investigator consider that rescue medication for IgAN (systemic steroids and/or immunosuppressive treatment) be warranted after Week 36, such treatment can be initiated at the discretion of the Investigator. However, in consideration of current guidelines ([International Society of Nephrology 2021](#)), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

- Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] (although treatment toxicity must be considered in those with $\text{eGFR} < 50 \text{ mL/min/1.73m}^2$); and/or
- Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., $> 3.5 \text{ g/day}$] and hypoalbuminemia [albumin $< 3.0 \text{ g/dL}$])

Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. If rescue medication is required, it is the Investigator's

decision to implement new treatment. In this case, the Medical Monitor must be notified within 48 hours after the initiation rescue therapy, as continued dosing with IMP may, in this circumstance, be discontinued. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of rescue medication, but this at the Investigator's discretion if feasible.

Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 15.7.1.

15.7.2 Prohibited Medicines

The following treatments are not permitted during the study:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or during the study.
 - For GCS, “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Use of systemic GCS is prohibited except for a maximum of 3 periods of 2 weeks duration with the equivalent of 0.5 mg/kg/day prednisolone or less
- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or during the study.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Use of systemic GCS is prohibited except for a maximum of 3 periods of 2 weeks duration with the equivalent of 0.5 mg/kg/day prednisolone or less
- Use of traditional Chinese medications or Ayurvedic medications within 12 weeks prior to screening, from screening to Day 1 or during the study.
- Use of B-cell-directed biologic therapies including belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time
- Use of endothelin receptor antagonist (ERA) for any period of time

Note: Intravenous (IV) hydrocortisone is permitted for stress dosing in emergency situations only, e.g., traumatic event requiring hospitalization. If administered, the event should be discussed with the Medical Monitor to ensure IMP does not need to be discontinued.

If the Investigator believes that treatment with a medication within the categories described above is required, and the potential benefits outweigh the possible risks, the Medical Monitor must be notified within 48 hours of initiation of treatment, as continued dosing with IMP may, in this circumstance, be discontinued (see Section 16.10.1). If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of prohibited medication, but this at the Investigator's discretion if feasible.

Refer to the inclusion and exclusion criteria (Sections 14.1 and 14.2) for prohibited medications before and during the study.

Subjects prescribed SGLT2 inhibitors and/or MRAs are required to be on a stable dosing regimen at screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes or the introduction of SGLT2 inhibitors and/or MRAs. If in the opinion of the Investigator, intervention is warranted, it the Medical Monitor must be notified within 48 hours of such intervention, as continued dosing with IMP may, in such circumstances be discontinued. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of prohibited medication, but this at the Investigator's discretion if feasible.

15.7.3 Other Interventions

Planned/expected major surgery during the entire study period is exclusionary. Unplanned major surgeries should be discussed in advance with the Medical Monitor with respect to whether the subject may continue on study treatment.

15.7.3.1 Vaccinations

It is recommended that subjects have up-to-date vaccinations, as per local guidelines, within 30 days of screening and during the study. Investigators should review the subject's vaccine status, and ensure they remain up to date with all non-live vaccinations throughout the treatment period as per local guidelines. Live and live-attenuated vaccinations will not be permitted during the study period.

15.8 Special Precautions

- Women of childbearing potential must be willing to use a form of highly effective contraception at least 7 days prior to randomization through 175 days after the last dose of study drug (Appendix 2)
- Male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of

male study subjects should consider using one of the highly effective methods of contraception as well. ([Appendix 2](#)) Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

- Caution should be exercised when administering atacicept to subjects with underlying conditions that may predispose them to infections (see Section [17.7.2](#))
- **Good hygiene practice should be employed:** Subjects should be consistently reminded of the importance of good hygiene practices such as hand washing for their care providers and/or social contacts, especially if they are suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. It is recommended they be vaccinated according to local recommendations for individuals with a chronic disease and/or immunosuppression. They should be advised to promptly report to the Investigator any signs or symptoms suggestive of an infection.

16 Phase 3: Study Assessments and Procedures

The following assessments will be conducted during screening and at selected timepoints specified in the Schedule of Assessments (Table 3). Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the Investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate eCRF. General considerations for study visits include, but are not limited to:

- No protocol waivers or exemptions are allowed
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the subject's routine medical care, the Investigator will obtain written informed consent as specified in Section 19.1.3 (Informed Consent Process). Upon subject's agreement, their primary health care provider should be informed about the subject's enrollment in the study.
- Recommended Order of Procedures:
 - Vital signs should be collected prior to blood draws.
 - 
 - Pharmacokinetics and immunogenicity sampling (if scheduled) and laboratory samples must be collected prior to dosing.
 - All other study assessments should also be performed, according to the Schedule of Assessments (Table 3).
- **Unscheduled visits:** may occur at any time during the study; assessments to be performed according to the Investigator's judgment.

16.1 Screening Period and Confirmation of Eligibility

The subject's eligibility will be assessed at the Screening Visit that will occur up to, at most, 4 weeks (28 days) before the Randomization Visit (Day 1). Demographic data will be collected at screening.

Subjects will arrive at the site and the following procedures will be done to determine the subject's eligibility to participate in the study:

- Obtain written informed consent prior to screening procedures
- The physical examination will be performed at the discretion of the site investigator if deemed necessary as per SoC.
- Obtain additional written informed consent if participating in the PK sub-study, as necessary
- Review inclusion and exclusion criteria
- Collect demographic data
- Complete medical and disease history
- Document the criteria for IgAN diagnosis for eligibility
- Assess vital signs: seated systolic and diastolic BP, pulse rate, temperature (oral or body – with same method to be used throughout the study), height and weight measurements (see Section 16.6.2 for details)
- Perform standard, single, 12-lead electrocardiogram (ECG) (see Section 16.6.3)
- Complete physical examination as specified in the schedule of events
- Collect blood and fresh clean catch urine samples for routine laboratory tests (see Table 4).

The laboratory tests will include:

- Clinical chemistry and hematology
- HbA1c
- Thyroid stimulating hormone (TSH)
- Follicle stimulating hormone (FSH) for woman only
- Immunoglobulins (IgG, IgA, IgM)
- Gd-IgA1
- Serum virology
- Quantiferon test for TB assessment
- Urinalysis and urine sediment from fresh, clean-catch, mid-stream specimen obtained in the clinic
- Dispense:
 - Two 24-hour urine collection containers (one for Screening and one for the Day 1 Visit)

- Serum pregnancy test (β -hCG) required only for WOCBP. Any woman with a positive pregnancy test will be ineligible for the study. [NOTE: It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 12 months or who are surgically sterile]
- If an archival kidney biopsy (within 10 years of Screening Visit) is unavailable, a pre-treatment kidney biopsy is required to confirm subject eligibility but is to be performed at the discretion of the Investigator.
- Safety
 - Record AEs beginning after the informed consent form (ICF) has been signed.
 - Review/record prior and concomitant medications
 - Review/record vaccinations. Administration of a vaccine is acceptable within 30 days of screening or planned during the study.

Subjects who meet the screening criteria and are to be randomized will be given instructions as to the date and time they are due back at the site for Day 1 (randomization/first day of dosing).

Subjects who do not meet the screening criteria can be re-screened upon approval of the Medical Monitor. In specific circumstances, repeat testing of screening testing may be allowed. See Section 14.3 for further details.

16.2 Randomization/First Administration IMP (Day 1)

The following assessments will be conducted on Day 1. All subjects will return to the site in the morning up to at most 4 weeks (28 days) after the Screening Visit. At this visit, subjects or caregivers will be provided with training to properly store and perform self-injection of IMP at home from Week 1 onwards. Retraining can be provided by the site at the Week 2 Visit as required.

These dosing instructions will be reviewed with the subject/caregiver before leaving the site. At each of these visits, site staff will contact the IWRS to obtain appropriate kit numbers and the specified kit will be dispensed.

Predose Assessments

Predose assessments on Day 1 are considered baseline measurements prior to first dose of study drug. The results of all assessments and procedures performed at the Screening Visit will be reviewed to assess the subject's eligibility. All eligible subjects will undergo the following procedures before IMP administration (unless stated otherwise):

- Review inclusion and exclusion criteria
- Record archival kidney biopsy (if obtained)
- Vital signs: BP, pulse rate, temperature (oral or body – with same method to be used throughout the study) (see Section 16.6.2 for details)
- Standard, single, 12-lead ECG (see Section 16.6.3)

- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, urinalysis, and spot urine) (see Table 4).
- Urine:
 - 24-hour collection for UPCR, [REDACTED] total protein and [REDACTED]

PK (see Section 16.7)

- Blood samples will be collected per schedule of assessments. The exact time and date of the last dose of study drug and of blood sampling should be recorded.
- Anti-drug antibodies (binding and neutralizing)

Other analyses (see Section 16.8)

- Blood samples will be collected to assess serum BLyS and APRIL **prior to the first dose** of IMP (predose).
- Serum immunoglobulins: IgG, IgA, and IgM
- Serum Gd-IgA1
- Blood sample for storage and future testing

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Randomization

Eligible subjects will be randomized in a 1:1 ratio to atacicept or placebo by the IWRS. The baseline visit should occur no later than 3 days of randomization.

Treatment with IMP

- The study staff will instruct the subject (or caregiver) in proper technique of SC administration and demonstrate it by administering the allocated IMP to the subject via SC injection.
- The first dose (on Day 1 and Week 104) will be given at the study site. After the first dose, subjects or caregivers will be permitted to administer the medication following instruction in injection technique and verification of satisfactory technique.
- On Day 1 and Week 104, the study staff will record the exact time and location of dosing and monitor the following:
 - Injection site reactions (ISRs) (local tolerability) (see Section 16.6.5).

- Pulse and BP will be recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
- If suspected hypersensitivity reaction occurs at any time, the subject will be treated symptomatically (see Section 17.7.1).
- At the Week 104 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 104 (Part C) will be the first OLE dose.

PK sampling (post-first dose)

- On Day 1 only, following ISR monitoring, a blood sample will be collected 2-4 hours after the first study dose.
- After Day 1, at PK timepoints, a blood sample for PK analysis will be collected to assess levels of serum atacicept.

Completion of Day 1

Following completion of all Day 1 procedures described above, the following additional procedure should be completed before the subject leaves the site:

- Provide subjects with emergency contact numbers (see Section 19.2.2).

16.3 Post-Randomization Visits

16.3.1 Treatment Periods

Following completion of Randomization (Day 1), study visits will occur at Day 1, Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, 96, and 104 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 106, 118, 132, 144, and 156. Note that for Weeks 4, 48, 84, 106, and 132, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP. For the Phase 3 study, facilitation of optional remote visit(s) is the responsibility of the investigator and site staff.

If in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted at Weeks 1, 3, and 105. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

16.3.2 End of Treatment or Early Termination

Criteria for discontinuation are provided in Section 16.10. Subjects who are discontinued from IMP will complete the Early Termination (ET) visit as soon as possible (within 10 days) after IMP discontinuation. These subjects should receive a 24-hour urine collection container in advance (e.g., at the prior visit), but no later than 2 days before the scheduled ET visit. Subjects who

prematurely discontinue study drug prior to completion of the 104-week treatment period should continue with study visits and assessments per protocol through the end of the double-blind period.

End of treatment is defined as subjects who complete Part C and D for a total of 156 weeks of study drug. The ET Visit follows the same schedule of assessments as Week 156.

16.3.3 Safety Follow-up Period

After the last dose of the IMP (whether subjects complete planned treatment or are discontinued prematurely from IMP), all subjects are required to be followed for safety for at least 26 weeks either as part of the 26-week Safety FU period or continuing in the double-blind treatment period up to week 104 (section 16.10.1).

The Safety FU period will consist of visits at Weeks 12 and 26.

16.4 Demographic and Other Baseline Characteristics

Demographic data such as date of birth, self-reported race and ethnic origin, gender, weight, height, and body mass index (to be calculated by CRO/Sponsor) will be assessed at screening. Information about previous and concomitant medications will also be recorded.

Complete medical and disease history will be recorded. This includes history of disease treatments, including but not limited to conditions that may affect eligibility (herpes zoster, cytomegalovirus, Epstein Barr virus, TB, cancer, infections [current active infections, recent serious infections, opportunistic infections, chronic or recurrent infections], congestive heart failure, hypersensitivity to drugs and other significant illnesses, smoking history, alcohol or drug abuse). In addition, a history and status of medications will be recorded, including surgeries and other procedures, with particular attention to current and previous treatments for IgAN.

Other baseline measurements such as physical examination, safety laboratory parameters, ECG, and vital signs will be assessed as specified below.

16.5 Efficacy Assessments and Procedures

Assessments for the endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 3).

Clinical renal disease assessments:

- UPCR, 24-hour total protein excretion, [REDACTED] by 24-hour urine collection.
- Active urinary sediments by urinalysis, including spot UPCR and [REDACTED]

- Renal function by eGFR will be calculated by the central lab as follows: (Levey 2011)
CKD-EPI: $eGFR = 141 \times \min(Scr / \kappa, 1)^\alpha \times \max(Scr / \kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.159$ (if black)
Scr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicated the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

Blood assessments:

- Predose Ig levels (i.e., IgG, IgA, and IgM), Gd-IgA1.
- Predose levels of free BLyS and free APRIL.

16.6 Safety Assessments and Procedures

Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, and evaluation of AE/SAEs, with attention given to infections (serious), cardiovascular events, local tolerability (ISRs) and hypersensitivity reactions.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

Adverse events of special interest (AESIs) are serious infections, hypersensitivity reactions, demyelinating disorders and cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease).

16.6.1 Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A complete physical examination will include, at a minimum assessment of the general appearance, skin, lymph nodes (cervical), head, ears, eyes, nose, throat (HEENT), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems. Height (at Screening Visit) and weight will also be measured and recorded.

At selected visits, a symptom-driven physical examination will be performed, and will include assessment of any new subject complaints or changes from baseline.

16.6.2 Vital Signs

Vital sign measurements (BP, pulse, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, at the visits specified in the Schedule of Assessments (Table 3).

- Temperature, pulse rate, respiratory rate
- Blood pressure and pulse measurements will be assessed with the subject seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
 - During the Screening Period, blood pressure will be measured up to 3 times with each measurement separated by up to 2 minutes (the lowest value will be recorded on the eCRF).
 - After first dose of study drug at randomization and at Week 104 during ISR monitoring, pulse and BP recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
- Vital signs to be taken before blood collection for laboratory tests
- Height will be measured at Screening only. Body weight will be measured with a balance beam scale if possible.

16.6.3 Resting Electrocardiogram (ECG)

Digital ECGs for all subjects will be recorded at the site using an appropriate ECG machine.

- A standard, single, digital 12-lead ECG will be obtained as outlined in the Schedule of Assessments after the subject has been resting in the supine position for 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals

All digital ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The Investigator will judge the overall interpretation as normal or abnormal. Clinical significance and the reason for the abnormality will be recorded on the eCRF.

Any changes in ECG values that are abnormal that are determined to be clinically significant by the Investigator will be recorded as AEs.

16.6.4 Clinical Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in the following table, at the timepoints listed in the Schedule of Assessments.

- All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations
- The tests will be performed by the central laboratory
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

- Non-fasting blood samples are acceptable for this study.
- Repeat laboratory testing may be required during the study for various reasons, e.g., loss of sample en route to the central laboratory. Any testing which is required to be repeated should be repeated as soon as possible after a visit.

For information on blinded laboratory results see Section 15.1.3. Between 15– 43 mL of blood will be collected per subject for each study visit. Approximately 757.5 mL of blood will be collected per subject for the duration of the blinded, open label and follow up periods. Blood collected will be use to assess routine hematology, chemistry, PK serum atacicept, PK anti-drug antibodies, PD immunoglobulins, PD Gd-IgA1, PD serum BLyS & APRIL, and exploratory biomarkers for each subject visit as per the schedule of assessments.

16.6.4.1 Clinical Safety and Screening Evaluations

Table 4 Phase 3: Clinical Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	<u>RBC Indices:</u> MCV MCH %Reticulocytes	<u>WBC Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	██████████ Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range)	Calcium Serum creatinine (eGFR will be calculated from serum creatinine using the CKD-EPI equation)	Glucose Potassium Sodium Total protein Uric acid
Urine Sediment Analysis	Urine red blood cells and white blood cells/high powered field Casts Organisms Crystals		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal). Spot urine (including spot UPCR ██████████)		
Quantitative Analysis (24 -hour Urine Collection)	Total volume Total protein ██████████ Total creatinine UPCR ██████████		

Laboratory Assessments	Parameters
Other Tests	Serum IgG, IgA, IgM Gd-IgA1 Complement (C3, C4) Serum BLYS and APRIL level (if assay is available) HBsAg, HBcAb [total and IgM] (hepatitis B) <ul style="list-style-type: none"> If HBsAg negative and HBcAb positive, HBsAb and HBV-DNA will be performed to determine eligibility. HBV-DNA will be monitored monthly through safety follow up in those randomized Anti-drug antibody titers (binding and neutralizing) anti-HCV (if anti-HCV positive with reflex testing for HCV RNA by PCR) anti-HIV 1 and 2 HbA1c TSH FSH (for women only) Serum pregnancy test (β -hCG) required only for WOCBP at Screening. Local urine testing will be standard all other visits unless serum testing is required by local regulation or IRB/IEC. Positive urine pregnancy test results will be confirmed by serum pregnancy testing. Quantiferon test for TB Urine drug screen for amphetamines, cocaine, methadone, and opiates

β -hCG= beta human chorionic gonadotropin; anti-HCV = anti-hepatitis C virus; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin-A1c; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBsAb=hepatitis B surface antibody; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; Ig=immunoglobulin; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid; TB=tuberculosis; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=woman of childbearing potential.

16.6.4.2 Urine Sampling and Testing

Urine samples need to be collected in different ways for different tests:

Quantitative proteinuria assessments: A 24-hour urine collection will be used to determine 24-hour total protein excretion, UPCr, [REDACTED] Total volume of the 24-hour collection will be measured and an aliquot taken for determining protein, [REDACTED] and creatinine concentration to calculate the proteinuria and [REDACTED] assessments. Subjects will be provided with the materials for conducting their 24-hour urine collections and will have to bring the collection to the clinic; for remote study visits, transport of the sample will need to be arranged. At the Screening Visit, the subject will receive the collection materials and the 24-hour collection should be conducted and brought into the clinic as soon as complete within the Screening Period. At other visits requiring a 24-hour urine collection, the subject is advised to collect the urine starting the day prior to the visit and bring it to the visit.

24-hour urine collection: The 24-hour urine collection should begin 1 day before the study visit and should start with discarding the first morning void, and collecting all urine produced thereafter (through the day and night) up to 24 hours later (including the first morning void of the second morning).

Urine collection: A urine sample from “fresh” urine will be collected during the scheduled clinic visit. Subjects will be provided a urine cup and instructions for a midstream collection to provide a clean catch specimen. The urine collection will be used for routine urinalysis, spot urine, and urine sediment analysis, and at specified visits, for sample storage for future exploratory biomarker analysis (see Section 16.8.1).

16.6.5 Local Tolerability (Injection Site Assessment)

Any clinically significant ISRs will be assessed by the Investigator or his/her designee and recorded as AEs in the eCRF, starting after first study drug administration and continuing through Parts C and D in Phase 3 or Early Termination (see Table 3).

Any clinically significant injection site symptoms should be reported with the AE verbatim term “injection site reaction”. These events will be captured on the AE page of the eCRF. Clinically significant, multiple symptoms for the same injection should only be entered once on the AE page of the eCRF. For this study, symptoms for ISR assessment include warmth, erythema, edema, pain or tenderness. The grading shown in the table below should be used to grade the severity of ISRs.

Qualitative Toxicity Scale for injection site reactions

Mild	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
Moderate	Pain; lipodystrophy; edema; phlebitis
Severe	Ulceration or necrosis; severe tissue damage; operative intervention indicated

Adapted from CTCAE Version 5.0

If the subject has any other injection site symptoms not included in the list above (e.g., injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (e.g., injection site abscess, injection site cellulitis) rather than the term “injection site reaction”.

Subjects who complete their last study visit with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required.

16.7 Pharmacokinetics

On Day 1, a blood sample will be collected pre-dose for assessment of baseline anti-drug antibodies (ADA). Another blood sample will be collected between 2-4 hours after first dose for assessment of serum atacicept concentration.

At the Week 12 and Week 118 visits, PK blood draws will be done for trough PK and ADA. And all efforts should be made to ensure that the last dose was given 7 days prior to the blood collection.

At the Week 104 visit, when the subject is expected to have an in-clinic observed injection, blood samples will be collected prior to administration of study drug for trough PK and ADA assessments. All efforts should be made to ensure that the last dose was given 7 days prior to the blood collection.

On other visits, where PK/ADA samples will be collected (detailed in Schedule of Assessment, [Table 3](#)), blood samples will be collected anytime during the visit for anytime PK and ADA assessments.

Instructions for collection, preparation and shipping these samples will be provided in a Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Blood samples for assessment of anti-drug antibodies, binding and/or neutralizing, samples will be tested first for binding activity, and those found to be positive will be tested for neutralizing activity when an assay is available.

16.8 Other Assessments

16.8.1 Biomarkers

Storage and analyses of samples will be handled according to the study Laboratory Manual, and described in the appropriate Informed Consent Form.

Serum Biomarkers

The following markers may be evaluated: predose serum BLyS and serum APRIL, and serum IgG, IgA, and IgM, serum Gd-IgA1.

Exploratory Biomarkers

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Pharmacodynamic Assessments

Blood samples will be collected at the timepoints specified in the Schedule of Assessments ([Table 3](#)). Immunoglobulin levels may be integrated into the Population PK, PD and exposure-response modeling and simulation analysis, including assessment of the influence of renal function (e.g., eGFR).

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16.9 Considerations for Coronavirus Outbreaks

The global coronavirus pandemic or outbreaks may impose difficulties with study conduct which may inhibit the subjects' ability of entering the study site. In cases of coronavirus limitations, it is the Investigator's responsibility to assure the safety of study subjects which should include phone or video contact to assess the subject's well-being including any adverse events, collection of study samples and clinical data as best as possible, and direct shipment of study drug to study subjects if necessary. These assessments can be performed at a scheduled or unscheduled study visit(s). Where available and appropriate, home health care may be considered to facilitate monitoring of subject safety and study continuity. Documentation of these cases and the site's management of subjects should be recorded in the Investigator study files.

16.10 Discontinuation of Study Drug and Subject Discontinuation/Withdrawal

16.10.1 Discontinuation of Study Drug

Study drug may be stopped at any time at the Investigator's discretion.

Double-blind treatment period:

If a subject prematurely discontinues study drug or is unblinded (subject should be discontinued from study drug) during the double-blind treatment period, the subject should remain in the study and continue to perform the required study-related procedures through Week 104 (see [Table 3](#)). An ET visit should be completed within 10 days of the last dose of study drug (section [16.3.2](#)). If the ET visit falls near a scheduled visit this will take the place of the scheduled visit. If the subject discontinued study drug more than 26 weeks before week 104, the subject does not need to complete a further 26 weeks of follow-up after the Week 104 visit. If discontinued less than 26 weeks before Week 104, the subject should complete all visits up to Week 104 and continue into the 26-week safety follow-up period for the appropriate amount of time to ensure 26 weeks of safety follow-up data are collected after the last dose of study drug.

Open label extension period:

Subjects who prematurely discontinue study drug during the open-label extension period should remain in the study, completing an ET Visit (within 10 days of the last dose of study drug, section [16.3.2](#)) and continuing in the 26-week safety follow-up period (section [16.3.3](#)).

For subjects who withdraw consent or are lost to follow-up or death, safety follow-up visits will not be possible.

The subject must be withdrawn from study drug in the event of any of the following:

- Occurrence of an AE/SAE that makes discontinuation of study drug desired or considered necessary by the Investigator and/or the subject.
- Participation in any other interventional study during the duration of this study for which the Investigator or the sponsor considers discontinuation of the IMP necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to Section 17.8).
- If disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes (Section 15.7) is warranted in the view of the Investigator. Discussion with the Medical Monitor should occur prior to discontinuing IMP for this reason.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on Investigator judgment.
- Use of a nonpermitted medicine, as defined in Section 15.7.2. This should first be confirmed with the Medical Monitor before discontinuation of study drug.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance to the required study considerations, as defined in Section 15.6.
- Discontinuation of LTBI therapy before completion if present at the Screening Visit.
- If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart.
- Surgery considered by the Investigator or Sponsor to be major (see Section 14.2).
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Atacicept is contraindicated in subjects with a history of MS, ON, or any other demyelinating disease. Any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as, but not limited to, MS, ON, or transverse myelitis) should stop dosing of IMP.

The Schedule of Assessments specifies the data to collect at study drug discontinuation and follow-up, and any additional evaluations that need to be completed.

16.10.2 Study Drug Interruption

The Medical Monitor must be notified if the subject has missed 2 consecutive doses or 2 doses within a month period. If treatment has been interrupted for ≥ 4 consecutive weeks, the Investigator should discuss with the Medical Monitor whether to restart or discontinue treatment.

If the subject is unable to resume study drug, see Section 16.10.

16.11 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent). Investigator or designee should make reasonable effort to obtain explanation for subject

withdrawal and ask about the occurrence of any AEs. The subject will be asked to return for an ET visit per Schedule of Assessments ([Table 3](#)).

- The subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed
- A subject is considered withdrawn from the study due to death
- A subject must be withdrawn from the study in the event the subject is lost to follow-up.
- Discontinuation of the study at the request of the sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

When a subject must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor.

If a subject is withdrawn from the study, the samples will be kept, and the subject may be asked to return for Safety Follow-up assessments. If the subject withdraws consent, the Sponsor may retain and continue to use any data collected prior to such withdrawal of consent; however, all samples not tested will be destroyed.

If there is a medical reason for withdrawal from the study, the subject will remain under the supervision of the Investigator until satisfactory health has returned or health has stabilized. The Investigator will inform the subject's primary health care provider as applicable and as agreed by the subject if the subject withdraws from the study, to ensure the subject receives the appropriate follow up and care.

Subjects who are withdrawn from the study for any reason after receipt of the study drug on or after Day 1 will not be replaced.

16.12 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). The Investigator reserves the right to discontinue the study should his/her judgment so dictate and should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

16.13 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study
- Before a subject is deemed “lost to follow-up”, the Investigator or designee must make every effort to regain contact with the subject:
 - 1 where possible, make 3 telephone calls, AND
 - 2 if necessary, send a certified letter (or an equivalent local method) to the subject’s last known mailing address.

These contact attempts should be documented in the subject’s medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

16.14 Medical Care of Subjects after End of Study

After a subject has completed the study including the Safety Follow- Up Period, or has withdrawn early, standard treatment should be administered, if required, in accordance with the study site’s SoC and generally accepted medical practice and depending on the subject’s individual medical needs.

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for patients with IgAN.

17 Phase 3: Adverse Events and Toxicity Management

17.1 Definitions of Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated and does not interfere with everyday activities.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out his or her usual activities. An AE that is assessed as severe should not be confused with an SAE. An event is defined as “serious” when it meets at least one of the predefined outcomes in the definition of SAE, and not when it is rated as severe.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study drug include, but may not be limited to, temporal relationship between the AE and the study drug, known side effects of study drug, medical history, concomitant medication, course of the underlying disease, and study procedures.

Investigators must also assess the causal relationship of AEs to the study treatment (atacicept or placebo).

- Not related:** Not reasonably related to the study drug. AE could not medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol. A reasonable alternative explanation must be available.
- Related:** Reasonably related to the study drug. AE could medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Clinically significant abnormal laboratory or other examination (e.g., electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., electrocardiogram abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

The severity of abnormal laboratory values or other abnormal clinical findings that are determined to be AEs should be graded using the Qualitative Toxicity Scale as described above for other AEs.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition(s).

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization

Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are baseline conditions (e.g., pre-existing) and are not to be considered AEs. Situations where an untoward medical occurrence has not occurred are not to be considered AEs (e.g., hospitalization for elective surgery, social and/or convenience admissions).

Adverse Events of Special Interest

Adverse events of special interest must be reported on the SAE/AESI Report Form and will follow the procedure described below for reporting SAEs and AESIs.

Categories of AESIs include:

- Serious infections
- Hypersensitivity reactions
- Demyelinating disorders
- Cardiac events (cardiac failure, cardiac arrhythmias, and ischemic heart disease)

17.2 Time Period and Frequency for Collecting Adverse Event, Adverse Event of Special Interest and Serious Adverse Event Information

The AE/AESI/SAE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Safety FU Visit. After informed consent, but prior

to initiation of study drug, all SAEs and adverse events related to protocol-mandated procedures should be collected.

- Following initiation of study drug, collect all AEs, regardless of cause or relationship.

Any SAE assessed as related to study drug must be recorded and reported, whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Section 17.5.

17.3 Method of Detecting Adverse Events, Adverse Events of Special Interest and Serious Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, regardless if reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and AESIs must be additionally documented and reported using the appropriate report form as specified in Section 17.5.

17.4 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 17.2, and are assessed for their outcome at the last Safety FU Visit. All SAEs ongoing at the last Safety FU Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

17.5 Investigator Requirement and Instructions for Reporting Adverse Events, Serious Adverse Events, Adverse Events of Special Interest

Recording and Follow-Up of AEs

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study drug administration time), its severity, its causal relationship with the study drug, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All reports should be transmitted using the AE page and indicating the AE meets criteria for an SAE in the eCRF. Required information in the eCRF must be completed by the Investigator following specific completion instructions.

In exceptional circumstances (e.g., eDC system is down), an SAE (or follow-up information) may be reported by fax or email; in these cases, a written report using the back-up paper SAE Reporting Form must be sent immediately by fax or email contacts listed below by any study site. Once the eDC system becomes accessible, the SAE needs to be entered into the system immediately.

IQVIA Safety (Back Up Contact Information):

Email (preferred): PhV_TZA74011_SO@IQVIA.com

Fax: refer to country specific fax numbers provide with paper forms

Additional documents will be provided by the Investigator, if requested by the Sponsor or its designee (e.g., laboratory results, hospital report, autopsy report) depending on the availability of the document.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports, by updating the (S)AE form in the eCRF and submitting any supporting documentation (e.g., subject discharge summary or autopsy report) to IQVIA via e-mail (preferred) or fax. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE information in the eCRF and submit any supporting documentation as requested (e.g., subject discharge summary or autopsy report) to IQVIA Safety via e-mail (preferred) or fax. If it is not possible to access the eDC system, refer to the procedures outlined above for initial reporting of SAEs.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will enter the AE into the eCRF and indicate the AE is an AESI in a timely manner. AESIs that meet the definition of an SAE must be reported in the same timely manner and process as SAEs as outlined above.

17.6 Regulatory Reporting Requirements for Serious Adverse Events

Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For atacicept, the reference safety information is included in the Investigator’s Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report where possible.

Regulatory Reporting

The Sponsor or designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the Independent Ethics Committee / Institutional Review Board (IEC/IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC’s/IRB’s approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor’s responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

17.7 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are hypersensitivity reactions, serious infections, cardiac disease/disorders (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and demyelination disorders.

17.7.1 Hypersensitivity Reactions

Atacicept is contraindicated in subjects with known hypersensitivity to the drug substance or to any of the excipients. If allergic angioedema or other serious hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions occur, administration of IMP should be discontinued immediately, and appropriate therapy initiated. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for resumption of IMP or permanent discontinuation.

Local ISRs may be treated as per Section 16.6.5.

17.7.2 Serious Infections

Treatment of infections must be prompt and done in accordance with local SoC depending on considerations such as the nature and severity of the infection, patient's overall health status, etc.

- Subjects must be carefully examined for signs of infection and questioned about recent infective illnesses and recent vaccination(s)
- If laboratory findings raise concern, in the opinion of the Investigator, that there may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section 14.2, and may lead to study drug discontinuation
- Subjects will be instructed by study site personnel to monitor for early signs of infection, such as upper respiratory symptoms, fever, painful urination, productive cough, breathlessness, constitutional symptoms, etc. Subjects should inform the study site if any of these symptoms or signs are present and should be evaluated and treated in a timely manner according to the local SoC. At each study visit, monitoring for subject's symptoms and signs should also be done. Standard medical care will be provided at the study sites for all AEs occurring during the study. Any subject who experiences a chronic or recurrent significant infection, or opportunistic infection, should be re-evaluated (as per Investigator's clinical judgment and discussion with Medical Monitor) as to whether or not continued treatment with atacicept is appropriate.

For infections associated with severe hypogammaglobulinemia (serum IgG < 3 g/L), consideration can be given to administration of Ig and discontinuation of study drug. If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart, then the subject will be discontinued from study drug (see Section 16.10.1).

17.7.3 Cardiac Disease/Disorders

Treatment with study drug (atacicept/placebo) must be temporarily discontinued in subjects who develop new onset or worsening of clinically significant symptomatic arrhythmias that require medical intervention (such as paroxysmal atrial tachycardia, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia, ventricular fibrillation or ventricular tachycardia), cardiac failure, or cardiac ischemic symptoms. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for discontinuation or resumption of study drug.

17.7.4 Demyelination Disorders

Based on the clinical trial results, MS patients who received atacicept developed significantly more relapses than patients in the placebo group. Therefore, any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as but not limited to MS, optic neuritis or transverse myelitis) should discontinue the study drug.

17.8 Pregnancy

Pregnancy should not be captured as an AE. However, pregnancies with an estimated conception date during the period defined in Section 17.2 must be recorded in the eCRF for both pregnancies in female subjects and pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Section 17.5.

Investigators must actively follow up, document and report on the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Reporting Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 17.2, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the study, the subject must be discontinued from study drug. The Sponsor/designee must be notified without delay and the subject must be followed as indicated above.

17.9 Special Situation Reports

Special situation reports include site reported instances of overdose, misuse, abuse, medication error, and adverse reactions associated with product complaints.

- **Overdose:** For this study, any instance when IMP is given 3 times or more per week is considered an overdose. Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is

above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).

Note: The Sponsor does not recommend specific treatment for an overdose. The effects of an overdose of atacicept are unknown and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and appropriate supportive treatment should be given as needed per Investigator's clinical judgment.

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events should be reported as a protocol deviation and any associated events reported as an AE. Special Situations that are considered to meet SAE criteria will be managed per the same process as SAEs in Section 17.5.

18 Phase 3: Statistical Considerations

The Statistical Analysis Plans (SAPs) for Phase 3 will be separate from the Phase 2b SAP and will be developed and finalized before the database lock for the first analysis. The SAP will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary efficacy and safety endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Any deviations from this plan will be noted in the final Clinical Study Report.

Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number. Formal statistical comparisons will be conducted for the data collected in double-blinded period only. Strategies for alpha control for multiple comparisons are specified in Section 18.6.1.4 Data collected in open-label extension part will be summarized using descriptive statistics.

All statistical analyses will be conducted by the Sponsor or its agent using SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA 27513).

18.1 Planned Analyses

The primary analysis of UPCR will be performed after the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study. An End of Part C analysis will be performed when all subjects complete the double-blind portion of the study (Week 104) or prematurely discontinue from the study. A final analysis will be conducted once all subjects complete the OLE and safety follow-up visits or discontinue from the trial. Additional analyses may be conducted at the discretion of the Sponsor to plan future trials. The details of these analyses will be provided in the SAP.

18.2 Stratification

Subjects will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/1.73 m² or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m²), screening total urine protein excretion (<2 g/24h or ≥ 2 g/24h), SGLT2 inhibitor use at screening (Yes or No) and Region (Asia or Other).

18.3 Statistical Hypotheses

The primary efficacy endpoint is the change from baseline at Week 36 in natural log transformed UPCR. The primary comparison of interest is a 2-sided test of superiority comparing the atacicept 150 mg dose to placebo.

$$H_0: \mu_{\text{placebo}} = \mu_{\text{ATC}} \text{ vs } H_1: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

18.4 Sample Size Determination

The selected sample size provides sufficient power for both the primary endpoint UPCR and the key secondary endpoint eGFR.

The primary efficacy endpoint is the ratio of UPCR at Week 36 compared with baseline, based on 24-hour urine collection. Due to the skewed distribution, UPCR will be natural log transformed. The primary efficacy endpoint becomes the change from baseline at Week 36 in natural log transformed UPCR. A two-sample t-test for ratio was used to determine the sample size for UPCR. It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo groups is 0.67 (ie., the percentage reduction is 33% higher for atacicept than placebo) and the standard deviation (SD) for the mean change of log(UPCR) from baseline is assumed to be 0.7 in both groups (based on Origin Phase 2b Primary Endpoint Analysis [data on file]). Based on these assumptions, 85 subjects per group will provide 95% power to detect a ratio of 0.67 with a two-sided alpha of 0.04 when the ratio under the null hypothesis is 1 [PASS 2015: two-sided two Sample t-test for ratios]. Adjusting for a dropout rate of approximately 15%, 200 subjects in total (100 subjects per group) will be needed to support the primary endpoint analysis at Week 36.

Table 5 displays statistical power under different scenarios, accounting for uncertainty in estimating UPCR percentage reductions and standard deviations; 85 subjects per group will provide at least 85% power at two-sided significant level of 0.04 even if the treatment effect on UPCR reduces from 33% to 30% and/or the standard deviation of the mean change of log(UPCR) from baseline increased from 0.7 to 0.75.

Table 5: Power Calculation for Primary Endpoint of UPCR Under Different Assumptions.

Sample Size	Treatment Effect on UPCR		Standard Deviation	Alpha	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction			
85	0.67	33%	0.7	0.04	95%
			0.75	0.04	92%
	0.7	30%	0.7	0.04	89%
			0.75	0.04	85%

For the key secondary endpoint, a meta-analysis for the association of treatment effects on early change in UPCR and treatment effect on eGFR annualized slope in IgAN patients by [Inker et al \(2021\)](#) is referenced to estimate the expected treatment effect on eGFR annualized slope. The mixed-effects model with random intercept and random slope is planned for comparing 2 slopes, when we estimate the sample size for eGFR slope evaluation ([Ahn, Heo, and Zhang \[2014\]](#)). It is assumed that the ratio of geometric mean ratio of week 36 UPCR to baseline between atacicept and placebo is 0.67 based on ORIGIN Phase 2b Primary Endpoint Analysis. According to the established association between UPCR change at 9 month and eGFR annualized slope by Inker et al and the observation that atacicept did not show an acute eGFR effect in Origin Phase 2b Primary Endpoint Analysis and historical data, the expected difference in annualized slope in eGFR is 2 mL/min/1.73m²/year using linear extrapolation. The variance of random slope is 27 and the variance of residuals is 32 based on an internal Phase 2a study (JANUS trial). The follow-up period is approximately 2 years (ie., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between the atacicept and placebo. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) will be enrolled.

[Table 6](#) displays statistical power for annualized eGFR comparison under different scenarios; 171 subjects per group will provide at least 87% power at two-sided significant level of 0.05 to detect an annualized slope difference of at least 2.0 mL/min/1.73m²/year, even if the variances of random slope and residuals increase by approximately 10% to 30 and 36, respectively. The power will be 77% if the expected annualized slope difference decreases to 1.67 mL/min/1.73m²/year, which associated with a 30% more decrease in UPCR at week 36 in atacicept compared to placebo. If the Phase 3 Week 36 primary endpoint analysis suggests a smaller treatment effect in UPCR (ie., 30%) but similar variances, 210 subjects per group will be needed to provide 85% power to detect a smaller difference in eGFR annualized slope of 1.67 mL/min/1.73m²/year. If the Phase 3 Week 36 primary endpoint analysis suggests both a smaller treatment effect in UPCR (ie., 30%) and a larger variance (ie., 10% increase), 234 subjects per group will be needed to provide 85% power to detect a smaller difference in eGFR annualized slope of 1.67 mL/min/1.73m²/year for larger variances of 30 and 36, respectively.

18.4.1 Potential Adjustment to Sample Size Determination for eGFR

In sample size calculation for the evaluation of difference in 2-year eGFR slope, multiple uncertainties were accounted for, including the treatment effect on UPCR, the modeled relationship between changes in UPCR at 9 months and eGFR over 2 years, and the variances of slope and/or residuals in eGFR.

After the completion of Phase 2b End of Part A analysis at Week 36, the sponsor will confirm whether the observed treatment effect on UPCR is supportive of the current assumption prior to the first subject enrollment in Phase 3 part of the study. Given the short duration, the sponsor won't plan to check the assumption of the variances in eGFR.

After the completion of Phase 2b final analysis, the sponsor will check the assumption of the variances in eGFR. If the Phase 2b final analysis suggests a noticeable difference in variances from the assumed variances, the sample size may be adjusted accordingly to ensure the trial has sufficient power and a protocol amendment will be used to document this change. Since this check is based on data from a separate Phase 2b part of this study to estimate the 'nuisance parameter' of variances, no alpha spending is required.

After the completion of Phase 3 primary endpoint analysis of UPCR at week 36, the sample size for the key secondary endpoint eGFR will be re-examined again. If Phase 3 Part C data suggests noticeable differences from the assumptions made for the current sample size calculation in treatment effect on UPCR or in variances of slope and/or residuals in eGFR, the sample size will be adjusted accordingly to ensure the trial is adequately sized to verify the clinical benefit and a protocol amendment will be used to document this change.

Details regarding this sample size re-estimation will be documented in Phase 3 SAP, which will be finalized before the Phase 3 primary endpoint analysis of UPCR at Week 36.

18.5 Populations for Analyses

The analysis populations are specified below. The final decision to exclude subjects from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Population	Description
Screening	All subjects who sign informed consent.
Intent-to-treat (ITT) Analysis Set	The ITT Analysis Set consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.
Full Analysis Set (FAS)	The FAS consists of all randomized subjects who have received at least 1 dose of treatment. Subjects will be analyzed according to randomized treatment and the primary analysis for all efficacy endpoints will be based on the FAS.
Per-Protocol (PP) Analysis Set	The PP Analysis Set consists of all subjects in the FAS who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the PP Analysis Set will be provided in the SAP, including exclusion of subjects who take prohibited/rescue medications. The PP Analysis Set will be used for supplementary analyses on the primary and selected efficacy endpoints. Subjects will be analyzed according to treatment received.
Safety Analysis Set	The Safety Analysis Set consists of all randomized subjects who receive at least 1 dose of treatment. The Safety Analysis Set is the analysis population for the safety endpoints. Subjects will be analyzed according to treatment received.
Pharmacokinetics Analysis Set	The PK Analysis Set consists of all randomized subjects who were administered at least 1 dose of treatment and have at least 1 evaluable PK sample. All PK evaluations will be based on this analysis population. Subjects will be analyzed according to treatment received.

Unless otherwise indicated, the Full Analysis Set (FAS) is the primary analysis population for efficacy endpoints and the Safety Analysis Set is the primary analysis population for safety endpoints.

18.6 Statistical Analysis

18.6.1 Efficacy Analysis

18.6.1.1 The Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR at Week 36. The estimand for the primary analysis of the primary endpoint is as follows:

- The population for the trial is defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The analysis population is based on the FAS and includes all randomized subjects who have received at least 1 dose of study treatment.
- The variable of interest is the change from baseline in natural-log transformed UPCR.
- The intercurrent events include treatment discontinuation, prohibited/rescue medication use, study withdrawal, lost to follow-up, and death. The hypothetical policy estimand will be used for the primary analysis. For subjects who take prohibited/rescue medications during the double-blinded period, data will be censored after the prohibited/rescue medications use. For treatment discontinuation due to reasons other than prohibited/rescue medication, all data, including data collected after treatment discontinuation, will be used for the primary analysis. Missing 24-hour UPCR will be imputed by the available spot urine samples; other missing data will be assumed as Missing at Random (MAR) and handled implicitly by the analysis model.
- The population level summary measure is the reduction in the geometric mean ratio of UPCR relative to baseline in atacicept group compared to placebo group at Week 36, the associated 2-sided 95% confidence intervals (CI), and the p-value.
- The analysis approach uses a mixed-effects model repeated measures analysis. Change from baseline in natural log transformed UPCR will be the dependent variable. Effects for stratification factor(s), natural log transformed baseline value, randomized treatment, visit, and treatment-by-visit interaction will be included as independent fixed effects, and subject will be included as a random effect. The primary comparison will test the mean difference between atacicept and placebo groups at Week 36. This statistical comparison will be based on linear contrasts of the Least Squares Means (LSMs) estimated from this model. LSM differences will be exponentiated to obtain the mean ratio, the associated 2-sided 95% CIs, and the p-value.
- Sensitivity Analyses will investigate the effect, if any, of the intercurrent events and missing data on the estimation of treatment effect. These analyses include a two-dimensional tipping point analysis and an evaluation of the primary endpoint utilizing the treatment policy (ie., all data collected regardless of the prohibited/rescue medication use will be used).
- Supplementary Analyses will include an evaluation of the primary endpoint using per-protocol population.
- Subgroup Analyses for the primary endpoint may be conducted for the following subgroups as appropriate: age (< median age vs. ≥ median age), sex, region (Asia vs. Others), country (US vs. ex- US), race (White vs. Others), baseline UPCR (<1.5 g/g vs. ≥1.5 g/g), baseline proteinuria (<2 g/24h vs. ≥2 g/24h), baseline eGFR (<45 mL/min/1.73 m², ≥45 and <90 mL/min/1.73m², vs. ≥ 90 mL/min/1.73m²), stable SGLT2 use at baseline (Yes vs. No).

18.6.1.2 The Key Secondary Efficacy Analysis

The key secondary endpoint is the annualized rate of change in eGFR. The estimand for the primary analysis of the key secondary endpoint is as follows:

- The population for the trial is defined in a similar manner as for the primary endpoint.

- The intercurrent events are defined in a similar manner as for the primary endpoint. Hypothetical policy estimand will be used as the primary analysis for the key secondary endpoint, where data will be censored after the prohibited/rescue medication use. The treatment policy will be used as the sensitivity analysis, where all data collected regardless of the prohibited/rescue medication use will be used. Missing data will be assumed as Missing at Random (MAR) and handled implicitly by the analysis model.
- The variable of interest is the eGFR.
- The population level summary measure is the difference between atacicept and placebo group in the eGFR slope over time through Week 104, the associated 2-sided 95% confidence intervals (CI), and the p-value.
- The analysis approach uses a mixed-effects model random coefficients analysis to analyze the rate of change in eGFR. eGFR will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for stratification factor(s), baseline eGFR, randomized treatment, time, and the treatment-by-time interaction. The actual time measurements, in years after the first injection, will be included in the model as a continuous variable. The baseline eGFR value recorded per subject will be assigned a time value of 0. The analysis testing the differences between the treatment groups will be constructed using linear contrasts of the appropriate LS Means from the mixed-effects model, where the difference in eGFR slope corresponds to the parameter for the treatment-by-time interaction term.

18.6.1.3 Other Efficacy Analyses

All other efficacy endpoints will be evaluated based on FAS and including all available data following the treatment-policy strategy.

Continuous efficacy endpoints will be analyzed in a similar manner as for the primary efficacy endpoint.

Binary efficacy endpoints will be presented as the number and percentage of responders by treatment group. The population level summary measure is the odds ratio comparing the odds of being a responder in atacicept vs. placebo group, which will be evaluated by a logistic regression model controlling for stratification factor(s), randomized treatment, and the appropriate baseline value. The odds ratio for the treatment effect, 95% CIs, and p-value will be estimated from the model.

Time-to-event efficacy endpoints will be displayed using Kaplan-Meier methodology. The population level summary measure is the ratio of the hazard rates of atacicept vs. placebo group for the corresponding endpoint. The population level study measure will be evaluated using the Cox proportional hazard model with effects for stratification factor(s), randomized treatment, and the appropriate baseline value. Subjects who do not have an endpoint of interest will be censored at the last assessment of the endpoint. The adjusted hazard ratio of the risk of the event between the atacicept and the placebo group, the corresponding 95% CIs, and p-value will be estimated from this model.

18.6.1.4 Multiple Comparisons

To control the overall type 1 error in the evaluation of the primary and key secondary efficacy endpoint at a two-sided alpha of 0.05, the hypothesis testing will be performed in sequential order by fallback procedure. The primary efficacy endpoint will be tested first at a two-sided significant level of 0.04. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at two-sided significant level of 0.05. If the statistical significance is not met for the primary endpoint, the key secondary efficacy endpoint will be tested at a two-sided significant level of 0.01. If the statistical significances are met for both the primary and key secondary endpoints, the sequential testing approach will be used to test other secondary endpoints with a two-sided significant level of 0.05. More details regarding the order of sequential testing will be pre-specified in Phase 3 statistical analysis plan.

18.6.2 Safety Analyses

Safety analyses will include the examination of vital signs, physical exam, 12-lead ECG, routine clinical laboratory tests (including hematology, blood chemistries, urinalysis), and AEs. All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

18.6.2.1 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent adverse events (TEAEs) will be summarized using descriptive statistics by treatment group. Treatment-emergent adverse events are defined as AEs with onset dates occurring during the study period (i.e., from the first dose until the subject's last study visit) and will be assigned to the most recently received treatment at the start of the AE. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each MedDRA System Organ Class and MedDRA Preferred Term, by treatment group. Treatment-emergent adverse events will also be summarized by relationship to treatment and by severity within each treatment group, and by predefined AESIs.

18.6.2.2 Other Safety Analyses

Laboratory data, vital sign data, and ECG data will be summarized by timepoint and treatment group with descriptive statistics.

18.6.3 Pharmacokinetic and Pharmacodynamic Analyses

Analyses of the PK, serum BLYS, APRIL, and other exploratory biomarkers will be summarized using descriptive statistics. Additional analyses may be detailed in the corresponding SAP.

19 Phase 3: Responsibilities

19.1 Investigator Responsibilities

19.1.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

19.1.2 Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

19.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions on the study.
- Subjects must be informed that their participation is voluntary.
- Subjects or their legal representative under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, subjects must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the subject.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

19.1.4 Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected.

- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study subject. The file must identify each subject, contain the following demographic and medical information for the subject, and should be as complete as possible:
Subject's full name, date of birth, sex, height, and weight
Medical history and concomitant diseases
Prior and concomitant therapies (including changes during the study)
Study identifier (i.e., the Sponsor's study number) and subject's study number
Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
Any medical examinations and clinical findings predefined in the protocol
All AEs
Date that the subject left the study, including any reason for early withdrawal from the study or study drug, if applicable
- All source data must be filed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] scan images, ECG recordings, and laboratory results). Each document must clearly identify the subject and the procedure date, ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. Investigators must notify Sponsor in advance if source documents are to be moved to another location, such as for archiving.

19.1.5 Data Protection

- The Sponsor will assign a unique identifier to subjects after obtaining their informed consent. All subject records or datasets transferred to the Sponsor will contain the identifier only; subject names or any identifiable information will not be transferred.
- The Sponsor must inform subjects that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain subjects' confidentiality.
- The Investigator will complete the subject registration using the IWRS (Section 5.1). If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject will be registered by IWRS. If the subject is ineligible for the study, a subject number will be allocated and documented.

19.2 Sponsor Responsibilities

This clinical study will be Sponsored by: Vera Therapeutics, Inc.

The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

An iDMC will be formed in this study (see Section 13.3).

19.2.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
 - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study subjects. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
 - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
 - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

19.2.2 Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to subjects for use during the study. These provide the means for subjects to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the subject. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician (or designee). This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician (or designee) to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

19.2.3 Clinical Study Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

19.2.4 Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator. Selection of the Coordinating Investigator will be performed by the Sponsor, based on the requirements of the study.

19.2.5 Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

19.2.6 Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

19.3 Data Quality Assurance

- All subject study data will be captured:
 - In the eDC system.
 - Through files transmitted to the Sponsor, or designee, electronically (e.g., laboratory data).
- The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by electronically signing the subject casebook.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of subject casebooks will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of subjects are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed

during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

19.4 Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
 - Inadequate recruitment of subjects by the Investigator
 - Discontinuation of further development of the Sponsor's compound

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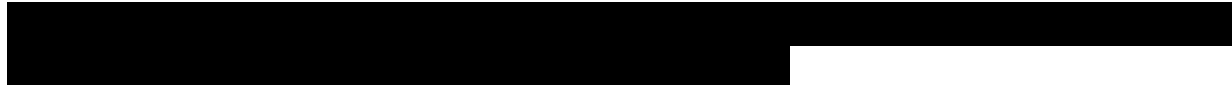
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21 Appendices

Appendix 1	Abbreviations
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Appendix 3	Management of Abnormal and Medically Important Laboratory Abnormality
Appendix 4	Key Differences Between Phase 2b and Phase 3 Studies
Appendix 5	Investigator Signature Page

Appendix 1 Abbreviations

0035	MS700461-0035
024	EMR700461-024
β-hCG	beta human chorionic gonadotropin
ACEi	angiotensin converting enzyme inhibitor
ADDRESS II	EMR700461-023 Phase II study
AE	adverse event
AESI	adverse event of special interest
anti-HBc	anti-hepatitis B core
APRIL	a proliferation-inducing ligand
APRIL-SLE	EMR700461-27646 Phase II study
ARB	angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker
ATC	Atacicept
BILAG	British Isles Lupus Assessment Group (BILAG) Disease Activity Index
BLyS	B lymphocyte stimulator (also called B-cell activating factor)
BP	blood pressure
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	clinical research organization
CS	corticosteroid(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
DBPC	double-blind placebo-controlled
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic Data Capture

eGFR	estimated glomerular filtration rate
EOT	end of treatment
ePRO	electronic patient reported outcome
ERA	endothelin receptor antagonist
ESRD	end stage renal disease
ET	early termination
EWB	emotional well-bring
FAS	Full Analysis Set
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
FU	follow-up
FWB	functional well-being
GCP	Good Clinical Practice
GCS	glucocorticosteroids
Gd-IgA1	galactose-deficient IgA1
GN	Glomerulonephritis
HbA1c	hemoglobin-A1c
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDA	high disease activity
HEENT	Head, Ears, Eyes, Nose, Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form

ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin (G, A, and M)
IgAN	IgA Nephropathy
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IWRS	interactive web response system
LDA	low disease activity
LSMeans	Least Squares Means
LTBI	latent TB infection
LTE	long-term extension
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MMRM	mixed-effect model with repeated measurement
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTD	maximally tolerated dose
OLE	open label extension
ON	optic neuritis
PCR	polymerase chain reaction

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
pmp	per million people
PP	per-protocol
PRO	patient-reported outcome
PWB	physical well-being
QoL	quality of life
RAS(i)	renin angiotensin system (inhibitor)
RAAS(i)	renin-angiotensin-aldosterone system (inhibitor)
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
	
SGLT2(i)	sodium-glucose cotransporter-2 (inhibitor)
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index-2000
SoC	standard of care
SRI	SLE Responder Index
SUSAR	suspected unexpected serious adverse reaction
SWB	social/family well-being
TACI	Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor
TB	tuberculosis
TEAEs	treatment emergent adverse events
Tmax	time to maximum concentration
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone

ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US, USA	United States (of America)
VAS	visual analog scale
WBC	white blood cell
WOCBP	woman of childbearing potential

Appendix 2 Contraception

Woman of Childbearing Potential (WOCBP)

A WOCBP (i.e., fertile), following menarche and until either:

- 1 Becoming postmenopausal; or,
- 2 Is permanently sterile by means of a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly and are the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - Oral, intravaginal, transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation - Oral, injectable
- Implantable progestogen*-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)*
- Intrauterine hormone-releasing system (IUS)*
- Bilateral tubal occlusion*
- Vasectomized partner*: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject

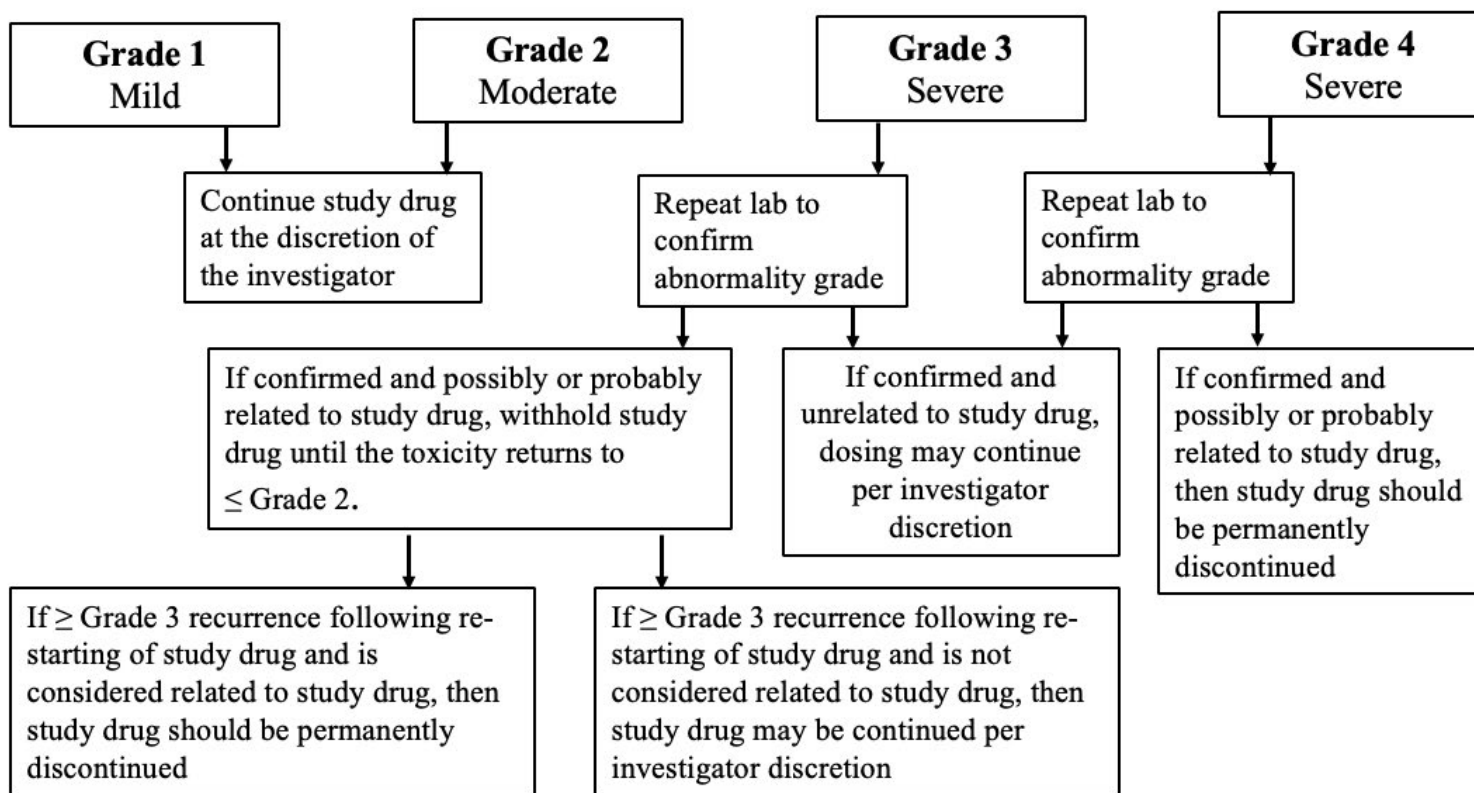
Caution should be taken for hormonal contraception, as the effect of atacicept on hormonal contraception is unknown. Subjects taking hormonal contraception should use a supplementary barrier method (preferably male condom) during screening, during the study drug administration period and for at least 175 days after the last dose of study treatment.

* Invasive Methods: User-independent invasive contraceptive methods herein mentioned in this appendix is provided as a guidance. Women of childbearing potential who are already using one of these highly effective invasive contraceptive methods prior to inclusion OR who will begin using any of these highly effective contraceptive methods by their own decision will be eligible for inclusion.

Contraception for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of child-bearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

Appendix 3 Management of Abnormal and Medically Important Laboratory Abnormality



Appendix 4 Key Differences Between Phase 2b and Phase 3 Studies

	Phase 2b	Phase 3
Objectives and Endpoints		
Primary endpoint	UPCR at Week 24	UPCR at Week 36
Secondary endpoint	UPCR at Week 36	Key: Annualized rate of change in eGFR at Week 104 Other: <ul style="list-style-type: none"> GdIgA1 at Weeks 24, 36, 52, and 104 UPCR at Week 24 Annualized rate of change in eGFR at Week 52 Composite kidney failure endpoint
Exploratory endpoints	<ul style="list-style-type: none"> UPCR at Week 12 [REDACTED] eGFR at Week 12, 24, and 36 IgA, IgG, IgM levels, C3, C4, and Gd-IgA1 levels at Weeks 12, 24, and 36 PK of atacicept 	[REDACTED]
Study Design		
Randomization and treatment	2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or placebo	1:1 to atacicept 150 mg or placebo
Stratification	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (≥ 30 to < 45 mL/min/1.73 m² and ≥ 45 mL/min/1.73 m² by CKD-EPI) 	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (< 45 mL/min/1.73 m², or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI) Screening total urine protein excretion (< 2 g/24h or ≥ 2 g/24h) Region (Asia or Other) <ul style="list-style-type: none"> SGLT2 inhibitor use at screening (Yes or No)

	Phase 2b	Phase 3
Double-blind period duration	36 weeks	104 weeks
Study visits and assessments after premature study drug discontinuation in the double-blind period	Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination (ET) Visit and have a 26-week follow-up period.	Subjects who prematurely discontinue study drug prior to completion of the 104-week treatment period should continue with study visits and assessments per protocol through the end of the double-blind period.
Open-label extension duration	60 weeks	52 weeks
Duration of treatment	Up to 96 weeks	Up to 156 weeks
Number of sites / subjects	90 / 105	200 / 376
Eligibility Criteria – Inclusion criteria		
Upper age limit	Not defined	≤70 years
Screening proteinuria allowed	Ttotal urine protein excretion >0.75g or UPCR >0.75 mg/mg based on a 24-hour urine sample	Total urine protein excretion ≥1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥1.0 mg/mg based on a 24-hour urine sample
Criteria for RAASi use during Screening	On a stable prescribed regimen of RAASi (ACEi, ARB or MRA) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening.	On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1.
Eligibility Criteria – Exclusion criteria		
Systemic corticosteroids	Corticosteroids for the treatment of IgAN within 3 months prior to screening.	Corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening.
Criteria for clinically significant or predefined abnormalities	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN. - If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase 	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin >1.5 x ULN. - If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase

	Phase 2b	Phase 3
	in liver transaminases), contact the Medical Monitor for further discussion.	in liver transaminases), contact the Medical Monitor for further discussion. <ul style="list-style-type: none"> hemoglobin <10 g/100 ml in men and hemoglobin <9 g/100 ml in women platelets <100 000/1 mm³
Hepatitis C virus (HCV)	Subjects with any hepatitis C virus (HCV) are excluded	Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
History of malignancy	History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix	History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ), with no evidence of recurrence
Permitted Medications		
Use of SGLT2 inhibitors and mineralocorticoid receptor antagonists	In subjects receiving SGLT2 inhibitors at the time of enrollment, the dose must be stable for at least 8 weeks prior to screening and is expected to be at a stable dose over the study period. The Investigator should discuss planned use of an SGLT2 inhibitor with the Medical Monitor prior to initiation for their awareness.	As with RASi medications, subjects prescribed SGLT2 inhibitors and/or mineralocorticoid receptor antagonists (MRAs; e.g. aldactone, eplerenone or finerenone) are required to be on a stable dosing regimen for at least 12 weeks prior to screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes or the introduction of SGLT2 inhibitors and/or MRAs. If, in the opinion of the Investigator, intervention is warranted, it is strongly recommended that the Investigator the Medical Monitor must be notified within 48 hours of such intervention. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the introduction of SGLT2

	Phase 2b	Phase 3
		inhibitors and/or MRAs, but this at the investigator's discretion if feasible.
RAAS inhibitor changes during treatment period	It is recommended that changes in RAASi medication be avoided for the duration of the study.	To be eligible for randomization, all subjects who tolerate RASi (ACEi or ARB) medication are required to be on stable RASi treatment for at least 12 weeks prior to Screening that is at the maximum labeled or tolerated dose, which must be maintained through the screening period to Day 1. For subjects who are unable to tolerate RASi medication, management of IgAN will be SoC according to local practice. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes and changes in type of RASi medication; every effort should be made to maintain subjects on their stable RASi dose, unless required for safety reasons. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non RASi medications should have been considered before these specific drug classes. In certain instances (i.e. hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].
Rescue medications	Not defined	Defined as: Should the Investigator consider that rescue medication (steroids and/or immunosuppressive treatment) be needed, such treatment can be initiated by the Investigator. However, in consideration of current guidelines (2021 KDIGO guidelines), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

	Phase 2b	Phase 3
		<ul style="list-style-type: none"> • Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] (although treatment toxicity must be considered in those with eGFR < 50); and/or • Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., >3.5 g/day] and hypoalbuminemia [albumin < 3.0 g/dL]) <p>Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. If rescue medication is required, it is the Investigator's decision to implement new treatment. In this case, the Medical Monitor must be notified within 48 hours after the initiation of rescue therapy, as continued dosing with IMP may, in this circumstance, be discontinued. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible) , prior to the initiation of rescue medication, but this at the investigator's discretion if feasible.</p> <p>Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 15.7.1.</p>
Prohibited Medications		

	Phase 2b	Phase 3
Systemic corticosteroids	Corticosteroids for the treatment of IgAN within 3 months prior to screening.	Corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening.
<i>Schedule of Assessments</i>		
Additional site visits not included in SOA table	N/A	Additional visits can be conducted at Weeks 1, 3, and 105.
<i>Treatment with IMP</i>		
Pulse and BP monitoring on Study Day 1	Pulse and BP will be recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes	Pulse and BP will be recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
<i>Local Tolerability (Injection Site Assessment)</i>		
Grading scales for severity of manifestations	Any local injection site reactions (ISRs) will be assessed by the Investigator and recorded as AEs. Severity of the ISR reported on the AE form should reflect the highest severity of the manifestation.	Any clinically significant ISR as per Investigator judgement will be reported as an AE. Severity of the ISR reported on the AE form based on grading scale provided in protocol Section 16.6.5.
<i>Clinical Laboratory Assessments</i>		
Amount of blood collected per subject per visit / total	14-16 mL / 552 mL	15-43 mL / 757.5. mL
Abnormal lab values	Adverse events related to abnormal lab values are graded based on CTCAE scale.	Adverse events related to abnormal lab values are graded based on the Toxicity Scale used for all other adverse events.
<i>Study Questionnaires</i>		

	Phase 2b	Phase 3
Contraception		
Female subjects	Not defined	Invasive Methods defined as user-independent invasive contraceptive methods herein mentioned in this appendix is provided as a guidance. Women of childbearing potential who are already using one of these highly effective invasive contraceptive methods prior to inclusion OR who will begin using any of these highly effective contraceptive methods by their own decision will be eligible for inclusion.
Male subjects	Not included	It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.
Statistical Methods		
Statistical testing	Statistical testing will be conducted for the primary and secondary efficacy endpoints with no adjustments for multiple comparisons with a significance level of 0.05.	To control type 1 error in the evaluation of the primary and key secondary efficacy endpoints, the hypothesis testing will be performed in sequential order. The primary efficacy endpoint will be tested first at a significance level of 0.05. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at a significance level of 0.05. If the statistical significance is not met for the primary endpoint, the key

	Phase 2b	Phase 3
		secondary efficacy endpoint cannot be deemed statistically significant, although nominal p-values and 95% CIs may be reported and considered descriptive. Similarly, the sequential testing approach will be used to test other selected secondary endpoints.

Appendix 5 Investigator Signature Page**Study Acknowledgement**

Study Title: A Phase 2b/3, Multi-part Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)

Clinical Study Protocol Version: Amendment 5 Dated 23 February 2023

This protocol has been approved by Vera Therapeutics, Inc. The following signature documents this approval.



Name (Printed)
Chief Medical Officer



Signature

Feb-2023 | 19:12 PST

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I understand and agree that it contains all necessary details for me and my staff to conduct this study as described.

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation, Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vera Therapeutics, Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number



CLINICAL STUDY PROTOCOL

Clinical Study Protocol Title:	A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)		
Protocol Number:	VT-001-0050		
Short Title:	Atacicept in Subjects with IgA Nephropathy (ORIGIN and ORIGIN 3)		
Sponsor Name and Legal Registered Address:	Vera Therapeutics, Inc. 2000 Sierra Point Parkway, Suite 1200 Brisbane, CA 94005 United States of America		
Regulatory Agency Identifying Numbers:	US IND: 122043 EU CT No. 2023-503772-24-00		
Clinicaltrials.gov Identifier	NCT04716231		
Protocol Version:	Original: 28 December 2020 Amendment 1: 15 March 2021 Amendment 2: 14 April 2021 Amendment 3: 03 December 2021 Amendment 4: 10 March 2022 Amendment 4.1 European Union Consolidated: 03 February 2023 Amendment 5: 23 February 2023 Amendment 6: 23 August 2023 Amendment 7: 23 December 2024 Amendment 8: 01 June 2026		
Vera Therapeutics Name and Contact Information:	[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]



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IMPORTANT CLINICAL STUDY NOTE

It is important to note to all study investigators, regulators, competent authorities, ethics committees, institutional review boards, scientific committees, site staff, clinical research organizations, and individuals involved in the review or conduct of this study that the design of this protocol is a multi-part study as described below. Some study sites and countries will be participating in the Phase 2b component only, the Phase 3 component only, or both components.

This is a multi-part study comprising of the original Phase 2b study (Parts A and B) and the addition of a separate Phase 3 study (Parts C and D). The Phase 3 study has been added as a separate component to the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from the Phase 2b study have been used to inform the Phase 3 study design including selection of dose and determination of sample size.

The Phase 2b study is referred to as ORIGIN and the Phase 3 study is referred to as ORIGIN 3.

To ensure clarity, this protocol is organized by study phase, as outlined below. The study phase-specific background information and procedures are kept distinctly within these sections. All updates made in Amendment 8 apply only to the Phase 3 portion of the study, as all patients have already completed the treatment visits for the Phase 2b portion.

Phase 2b:

- a. Synopsis: Pages [10](#) through [21](#)
- b. Protocol: Sections [1](#) through [9](#)

Phase 3:

- a. Synopsis: Pages [86](#) through [101](#)
- b. Protocol: Sections [11](#) through [19](#)

Key differences between the Phase 2b and Phase 3 studies are summarized in Section [10](#) and [Appendix 4](#).

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PHASE 2B STUDY (ORIGIN)

1. **Synopsis:** Pages 10 through 21
2. **Protocol:** Sections 1 through 9

PHASE 2B (ORIGIN) PROTOCOL SYNOPSIS

Vera Therapeutics, Inc.
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Rationale: Atacicept (also known as VT-001) targets B-cells by inhibiting B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), and has been studied in a pilot Phase 2a clinical study for immunoglobulin A (IgA) Nephropathy (IgAN). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and galactose-deficient IgA1 (Gd-IgA1), and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. Based on the available clinical data, the targeted population for this Phase 2b study component is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of renin-angiotensin-aldosterone system inhibition (RAASi) with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). The objectives of the study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN. An additional objective of the Phase 2b study is to determine the appropriate dose(s) for further clinical development.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 24
Secondary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	UPCR ^a	Week 36
Exploratory		
Evaluate the effect of atacicept on change in proteinuria in adult subjects with IgAN	UPCR ^a	Weeks 12, 48 and 96
Evaluate the effect of atacicept on rate of change in estimated glomerular filtration rate (eGFR)	Rate of change in eGFR ^b	Weeks 12, 24, 36, 48 and 96
Evaluate the effect of atacicept on change in serum immunoglobulin levels, complement levels and on serum Gd-IgA1 levels	IgA, IgG, IgM levels, C3 and C4 levels Gd-IgA1 levels	Weeks 12, 24, 36, 48, 96 and Follow Up Weeks 12 and 26
Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, adverse events	Entire study
Evaluate serum PK of atacicept	Serum concentration of atacicept	Entire study

AEs=adverse events; eGFR=estimated glomerular filtration rate; Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin; IgAN=immunoglobulin A Nephropathy; PK=pharmacokinetic; UPCR=urine protein to creatinine ratio.

^a Based on 24-hour urine sample

^b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults

Overall Design: This Phase IIb study is a multicenter, randomized, double-blind, placebo-controlled study. Subjects will be randomized 2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 75 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 25 mg once weekly subcutaneous (SC) injections (N=15)
- Placebo-to-match once weekly subcutaneous (SC) injections (N=30)

The study is composed of a (up to) 4-week Screening Period, a 36-week Blinded Treatment Period (Part A), followed by a 60-week Open-Label Extension (OLE) Period (Part B), and a 26-week Safety Follow-up (FU) Period. Upon completion of the 36-Week Blinded Treatment Period, including attendance at Weeks 24 and 36 Visits for key study assessments, all subjects will be offered open-label atacicept 150 mg for an additional 60 weeks. At the Week 36 Visit after completion of all study visit assessments, subjects will switch from double-blinded treatment to open label treatment. Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination (ET) Visit and have a 26-week follow up period. After the last subject completes the Week 36 Visit or completes an Early Termination Visit, the study will be unblinded. The study will be conducted on an outpatient basis.

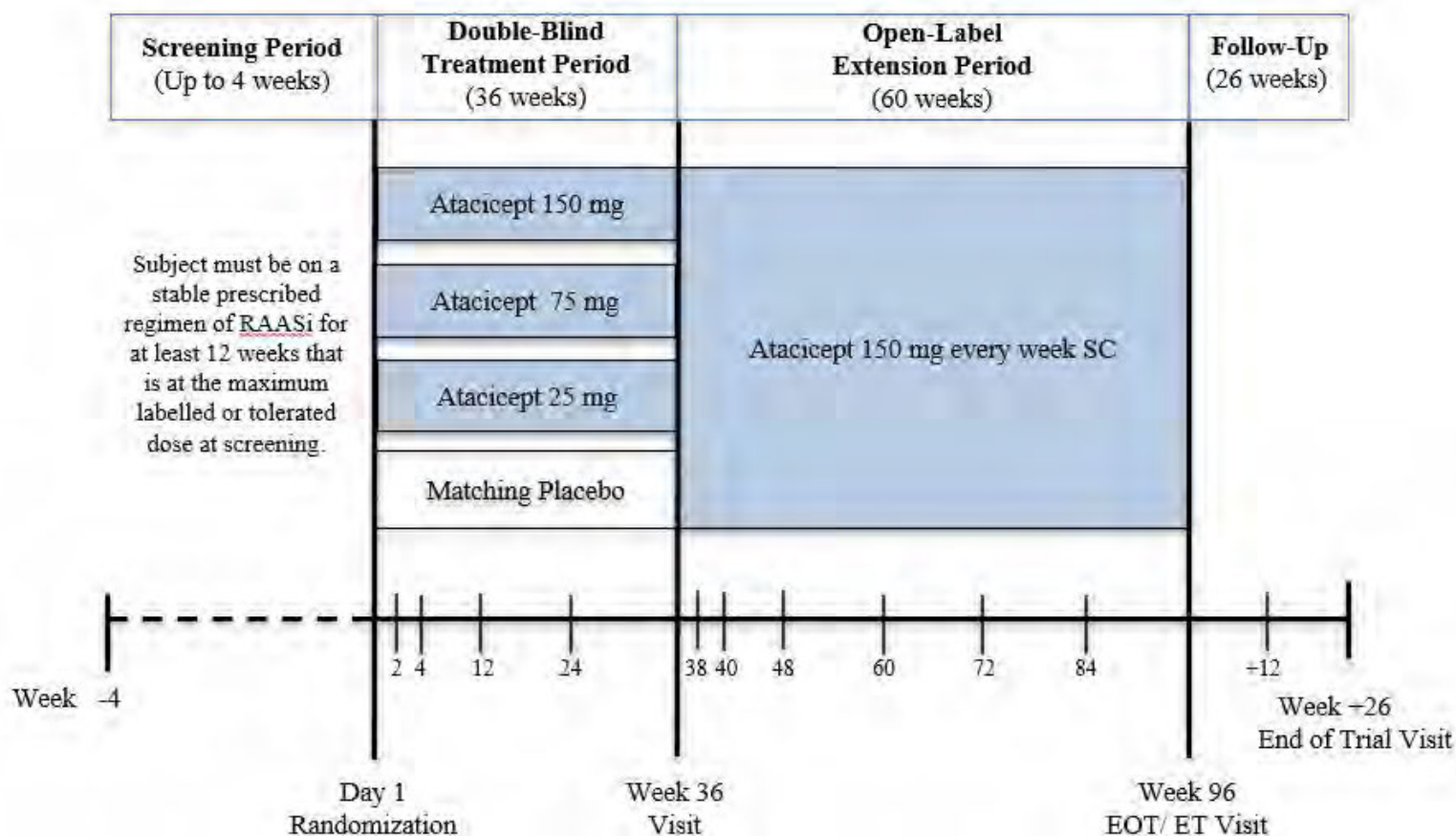
At selected sites, a subgroup of subjects (approximately 32 subjects, with 8 subjects per each Part A treatment arm) enrolled will have additional PK sampling visits that will be done at Day 2 and/or Day 3, approximately 24 and 48 hours after the first dose, respectively.

Number of Study Sites: Approximately 90 sites globally

Number of Subjects: Approximately 105 randomized

Involvement of Special Committee(s): An independent Data Monitoring Committee (iDMC) will review safety data on an ongoing basis.

Study Schema*



Note: Subject's stable dose of ACEi and/or ARB must be maintained for the duration of the study.

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; EOT=end of treatment; ET=early termination; RAASi=renin-angiotensin-aldosterone system inhibitor; SC=subcutaneous.

* For Czech Republic only, additional visits were conducted at Week 1 and Week 37.

* For Germany only, additional visits were added at Week 1 and Week 3

Target Population: Male or female with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose.

Duration of Study Drug Treatment: Up to 96 weeks (36 weeks blinded + 60 weeks OLE)

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
 - For the Czech Republic an age limit of ≤ 70 also applies
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit
4. Total urine protein excretion $> 0.75\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCR) $> 0.75\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
5. $\text{eGFR} \geq 30\text{ mL/min/1.73 m}^2$ at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
6. On a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose at screening
 - The subject is eligible if they do not tolerate RAASi, provided their management of IgAN is standard of care (SoC) according to local guidelines. This must be documented by the Investigator.
7. Systolic blood pressure $\leq 150\text{ mmHg}$ and diastolic blood pressure $\leq 90\text{ mmHg}$ at screening
8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).
OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

Exclusion Criteria:

1. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis
2. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
3. Evidence of nephrotic syndrome within 6 months of screening (serum albumin < 30 g/L in association with UPCR > 3.5 mg/mg)
4. Total urine protein excretion ≥ 5 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 5 mg/mg based on a 24-hour urine sample during the Screening Period
5. Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants
6. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
7. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $> 7.5\%$ at screening
8. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
 - Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.
9. Prohibited medications:
- Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic, and intranasal.
 - For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 3 months prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for > 1 week or 0.5 mg/kg/day prednisolone or equivalent
 - Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time

- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics
10. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:
- serum IgG below 7 g/L
 - aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level $> 2.5 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN
 - If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
 - For The Czech Republic only, the following criteria also apply:
 - hemoglobin < 10 g/100 mL in men and hemoglobin < 9 g/100 mL in women
 - platelets $< 100,000/\text{mm}^3$
11. Administration of live and live-attenuated vaccinations within 30 days prior to randomization
12. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
13. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
14. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
15. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.
- For Germany only, the following criteria also apply:

Specifically for COVID-19: Evidence of positive test for SARS-CoV-2, by PCR, at the Screening Visit; Subjects with a previous COVID-19 infection may be included provided the PCR test is negative for SARS-CoV-2 and they do not have chronic symptoms as a result of COVID-19. COVID-19 testing may be performed at local lab, per site/local guidelines.
16. History of acute or chronic infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus.
- Positive hepatitis B surface antigen (HBsAg): Subjects who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow up
17. History of splenectomy

18. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix
 - For Germany only the following criteria apply:
History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).
19. Known hypersensitivity to atacicept or any component of the formulated atacicept
20. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)
21. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
22. Unwillingness or lack of capacity to follow all study procedures
23. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

Study Procedures/Frequency: Study visits will occur at Screening, Day 1, Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

There will be a 26-week follow up period after subject's end of treatment visit (EOT, Week 96). Subjects discontinuing study intervention early will require an Early Termination Visit within 10 days of the last dose and continue safety follow up for 26 Weeks from the ET visit. Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 1](#)).

Test Product, Dose, Mode of Administration, and Reference Therapy: In a blinded fashion, 150 mg atacicept, 75 mg atacicept, 25 mg atacicept or placebo to match, given as once weekly subcutaneous (SC) injections for 36 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept, given as once-weekly SC injections for 60 weeks by prefilled syringe. Subject must also be on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose. It is recommended that changes in RAASi medication be avoided for the duration of the study.

Statistical Methods: The Statistical Analysis Plan (SAP) will be developed and finalized before the database lock for the first interim analysis and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Any deviations from this plan will be noted in the final clinical study report.

All endpoints will be summarized using descriptive statistics. Statistical testing will be conducted for primary and secondary efficacy endpoints with no adjustments for multiple comparisons. For the purposes of this trial, a significance level of 0.05 will be utilized.

Sample size and power calculations

Sample size and power are estimated for the primary efficacy endpoint, change from baseline to Week 24 in natural log transformed UPCR. It is assumed that the absolute difference (placebo – active) in the mean ratio of Week 24 UPCR to baseline UPCR is 0.28. The geometric mean ratio of Week 24 UPCR to baseline for placebo is expected to be 0.88. The coefficient of variation is estimated as 0.594 (i.e., pooled log standard deviation [SD] of 0.55). The expected placebo response and study intervention effect size are based on the analysis of the phase 2 study for atacicept and placebo in IgAN and placebo responses seen in other large IgAN studies. Based on these assumptions, 25 subjects in the placebo group and a combined total of 50 subjects in the atacicept 75 mg and 150 mg groups sufficient to provide at least 80% power to detect a ratio of 1.47 when the ratio under the null hypothesis is 1 [PASS 2008: two-sided two Sample t-test for ratios, $\alpha=0.05$, coefficient of variation on the original scale is 0.594]. Adjusting for a 15% dropout rate, 30 subjects should be enrolled in each of the placebo, atacicept 75 mg, and atacicept 150 mg groups to ensure 25 subjects complete Week 24 in each of these groups. The sample size of 15 for the atacicept 25 mg group is chosen to provide preliminary safety and efficacy information and is not based on statistical considerations.

Planned Analyses

The primary analysis of UPCR will be performed after all subjects complete the Week 24 visit or prematurely discontinue from the study. An End of Part A analysis will be performed when all subjects complete the double-blind portion of the study or prematurely discontinue from the study. A final analysis will be conducted once all subjects complete the OLE or discontinue from the trial. Additional analyses may be conducted at the discretion of the Sponsor to plan future trials. The details of these analyses will be provided in SAP.

Analysis Sets

All randomized subjects receiving at least one dose of study intervention will be included in the Safety Analysis Set. Subjects in the Safety Analysis Set who have at least one post-baseline evaluation of UPCR will be included in the Full Analysis Set (FAS). Subjects in the FAS will be analyzed according to randomized treatment assignment and all efficacy analyses will be based on the FAS. Safety analyses will be based upon treatment actually received.

Primary and key secondary efficacy endpoint analysis

The primary analysis of proteinuria will assess UPCR data via a mixed-model repeated measures analysis. Change from baseline in natural log transformed UPCR will be the dependent variable. Effects for randomized treatment, natural log transformed baseline value, time, and treatment-by-time interaction will be included as independent fixed effects, and subject will be included as a random effect. The primary comparison will test the mean difference between the combined 75 mg and 150 mg atacicept groups versus the placebo group at Week 24. This statistical comparison will be based on linear contrasts of the Least Squares Means (LSMeans) estimated from this model. LSMean differences will be exponentiated to obtain the mean ratio. The key secondary endpoint comparison at Week 36 will be assessed similarly.

Other efficacy endpoint analyses

A mixed-model random coefficients analysis will be used to analyze the rate of change in eGFR. Estimated glomerular filtration rate (eGFR) will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for randomized treatment, baseline eGFR, time, and the treatment-by-time interaction.

A mixed-model repeated measures analysis (as described for the primary endpoint) will be used to analyze the mean change from baseline over time for IgA, IgG, IgM, C3, C4, and Gd-IgA1 levels using appropriate data transformations. Differences between the treatment groups at each study visit will be presented.

Safety endpoint analyses

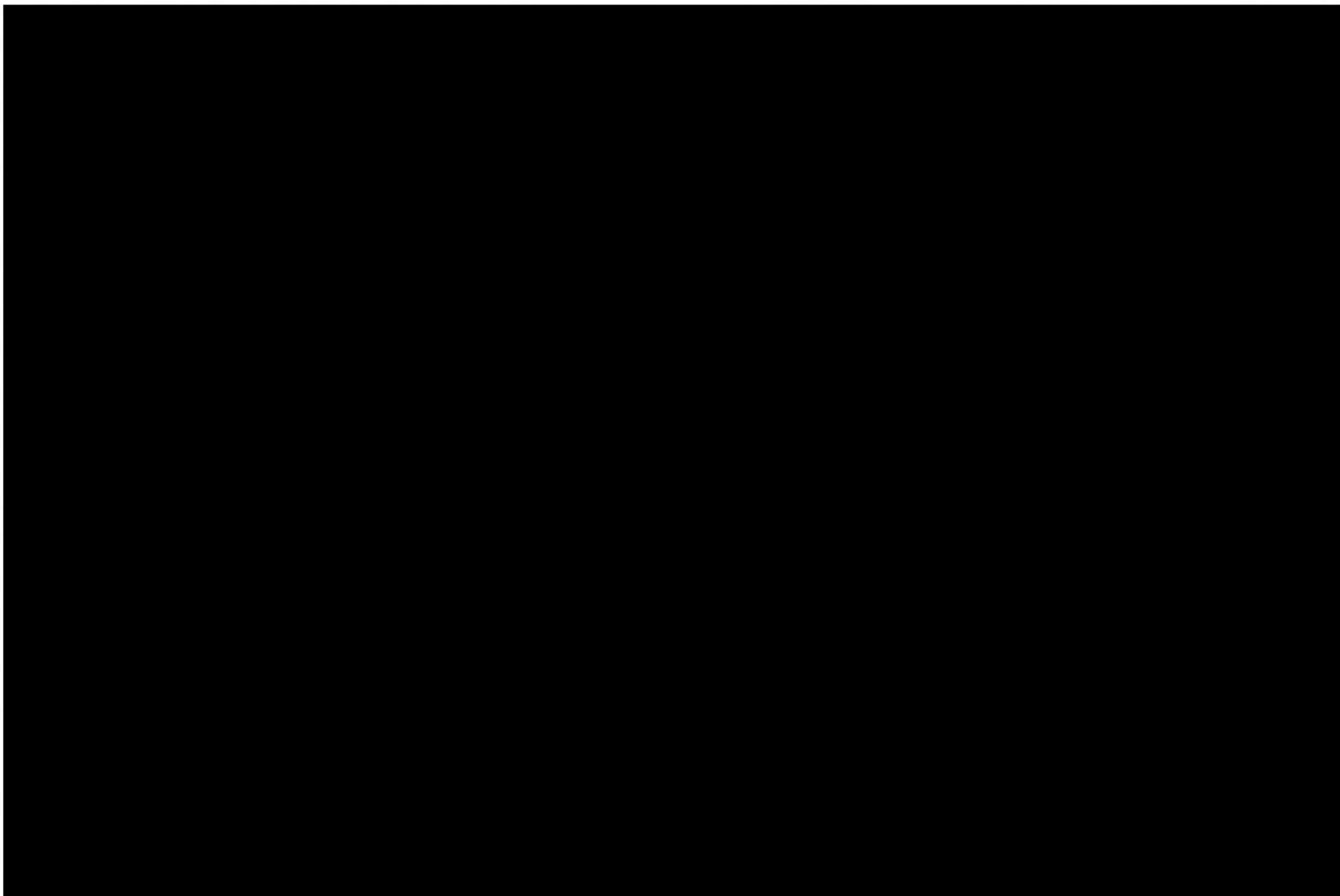
All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

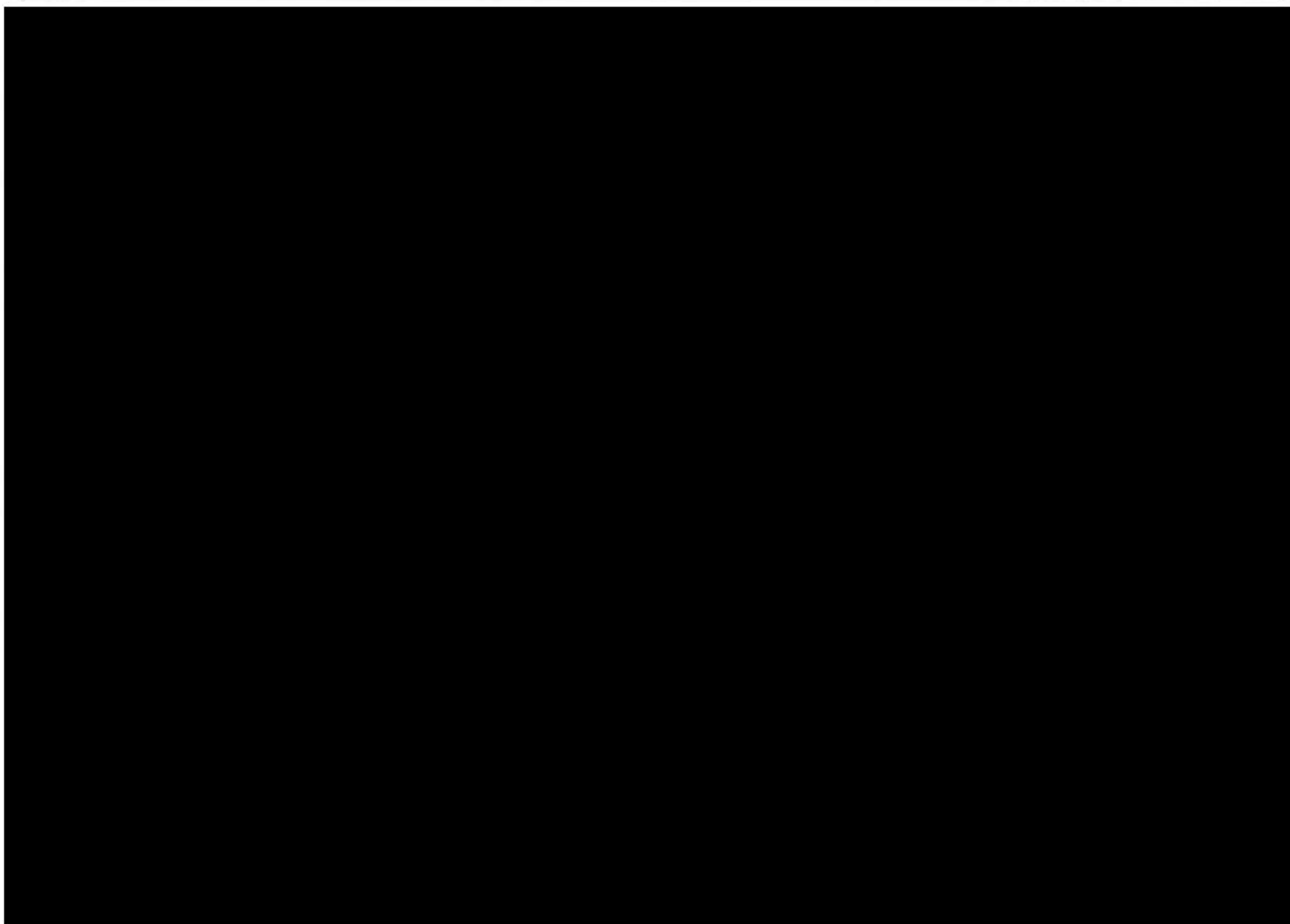
Blinding and unblinding considerations

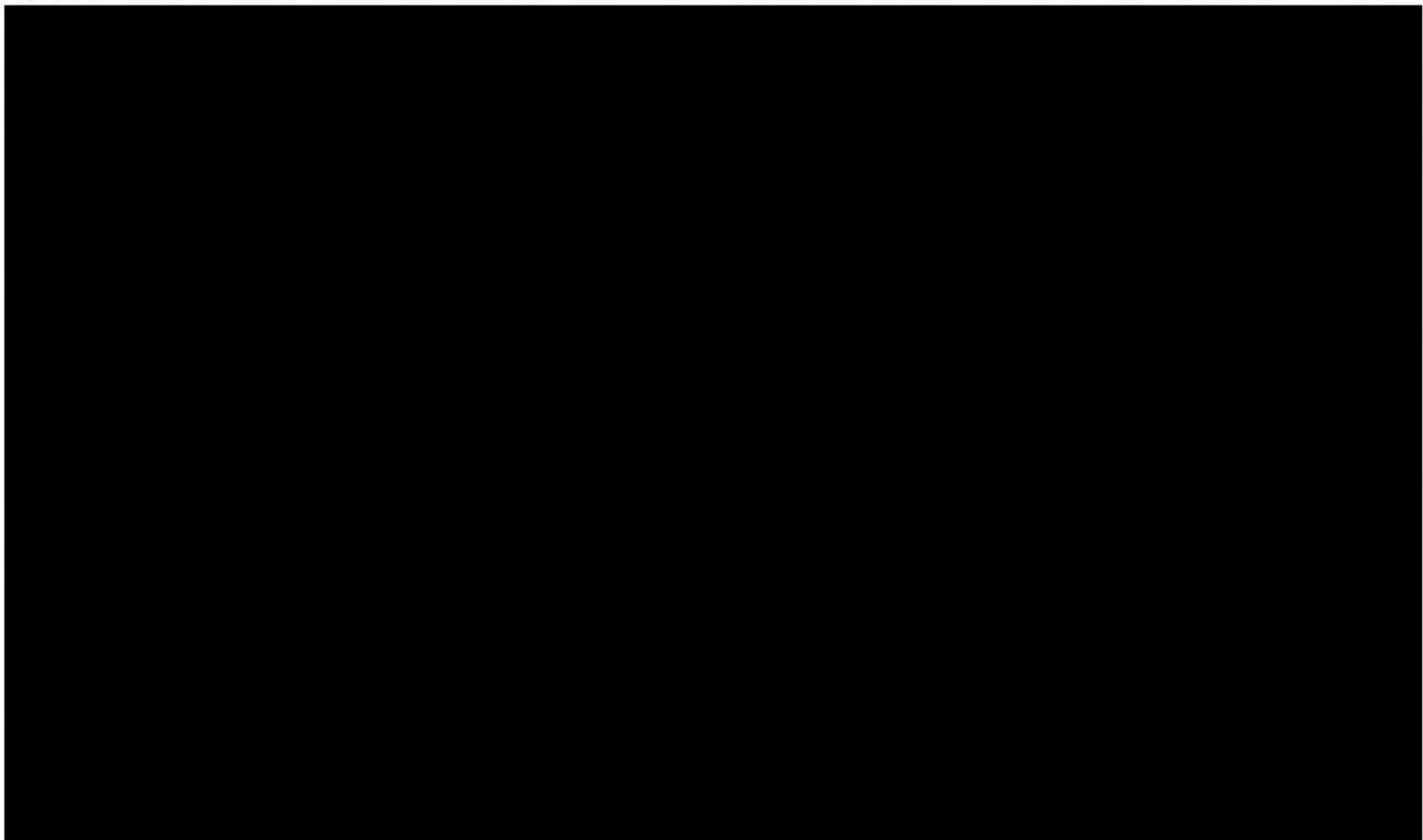
Subjects will be randomly assigned based on a predefined randomization code via the interactive web response system (IWRS) at the Day 1/Randomization visit. The site staff, Sponsor, and contract research organization (CRO) will be blinded to the subject's treatment allocation, with the exception of the selected study drug supply, and serious adverse event (SAE) reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of analysis of the primary endpoint. For emergency unblinding only, corresponding treatment assignments will be made available to the Investigator through the IWRS.

Compliance

The study will be conducted in compliance with the protocol, with the Regulation (EU) No 536/2014, and with the guidelines of Good Clinical Practice (GCP).







1. PHASE 2B: INTRODUCTION

Atacicept (also known as VT-001) is a novel immunomodulator, administered by subcutaneous (SC) injections, dual-blocking the activity of B lymphocyte stimulator (BLyS, also known as B cell activating factor) and a proliferation-inducing ligand (APRIL). Inhibition of BLyS and APRIL leads to a decrease in the maturation, differentiation, and effector function of B cells and plasma cells (Dillon 2006, Dillon 2010, Moore 1999, Ramanujam 2004, Schneider 1999). Atacicept is being developed for the treatment of patients with IgA Nephropathy (IgAN).

Complete information on the atacicept nonclinical and clinical program, and summaries of key chemistry, pharmacology, efficacy, and safety data of atacicept are provided in the Investigator's Brochure (IB).

1.1. Background

Immunoglobulin (Ig) A nephropathy (IgAN) or Berger's disease is the most frequent biopsy-proven primary glomerular disease, but with widely variable geographic distribution (Lai 2016, Schena 2018). The prevalence of IgAN can be difficult to ascertain because of regional variability in screening and renal biopsy practices, however; a 15-year retrospective study of the United States (US) Renal Data System found that of over 84,000 end stage renal disease (ESRD) patients with glomerulonephritis (GN) etiology, around 15% were attributed to IgAN (O'Shaughnessy 2015). The global incidence of primary GN ranges from 2 to 25 per million people (pmp) per year, with a worldwide IgAN incidence of at least 25 pmp per year in adults (McGrogan 2011), and an age adjusted US incidence of approximately 21 pmp per year (Swaminathan 2006). Consistent with differences in incidence based on ethnicity and genetic predisposition, biopsy data from autopsy and donor registries support a higher prevalence of IgAN in East and Pacific Asian countries (Rodrigues 2017), as compared to Southern Europe and Africa (Kiryuk 2012).

Immunoglobulin A nephropathy (IgAN) is highly variable, both clinically and pathologically. The classic presentation of IgAN is visible hematuria following an infection, but, more typically, IgAN presents as asymptomatic non-visible hematuria, with or without proteinuria. Renal impairment and hypertension are often present in subjects with older age at presentation (Barratt 2005). Up to 40% of all subjects with IgAN will progress to ESRD over 30 years (D'Amico 2000). In the US, IgAN accounted for 1.8% (10,557) of all prevalent subjects on dialysis at the end of 2011 (Collins 2014), with 5,044 incident subjects during the 5-year period from 2007 to 2011, or approximately 1000 subjects per year (Collins 2014). The annual incidence of ESRD due to IgAN can be estimated as 0.32/100,000 using the US population estimate from the US Census of 309 million people undertaken in 2010 (Mackun 2010).

A histopathological hallmark of IgAN is accumulation of poorly O-galactosylated IgA1 (Gd-IgA1) in the glomerular mesangium, either alone or in combination with IgG and/or IgM (Wyatt 2013). Sampling of the serum and plasma of subjects with IgAN has confirmed the presence of elevated levels of IgA-containing immune complexes containing Gd-IgA1 (Czerkinsky 1986). Circulating Gd-IgA1 containing immune complexes were later shown to be the target antigens for IgG antibodies with specificity for the O-glycans of the IgA1 hinge region (Suzuki 2009). Hence, IgAN is a unique autoimmune disease whereby the pathogenesis is driven by an autoantigen (Gd IgA1) eliciting an autoantibody (IgG anti-glycan) response.

1.1.1. Medical Need in IgA Nephropathy

The level of 24-hour protein excretion is a risk indicator for morbidity and mortality in patients with renal disease. Patients with IgAN with persistent proteinuria > 1 g/day are at increased risk of progression to ESRD ($> 60\%$ over 20 years) (Berthoux 2011, Lee 2012, Moriyama 2014, Reich 2007). They are also at increased risk of cardiovascular mortality; up to 50% experience a cardiovascular event prior to reaching ESRD and their mortality risk is 43% higher compared with age/sex-matched controls in the general public (Lee 2012). By contrast, subjects with IgAN with proteinuria < 1 g/day have mortality rates similar to those of the general public.

Furthermore, in the STOP-IgAN study which recruited IgAN patients with proteinuria (urine protein to creatinine ratio [UPCR] ≥ 0.75 mg/mg), $>50\%$ of patients progressed to death, ESRD, or eGFR decline of over 40% after 7.4 years, and use of immunosuppression, including corticosteroids, made no difference to outcome (Rauen 2020).

Since first being described in 1968, there have been limited advances in the treatment for IgAN. The central component of supportive care consists of appropriate blood pressure (BP) control and proteinuria management using Angiotensin Converting Enzyme Inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis (KDIGO 2012). The use of renin-angiotensin-aldosterone system inhibitor (RAASi) has been shown in randomized controlled studies to decrease proteinuria and correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day (Descamps-Latscha 2004).

Other treatments, such as corticosteroids (CS) and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is cautiously suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate blood pressure control and treatment with ACEis (KDIGO 2012), a recent review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist particularly in light of the prematurely halted TESTING study (Lv 2012, Lv 2017).

There is a significant unmet medical need for the treatment of IgAN, as there are currently no therapies proven effective in large randomized controlled trials. Current management includes BP control, renin-angiotensin system (RAS) blockade (with ACEi/ARB) and in rare instances combination immunosuppression with cyclophosphamide and corticosteroids for rapidly progressive IgAN (KDIGO 2012). In Japan, tonsillectomy is sometimes performed (Liu 2015). There are insufficient data supporting the use of most of the above listed therapies for IgAN, with the exception of RAASi. Reviews of randomized controlled trials suggest benefit from RAS blockade in reducing proteinuria and improving renal outcomes, but it is unclear whether this latter outcome is beyond the benefit expected from the control of hypertension alone (Cheng 2009, Hotta 2013, Reid 2011). The benefits of corticosteroid therapy and tonsillectomy for IgAN remain unclear (Lv 2012, Zhou 2011).

Thus, available treatments for IgAN are currently inadequate. Given that outcomes in subjects with IgAN remain poor, particularly with respect to development of ESRD and overall mortality, IgAN cannot be considered an indolent disease and better treatments are required.

1.2. Scientific Rationale for Study Design

This Phase IIb study will evaluate the efficacy and dose-response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria despite being on a maximally tolerated dose (MTD) of a RAASi. High risk of progression in IgAN is currently defined as a minimum of proteinuria >0.75 g/d despite optimized supportive care.

Atacicept is capable of binding to all known conformations of BLYS and APRIL and is thus expected to inhibit the maturation, differentiation, and effector function of B cells. These mechanisms are consistent with the known pharmacological effects of atacicept, which include depletion of peripheral B cell subsets, naïve follicular, marginal zone and long lived plasma cell B cell subsets, impeded germinal center reaction, and reduced immunoglobulins, while leaving immature B cells and memory B cells intact (Dillon 2006, Dillon 2010, Gross 2001, Moore 1999, Schneider 1999, Schneider 2005). These effects are predicted to reduce the production and subsequent deposition of Gd-IgA1-containing immune complexes in kidney glomeruli, and thus reduce the extent of kidney injury in IgAN patients.

Atacicept has been studied in a pilot Phase IIa clinical study for IgAN (MS700461-0035). The data from this study suggested clinical efficacy based on reduction in proteinuria, serum immunoglobulins and Gd-IgA1, and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. Based on the available clinical data, the targeted population for this Phase IIb study is subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable and maximal supportive care regimen. The objectives of the study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN and determine the appropriate dose(s) for further clinical development.

Use of ACEis and ARBs:

The central component of supportive care in IgAN consists of appropriate BP control and proteinuria management using RAASi as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis (KDIGO 2021). The use of ACEis has been shown in randomized controlled studies to decrease proteinuria, and this correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day (Descamps-Latscha 2004). Therefore, in this study, subjects at the Screening Visit will be required to be on a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose (as determined by the Investigator), according to standard of care (SoC). Stable SoC background of RAASi medication is likely to decrease potential confounding of the study results and may help to better capture the effect of atacicept in this population. Therefore, subjects in all treatment groups will receive optimized, unchanged RAASi therapy 12 weeks prior to screening and throughout the duration of the study, thus providing a stable background SoC during this trial. Subjects who are unable to tolerate either RAASi medication may be eligible for participation in the study provided their management of IgAN is SoC according to applicable guidelines.

Subjects in atacept and placebo groups will continue to receive stable background SoC during this trial. Other treatments, such as CS and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate BP control and treatment with ACEis (KDIGO 2012), a review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist (Lv 2012, Lv 2017). Therefore, in this trial, the inclusion of a placebo group will allow differentiation of the effect of atacept treatment from the effect of SoC therapy alone, without potential confounding by other immunosuppressant use.

[REDACTED]

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1.4. Risk Benefit Assessment

The limited safety data available for atacicept in patients with IgAN are consistent with those reported in the much larger studies of atacicept in SLE. Data from 2 Phase II double-blind, randomized, placebo-controlled (DBPC) studies in SLE (APRIL-SLE and ADDRESS II) evaluated the efficacy and safety of atacicept 75 mg and atacicept 150 mg as compared to placebo for the treatment of SLE. These studies had different study designs, yet both studies were consistent in showing that atacicept 150 mg weekly SC injections were associated with efficacy and an acceptable safety profile, and thus a positive benefit:risk balance ([Isenberg 2015](#), [Merrill 2018](#), [Morand 2020](#)).

COVID Pandemic Risk/Benefit

Atacicept is an immune-modulator which may impact a patient's innate immune response to infection. In a patient receiving an immune-modulator, there may be a potential for limited or compromised immune response leading to more severe/serious complications of the SARS CoV 2 infection. However, in an integrated safety analysis ([Gordon 2019](#)) of over 1500 patients in previous atacicept clinical studies, serious infection rates were similar for atacicept and placebo. In addition, in the ADDRESS II study of SLE patients treated with atacicept 75 mg and 150 mg, titer status for both tetanus toxoid and diphtheria vaccinations remained protective from Day 1 to Week 72 ([Wallace 2021](#)). Risk mitigation includes excluding patients with active infection from study participation and recommendation to have up-to-date vaccinations as per local guidelines within 30 days of screening and to remain up to date with all non-live vaccination as per local guidelines during the study. Live and live-attenuated vaccines are not permitted during the study. In the setting of a pandemic or epidemic, the investigator should evaluate the best option of care for the patient including the screening for active infections prior to and during study participation according to the protocol, should this study be considered as an option.

IgAN patients continue to have too few approved therapies with a high unmet need given the risk for progression to end stage renal disease. Atacicept has promising potential to have clinical benefit for IgAN patients, while being supported with an acceptable safety profile.

2. PHASE 2B: OBJECTIVES AND ENDPOINTS

The Phase 2b study objectives, endpoints and endpoint timelines are defined in the table below.

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Urine protein to creatinine ratio (UPCR) ^a	Week 24
Secondary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	UPCR ^a	Week 36
Exploratory		
Evaluate the effect of atacicept on change in proteinuria in adult subjects with IgAN	UPCR ^a	Weeks 12, 48 and 96
Evaluate the effect of atacicept on rate of change in estimated glomerular filtration rate (eGFR)	Rate of change in eGFR ^b	Weeks 12, 24, 36, 48 and 96
Evaluate the effect of atacicept on change in serum immunoglobulin levels, complement levels and on serum Gd-IgA1 levels	IgA, IgG, IgM levels, C3 and C4 levels Gd-IgA1 levels	Weeks 12, 24, 36, 48, 96 and Follow Up Weeks 12 and 26
Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, adverse events	Entire study
Evaluate serum PK of atacicept	Serum concentration of atacicept	Entire study

AEs=adverse events; eGFR=estimated glomerular filtration rate; Gd-IgA1= galactose-deficient IgA1; Ig=immunoglobulin; IgAN=immunoglobulin A Nephropathy; PK=pharmacokinetic; UPCR=urine protein to creatinine ratio.

a Based on 24-hour urine sample.

b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults.

3. PHASE 2B: STUDY DESIGN

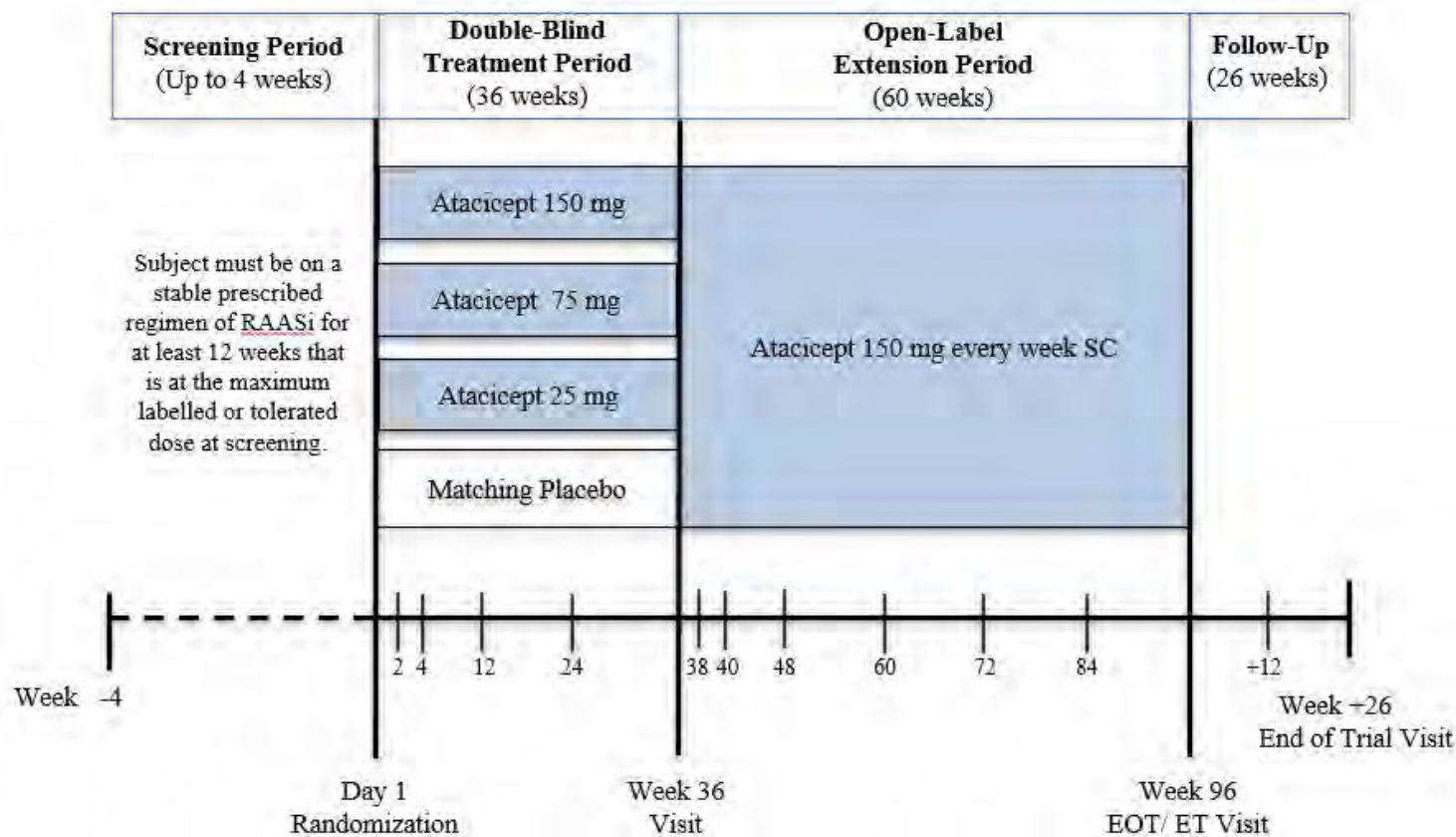
3.1. Overall Design

This Phase IIb study is a multicenter, randomized, double-blinded, placebo-controlled study. Approximately 105 subjects will be randomized 2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo.

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 75 mg once weekly subcutaneous (SC) injections (N=30)
- Atacicept 25 mg once weekly subcutaneous (SC) injections (N=15)
- Placebo-to-match once weekly subcutaneous (SC) injections (N=30)

The study is composed of a (up to) 4-week Screening Period, a 36-week Blinded Treatment Period (Part A), followed by a 60-week Open-Label Extension (OLE) Period (Part B), and a 26 week Safety Follow-up (FU) Period. Upon completion of the 36-Week blinded period, including attendance at Weeks 24 and 36 Visits for key study assessments, all subjects will be offered open label atacicept 150 mg for an additional 60 weeks. At the Week 36 Visit following completion of all study visit assessments, subjects will switch from double-blinded treatment to open-label treatment. Subjects who discontinue study drug prior to completion of the 96 week total treatment duration will complete an Early Termination Visit and have a 26-week follow-up period. After the last subject completes the Week 36 Visit, the study will be unblinded. The study will be conducted on an outpatient basis.

The target study population includes male or female subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen for at least 12 weeks with a RAASi that is at the maximum labeled or tolerated dose.

Figure 1: Phase 2b: Study Schema

Note: Subject's stable dose of ACEi and/or ARB must be maintained for the duration of the study.

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; EOT=end of treatment; ET=early termination; RAASi=renin-angiotensin-aldosterone system inhibitor; SC=subcutaneous.

* For Czech Republic only, additional visits were conducted at Week 1 and Week 37.

* For Germany only, additional visits were added at Week 1 and Week 3.

Study visits will occur at Screening, Day 1, Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

There will be a 26-week follow up after subject's end of treatment visit (EOT, Week 96). Subjects discontinuing study intervention early will require an Early Termination Visit within 10 days of the last dose and safety follow up for 26 Weeks from the ET visit. Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 1](#)).

A subject has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in the Schedule of Assessments ([Table 1](#)).

The end of the study is defined as the date of last contact with the last subject who participates in the study (i.e., last subject's last visit); see Section [9.4](#) for details on study and site closures.

3.2. Independent Data Monitoring Committee

An independent data monitoring committee (iDMC) will monitor the safety and welfare of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority on all aspects. Details regarding the role, responsibilities and data review requirements of the iDMC will be outlined in a separate iDMC charter.

4. PHASE 2B: STUDY POPULATION

The Phase 2b study eligibility criteria in Sections [4.1](#) (Inclusion Criteria) and [4.2](#) (Exclusion Criteria) are designed to enroll only subjects who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a subject is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the subject's routine medical care, the Investigator will confirm that the subject has provided written informed consent, as indicated in Section [9.1.3](#).

Subject eligibility (based on Screening Visit assessments of the inclusion and exclusion criteria) must be reviewed again by the Investigator on Day 1 prior to randomization. Eligible subjects will be randomized to treatment with atacicept or placebo through a central randomization process by an interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility.

4.1. Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
 - For the Czech Republic an age limit of ≤ 70 also applies.
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit
4. Total urine protein excretion >0.75 g per 24-hour or UPCR >0.75 mg/mg based on a 24-hour urine sample during the Screening Period
5. GFR ≥ 30 mL/min/1.73 m² at screening as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
6. On a stable prescribed regimen of RAASi for at least 12 weeks that is at the maximum labeled or tolerated dose at screening.
 - The subject is eligible if they do not tolerate RAASi, provided their management of IgAN is SoC according to local guidelines. This must be documented by the Investigator.
7. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening
8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).
 - OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

4.2. Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), SLE, dermatitis herpetiformis, ankylosing spondylitis
2. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
3. Evidence of nephrotic syndrome within 6 months of screening (serum albumin < 30 g/L in association with UPCR >3.5 mg/mg)

4. Total urine protein excretion $\geq 5\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCR) $\geq 5\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
5. Renal or other organ transplantation prior to, or expected during, the study with the exception of corneal transplants
6. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
7. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $>7.5\%$ at screening
8. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
 - Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.
9. Prohibited medications:
 - Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
 - For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc):
 - Within 3 months prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for > 1 week or 0.5 mg/kg/day prednisolone or equivalent
 - Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time
 - Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics
 10. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:
 - serum IgG below 7 g/L
 - aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level $> 2.5 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN.
 - i. If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.

- For The Czech Republic only, the following criteria also apply:
 - i. hemoglobin <10 g/100 mL in men and hemoglobin <9 g/100 mL in women
 - ii. platelets <100,000/mm³
- 11. Administration of a live and live-attenuated vaccinations within 30 days prior to randomization
- 12. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
- 13. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
- 14. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
- 15. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.
 - For Germany only, the following criteria also apply:

Specifically for COVID-19: Evidence of positive test for SARS-CoV-2, by PCR, at the Screening Visit; Subjects with a previous COVID-19 infection may be included provided the PCR test is negative for SARS-CoV-2 and they do not have chronic symptoms as a result of COVID-19. COVID-19 testing may be performed at local lab, per site/local guidelines.
- 16. History of acute or chronic infection with human immunodeficiency virus or hepatitis B virus.
 - Positive hepatitis B surface antigen (HBsAg) Subjects who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow up
- 17. History of splenectomy
- 18. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix
 - For Germany only the following criteria also apply:

History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).
- 19. Known hypersensitivity to atacicept or any component of the formulated atacicept

20. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull) and/or use of general anesthesia. Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)
21. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
22. Unwillingness or lack of capacity to follow all study procedures
23. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

4.3. Screen Failures

Repeat testing: Aside from the TB testing as delineated above, tests that do not meet the above inclusion/exclusion criteria may be repeated once within the 28-day Screening Period if the results are thought to represent a laboratory error or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values. If eligibility criteria are not met at the end of the 28-day Screening Period, the subject should be considered a screen failure and not be enrolled in the study.

Re-Screening: Subjects who do not meet the above eligibility criteria (in Sections 4.1, 4.2) within the screening period and screen fail may undergo re-screening upon approval by the Medical Monitor. If the subject is re-screened, then the subject will receive a new subject identification number (Subject ID). The second screening is a new 28-day screening episode.

5. PHASE 2B: INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational Medicinal Product (IMP) or study drug is atacicept or placebo intended to be administered to a study subject per the study protocol.

5.1. Randomization, Blinding, and Measures to Minimize Bias

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, is confirmed, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessments (Table 1).

Before the study is initiated, the login information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study drug administration for each subject.

5.1.1. Blinding of Investigational Medicinal Product

This study will be double-blinded for all subjects and investigators through Part A. Investigational Medicinal Product (IMP) packaging and labeling will be prepared to protect the blinded nature of the study. Study drugs will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part B of the study will be conducted in an open-label fashion.

5.1.2. Procedures for Breaking the Treatment Codes

If, at any time during Part A of this study, any site personnel are unblinded to the treatment code for any reason, the circumstances and reason must be documented. The Sponsor and clinical research organization (CRO) study staff will be blinded to the study group assignment with the exception of the selected study drug supply vendor, IDMC (if applicable) and SAE reporting contact personnel.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study drug discontinued.

In a medical emergency, the Investigator is solely responsible for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted in cases of suspected serious infection or where breaking the blind is required to provide medical care, the Investigator should contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study drug, except to the designated drug safety representative, as appropriate. The date of and reason for unblinding must be recorded in the source documents. Contact information for unblinding in an emergency is given on the subject emergency card provided to each subject, as noted in Section 9.2.2 (Emergency Medical Support).

The Sponsor (or delegate) will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

In the case of emergency unblinding, the subject must be discontinued from the study drug and complete all assessments and procedures specified for the Early Termination (ET) Visit and should remain in the study and continue the study visits completion of follow-up assessments.

Causality assessments if emergency unblinding is for an AE/SAE should be documented for the AE/SAE prior to unblinding. Further details on expedited reporting and SAEs are in Section 7.

5.1.3. Other Blinding Parameters

Laboratory results:

After Day 1, certain laboratory results can reveal the PD effects of atacicept. These laboratory/analyte results (serum IgG, IgA, and IgM) that could be indicative of treatment allocation will not be reported to investigative sites or other blinded personnel.

Serum IgG level is one of the blinded laboratory tests which will be monitored by the central laboratory. If serum IgG is < 3 g/L on two consecutive timepoints at least 28 days apart, representing severe hypogammaglobulinemia, the study drug will be discontinued. The central laboratory will notify the Medical Monitor that the study subject meets the treatment discontinuation criteria. The site will receive notification from the Medical Monitor to discontinue the treatment of study drug for this study subject. This event will likely unblind the treatment assignment for this subject.

Lymphocyte counts as assessed by routine complete blood counts will not be blinded; these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5% to 20%).

Independent Data Monitoring Committee (iDMC):

The iDMC will review available safety data in a blinded manner with the capability to review unblinded data in case of a safety concern. See Section 3.2 for further information on the iDMC.

Unblinding Clinical Studies for Sample Analysis of Special Data:

Bioanalysis and PK scientists may be unblinded to study treatment information in order to perform sample analysis and preliminary PK and PK /PD analysis activities. Anyone who will be unblinded prior to database lock will be named with clear instruction on how to ensure the integrity of the clinical study.

5.2. Investigational Medicinal Product(s)

The atacicept protein is a soluble glycoprotein containing [REDACTED] amino acids, resulting from the fusion of human IgG1-Fc and the extracellular domain of the BLyS and APRIL receptor TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor), with a predicted mass of [REDACTED] kilodaltons. The product conformation is dimeric, and thus atacicept has a predicted mass of [REDACTED] kilodaltons. [REDACTED]

[REDACTED]

5.2.1. Formulation

Atacicept is the active ingredient in the drug product. [REDACTED]

5.3. Packaging and Labeling

The drug product/placebo is manufactured, packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released under Good Manufacturing Practice conditions. The active dosage form and placebo will be supplied by the Sponsor as a ready-to-use, prefilled syringe with 1.0 mL or drug product/placebo.

Atacicept and placebo will be packed in kits containing pre-filled syringes (one syringe is needed for 1 administration). Each pre-filled syringe will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. The labeling configuration of the pre-filled syringes results in the active and placebo being identical in appearance. Full re traceability is provided from the unique medication number on the labels together with the packaging documentation, according to the current Good Manufacturing Practice guidelines.

5.4. IMP Administration

Study drug dosing is a single injection of 1.0 mL, once weekly from Day 1 to Week 96, subcutaneous (SC) administration by pre-filled syringe. Subjects will contact the Investigator any time they have any injection administration (pre-filled syringe) complaint.

Participants or family members/caregivers who receive appropriate training will be permitted to administer medication in this study. Participants and any caregivers who may give the injection will be trained at the investigational site on the appropriate use of the pre-filled syringe and storage of the IMP. The initial training will occur on the day of randomization. The first injection will be performed under supervision. After the first injection on Day 1 and Week 36, the participant will remain at the site for observation for 2 hours in case of hypersensitivity reaction.

- For the Czech Republic only, the injections at Week1, Week 2, Week 37 and Week 38 are performed on site with a 2-hour observation period.

It is recommended that the weekly dose of IMP be taken on the same day of the week as the original dose. For missed dose(s) of study drug, subjects should be instructed to take the missed dose(s) as soon as possible. If necessary, a dose can be given ± 3 days from the scheduled dose day as long as there is an interval of at least 4 days from the previous injection, with subsequent doses resumed to be taken on the original day of the week.

At the Week 36 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 36 will be the first OLE dose.

5.5. IMP Preparation, Handling, Storage, and Accountability

All study drug (atacicept and matching placebo) is provided in prefilled single-use syringe to the site via cooled transport. No additional preparation will be required at the site.

Storage

All study drug supplied to each site must be stored in their original containers carefully, safely, and temperature controlled. The storage facility at the study site must be locked and accessible only to authorized site personnel. The study drug must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light. The study drug temperature will be monitored and documented per the site's standard process for refrigerated medication. Atacicept and placebo must NOT be frozen.

To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the study drug back home and instructed not to leave their medicine unattended or in a place that might get too hot, e.g., inside a car, or exposed to light. Subjects should have access to refrigeration to store the study drug.

Handling

Each study drug syringe should be removed from the refrigerator and kept at room temperature for at least 30 minutes prior to SC injection. The syringe should not be left out at room temperature for more than 60 minutes. Additional details on the instructions for handling and storage will be provided to subjects as required for home injection.

Accountability

Information on the time, date, and location of each dose will be recorded by the subject for at-home administration and by the study staff for on-site dosing. Appropriate information from the Injection Diary and assessment worksheets will be entered into the eCRF.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study drug(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Only subjects enrolled in the study may receive study drug(s) and only authorized site staff may supply it.
- Study drug(s) accountability records at the study site will include the following:
 - Confirmation of receipt, in good condition and in the defined temperature range
 - The dose(s) each subject used during the study
 - The disposition (including return, if applicable) of any unused study drug(s)
 - Dates, quantities, study drug number, expiry dates, and the subject numbers
- The Investigator site will maintain records which adequately document that subjects were provided the doses specified in this protocol and all study drug(s) provided were fully reconciled

- Unused study drug(s) must not be discarded or used for any purpose other than the present study. No study drug that is dispensed to a subject may be re-dispensed to a different subject.
- A Study Monitor will periodically collect the study drug(s) accountability forms
- Further guidance and information for the final disposition of unused study drug(s) are provided in the Pharmacy Manual.

Pre-filled Syringe Disposal:

Pre-filled syringes will be disposed of according to the Pharmacy Manual (including the use of sharps containers).

Subjects will be instructed to dispose of used syringes in sharps containers at home, and to return the sharps containers to the site once full, at Week 36 and again at Week 96), or Early Termination Visit. Investigators will instruct subjects to store any syringes associated with an injection administration complaint separately and return them to the site in a separate container.

Destruction of used and unused study drug(s) should be performed at site if allowed by local law only after Sponsor authorization. If that is not possible, the Sponsor/designee will be responsible.

5.6. Study Drug Compliance

The study drug will be administered by the subject under supervision as defined in the Schedule of Assessments. All other dosing will be done by the subject, subject's caregiver, or home health nurse (if available) at home throughout the rest of the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient study drug for at-home dosing until the next scheduled visit.

Compliance will be determined based on the Injection Diary entries. Acceptable compliance for the study is defined as 80%-100% (inclusive) of study drug compliance based on drug accountability calculated for the blinded period and open-label extension period. If dosing is interrupted for any reason, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures. The Medical Monitor should be contacted if a subject misses 2 consecutive doses or 2 doses within a month period.

Subjects will be instructed to return their subject recorded Injection Diary at each clinic visit, in order to allow the assessment of compliance with study treatment, see Section 5.4 for details.

Consequences of noncompliance will lead to retraining and/or discontinuation of study drug as described in Section 6.10.1. In case of overdose see Section 7.10.

5.7. Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines) used from the time the subject signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, date(s) administered, and dosing information (as applicable).

Contact the Medical Monitor for any questions on concomitant or prior therapy.

5.7.1. Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study drug may be given at the Investigator's discretion.

Permitted medications are any medications that are required by the subject during the course of the study and which are not specifically prohibited by the protocol (see Section 5.7.2). Any such medications prescribed or used should be recorded in the eCRF.

All subjects who tolerate RAASi medication will have begun treatment with RAASi at least 12 weeks prior to Screening and will have been on a stable prescribed regimen for at least 12 weeks with an RAASi that is at the maximum labeled or tolerated dose. For subjects who are unable to tolerate either RAASi medication, management of IgAN will be SoC according to local practice. Changes in RAASi medication including dose changes should be avoided for the duration of the study. Changes in RAASi medication including dose changes are specifically prohibited up to Week 36 and every effort should be made to maintain the same dose of RAASi throughout the treatment period. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non RAASi medications should have been considered before these drug classes. In certain instances (i.e. hyperkalemia), it will be in the best interest of the subject to have their RAASi medication adjusted and in such cases investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].

All other antihypertensive medications, including diuretics, calcium channel blockers and β blockers, can be used at any timepoint during the study per the Investigator and following current guidelines.

Statins and dipyridamoles are permitted, but it is recommended to keep doses stable. In subjects receiving SGLT2 inhibitors at the time of enrollment, the dose must be stable for at least 8 weeks prior to screening and is expected to be at a stable dose over the study period. If deemed indicated by the Investigator, SGLT2 inhibitors may be initiated during the study after week 36, but it is expected that the doses will remain stable over the study period. The Investigator should discuss planned use of an SGLT2 inhibitor with the Medical Monitor prior to initiation for their awareness.

Use of these additional treatments commonly given to subjects with IgAN outside of above dose recommendations will incur protocol deviations but does not require IMP discontinuation. Any medications (other than those excluded by the protocol) that are considered necessary for the subjects' welfare and will not interfere with the study drug may be given at the Investigator's discretion.

- For the Czech Republic. The Investigator may initiate use of an SGLT-2 inhibitor prior to discussion with the Medical Monitor and will inform the Medical Monitor about any use of an SGLT2 inhibitor.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

For the Czech Republic only.

Rescue Medications

Should the Investigator consider that medication (steroids and/or immunosuppressive treatment) be needed, such treatment can be initiated by the Investigator. However, in consideration of current guidelines ([KDIGO 2021](#)), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

- Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] (although treatment toxicity must be considered in those with eGFR < 50); and/or
- Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., >3.5 g/day] and hypoalbuminemia [albumin < 3.0 g/dL])

Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. Although the Investigator is responsible for the decision to implement new treatment, the Medical Monitor must be notified prior to initiation to discuss potential discontinuation of study treatment which will affect eligibility of the open-label extension.

Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section [5.7.1](#).

5.7.2. Prohibited Medicines

The following treatments are not permitted during the study:

- Use of systemic corticosteroids or immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 3 months prior to screening or expected use during the study.
 - For GCS, “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
 - For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Use of systemic GCS is prohibited except for a maximum of 3 periods of 2 weeks duration with the equivalent of 0.5 mg/kg/day prednisolone or less
 - Use of B-cell-directed biologic therapies including blisibimod, belimumab, rituximab, ocrelizumab for any period of time
 - Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics
- Note: Intravenous (IV) hydrocortisone is permitted for stress dosing in emergency situations only, e.g., traumatic event requiring hospitalization. If administered, the event should be discussed with the Medical Monitor to ensure IMP does not need to be discontinued.

If the Investigator believes that treatment with a medication within the categories described above is required, and the potential benefits outweigh the possible risks, the Medical Monitor must be notified, as continued dosing with IMP may, in this circumstance, be discontinued (see Section 6.10.1).

Refer to the inclusion and exclusion criteria (Sections 4.1 and 4.2) for prohibited medications before and during the study.

5.7.3. Other Interventions

Treatment with a stable dose of over-the-counter supplements (herbal or non-herbal) is allowed if herbal supplements are initiated before the Screening Visit.

Planned/expected major surgery during the entire study period is exclusionary. Unplanned major surgeries should be discussed in advance with the Medical Monitor with respect to whether the subject may continue in the study.

5.7.3.1. Vaccinations

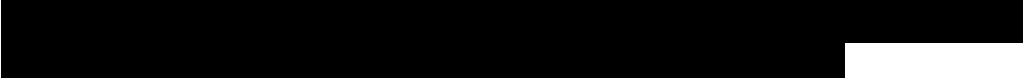
It is recommended that subjects have up-to-date vaccinations, as per local guidelines, within 30 days of screening and during the study. Investigators should review the subject's vaccine status, and ensure they remain up to date with all non-live vaccinations as per local guidelines. Live and live-attenuated vaccinations will not be permitted during the study period.

5.8. Special Precautions

- Women of childbearing potential must be willing to use a form of highly effective contraception at least 7 days prior to randomization through 175 days after the last dose of study drug ([Appendix 2](#))
- Male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the highly effective methods of contraception as well. ([Appendix 2](#)) Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.
- Caution should be exercised when administering atacicept to subjects with underlying conditions that may predispose them to infections (see Section 7.7.2)
- **Good hygiene practice should be employed:** Subjects should be consistently reminded of the importance of good hygiene practices such as hand washing for their care providers and/or social contacts, especially if they are suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. It is recommended they be vaccinated according to local recommendations for individuals with a chronic disease and/or immunosuppression. They should be advised to promptly report to the Investigator any signs or symptoms suggestive of an infection.

6. PHASE 2B: STUDY ASSESSMENTS AND PROCEDURES

The following assessments will be conducted during screening and at selected timepoints specified in the Schedule of Assessments (Table 1). Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the Investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate eCRF. General considerations for study visits include, but are not limited to:

- No protocol waivers or exemptions are allowed
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the subject's routine medical care, the Investigator will obtain written informed consent as specified in Section 9.1.3 (Informed Consent Process). Upon subject's agreement, their primary health care provider should be informed about the subject's enrollment in the study.
- Order of Procedures:
 - Vital signs should be collected prior to blood draws.
 - 
 - Pharmacokinetics and immunogenicity sampling (if scheduled) and laboratory samples must be collected prior to dosing.
 - All other study assessments should also be performed, according to the Schedule of Assessments (Table 1).
- **Unscheduled visits:** may occur at any time during the study; assessments to be performed according to the Investigator's judgment.

6.1. Screening Period and Confirmation of Eligibility

The subject's eligibility will be assessed at the Screening Visit that will occur up to, at most, 4 weeks (28 days) before the Randomization Visit (Day 1). Demographic data will be collected at screening.

Subjects will arrive at the site and the following procedures will be done to determine the subject's eligibility to participate in the study:

- Obtain written informed consent prior to screening procedures
- The physical examination will be performed at the discretion of the site investigator if deemed necessary as per SoC.

- Obtain additional written informed consent if participating in the PK sub study, as necessary
- Review inclusion and exclusion criteria
- Collect demographic data
- Complete medical and disease history
- Document the criteria for IgAN diagnosis for eligibility
- Assess vital signs: seated systolic and diastolic BP, pulse rate, temperature (oral or body – with same method to be used throughout the study), height and weight measurements (see Section 6.6.2 for details)
- Perform standard, single, 12-lead electrocardiogram (ECG) (see Section 6.6.3)
- Complete physical examination as specified in the schedule of events
- Collect blood and fresh clean catch urine samples for routine laboratory tests (see Table 2).

The laboratory tests will include:

- Clinical chemistry and hematology
- HbA1c
- Thyroid stimulating hormone (TSH)
- Follicle stimulating hormone (FSH) for woman only
- Immunoglobulins (IgG, IgA, IgM)
- Gd-IgA1
- Serum virology
 - For Germany only - COVID-19 PCR test (tested locally)
- Quantiferon test for TB assessment
- Urinalysis and urine sediment from fresh, clean-catch, mid-stream specimen obtained in the clinic
- Dispense:
 - Two 24-hour urine collection containers (one for Screening and one for the Day 1 Visit)
- Serum pregnancy test (β -hCG) required only for WOCBP. Any woman with a positive pregnancy test will be ineligible for the study. [NOTE: It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 12 months or who are surgically sterile]
- If an archival kidney biopsy (within 10 years of Screening Visit) is unavailable, a pre treatment kidney biopsy is required to confirm subject eligibility but is to be performed at the discretion of the Investigator.
- Safety
 - Record AEs beginning after the informed consent form (ICF) has been signed.
 - Review/record prior and concomitant medications
 - Review/record vaccinations. Administration of a vaccine is acceptable within 30 days of screening or planned during the study.

Subjects who meet the screening criteria and are to be randomized will be given instructions as to the date and time they are due back at the site for Day 1 (randomization/first day of dosing).

Subjects who do not meet the screening criteria can be re-screened upon approval of the Medical Monitor. In specific circumstances, repeat testing of screening testing may be allowed. See Section 4.3 for further details.

6.2. Randomization/First Administration IMP (Day 1)

The following assessments will be conducted on Day 1. All subjects will return to the site in the morning up to at most 4 weeks (28 days) after the Screening Visit. At this visit, subjects or caregivers will be provided with training to properly store and perform self-injection of IMP at home from Week 1 onwards. Retraining can be provided by the site at the Week 2 Visit as required.

- For Czech Republic only, subjects will be dosed in clinic on Day 1 and Weeks 1, 2, 36, 37, and 38.

These dosing instructions will be reviewed with the subject/caregiver before leaving the site. At each of these visits, site staff will contact the IWRS to obtain appropriate kit numbers and the specified kit will be dispensed.

Predose Assessments

Predose assessments on Day 1 are considered baseline measurements prior to first dose of study drug. The results of all assessments and procedures performed at the Screening Visit will be reviewed to assess the subject's eligibility. All eligible subjects will undergo the following procedures before IMP administration (unless stated otherwise):

- Review inclusion and exclusion criteria
- Record archival kidney biopsy (if obtained)
- Vital signs: BP, pulse rate, temperature (oral or body – with same method to be used throughout the study) (see Section 6.6.2 for details)
- Standard, single, 12-lead ECG (see Section 6.6.3)
- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Table 2).
- Urine:
 - 24-hour collection for UPCR, [REDACTED]
 - Urine sample at study visit for routine urinalysis

PK (see Section 6.7.1)

- Blood samples will be collected per schedule of assessments. The exact time and date of the last dose of study drug and of blood sampling should be recorded.
- Anti-drug antibodies (binding and neutralizing)

Other analyses (see Section 6.8)

- Blood samples will be collected to assess serum BLyS and APRIL prior to the first dose of IMP (predose).
- Serum immunoglobulins: IgG, IgA, and IgM
- Serum Gd-IgA1
- Blood sample for storage and future testing

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Randomization

Eligible subjects will be randomized in a 2:2:1:2 ratio to 1 of 4 treatment groups by the IWRS.

Treatment with IMP (first dose)

- The study staff will instruct the subject (or caregiver) in proper technique of SC administration and demonstrate it by administering the allocated IMP to the subject via SC injection.
- The first dose (on Day 1 and Week 36) will be given at the study site. After the first dose, subjects or caregivers will be permitted to administer the medication following instruction in injection technique and verification of satisfactory technique.
- On Day 1 and Week 36, the study staff will record the exact time and location of dosing and monitor the following:
 - Injection site reactions (ISRs) (local tolerability) (see Section 6.6.5).
 - Pulse and BP will be recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes.
- If suspected hypersensitivity reaction occurs at any time, the subject will be treated symptomatically (see Section 7.7.1).
- At the Week 36, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 36 will be the first OLE dose.

PK sampling (post-first dose)

- On Day 1 only, following ISR monitoring, a blood sample will be collected 2-4 hours after the first study dose.
- After Day 1, at PK timepoints, a blood sample for PK analysis will be collected to assess levels of serum atacicept.
- If participating in the PK substudy (see Section 6.7.1), additional blood samples will be collected only for PK analysis at the following timepoints after dosing: Day 2 and/or Day 3 post first dose. The subject can be registered to this subgroup analysis through the IWRS (this will be done during the randomization process).

Completion of Day 1

Following completion of all Day 1 procedures described above, the following additional procedure should be completed before the subject leaves the site:

Provide subjects with emergency contact numbers (see Section 9.2.2).

6.3. Post-Randomization Visits

Assessments to be performed for each visit are outlined in the Schedule of Assessments (Table 1).

6.3.1. Treatment Periods

Following completion of Randomization (Day 1), study visits will occur at Weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Subjects will then continue treatment in the OLE period with visits at Weeks 38, 40, 48, 60, 72, 84, and 96. Note that for Weeks 4, 38, 40, 60 and 84, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP.

For the Czech Republic and Germany only: If in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted on Day 1 and at Weeks 1, 2, 36, 37, and 38. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

6.3.2. End of Treatment or Early Termination

Criteria for discontinuation are provided in Section 6.10. Subjects who are discontinued from IMP will complete the Early Termination (ET) visit as soon as possible (within 10 days) after IMP discontinuation. These subjects should receive a 24-hour urine collection container in advance (e.g., at the prior visit), but no later than 2 days before the scheduled ET visit.

End of treatment is defined as subjects who complete Part A and B for a total of 96 weeks of study drug. The ET Visit follows the same schedule of assessments as Week 96.

6.3.3. Safety Follow-up Period

After the last dose of the IMP, all subjects are required to enter a Safety FU period. For subjects who completed the 96-week total treatment (36 weeks for Part A plus 60 weeks for Part B), or for subjects who are discontinued from IMP, the Safety FU period is 26 weeks, with visits at Weeks 12 and 26.

6.4. Demographic and Other Baseline Characteristics

Demographic data such as date of birth, self-reported race and ethnic origin, gender, weight, height, and body mass index (to be calculated by CRO/Sponsor) will be assessed at screening. Information about previous and concomitant medications will also be recorded.

Complete medical and disease history will be recorded. This includes history of disease treatments, including but not limited to conditions that may affect eligibility (herpes zoster, cytomegalovirus, Epstein Barr virus, TB, cancer, infections [current active infections, recent serious infections, opportunistic infections, chronic or recurrent infections], congestive heart failure, hypersensitivity to drugs and other significant illnesses, smoking history, alcohol or drug abuse). In addition, a history and status of medications will be recorded, including surgeries and other procedures, with particular attention to current and previous treatments for IgAN.

Other baseline measurements such as physical examination, safety laboratory parameters, ECG, and vital signs will be assessed as specified below.

6.5. Efficacy Assessments and Procedures

Assessments for the endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 1).

Clinical renal disease assessments:

- UPCR, 24-hour total protein excretion, [REDACTED]
- Active urinary sediments by urinalysis.
- Renal function by eGFR will be calculated by the central lab as follows: (Levey 2009)
CKD-EPI: $eGFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$
(if female) $\times 1.159$ (if black)

Scr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicated the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

Blood assessments:

- Ig levels (i.e., IgG, IgA, and IgM), Gd-IgA1.
- Baseline (predose) levels of free BLyS and free APRIL.

6.6. Safety Assessments and Procedures

Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, and evaluation of AE/SAEs, with attention given to infections (serious), cardiovascular events, local tolerability (ISRs) and hypersensitivity reactions.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

Adverse events of special interest (AESIs) are opportunistic infections, hypersensitivity reactions, demyelinating disorders and cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease).

6.6.1. Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A complete physical examination will include, at a minimum assessment of the General Appearance, Skin, Lymph Nodes (Cervical), Head, Ears, Eyes, Nose, Throat (HEENT), Neck, Thorax/Lungs, Cardiovascular, Abdomen, Musculoskeletal, and Neurological systems. Height (at Screening Visit) and Weight will also be measured and recorded.

At selected visits, a symptom-driven physical examination will be performed, and will include assessment of any new subject complaints or changes from baseline.

6.6.2. Vital Signs

Vital sign measurements (BP, pulse, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, at the visits specified in the Schedule of Assessments ([Table 1](#)).

- Temperature, pulse rate, respiratory rate
- Blood pressure and pulse measurements will be assessed with the subject seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
 - During the Screening Period, blood pressure will be measured up to 3 times with each measurement separated by up to 2 minutes (the lowest value will be recorded on the eCRF).
 - After first dose of study drug at randomization and at Week 36 during ISR monitoring, pulse and BP recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes
- Vital signs to be taken before blood collection for laboratory tests
- Height will be measured at Day 1 only. Body weight will be measured with a balance beam scale if possible.

6.6.3. Resting Electrocardiogram (ECG)

Digital ECGs for all subjects will be recorded at the site using an appropriate ECG machine.

- A standard, single, digital 12-lead ECG will be obtained as outlined in the Schedule of Assessments after the subject has been resting in the supine position for 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals

All digital ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The Investigator will judge the overall interpretation as normal or abnormal. Clinical significance and the reason for the abnormality will be recorded on the eCRF.

Any changes in ECG values that are abnormal that are determined to be clinically significant by the Investigator will be recorded as AEs.

6.6.4. Clinical Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in the following table, at the timepoints listed in the Schedule of Assessments.

- All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations
- The tests will be performed by the central laboratory
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- Non-fasting blood samples are acceptable for this study.
- Repeat laboratory testing may be required during the study for various reasons, e.g., loss of sample en route to the central laboratory. Any testing which is required to be repeated should be repeated as soon as possible after a visit.

For information on blinded laboratory results see Section 5.1.3. Approximately 14 – 46 mL of blood will be collected per subject for each study visit. Approximately 552 mL of blood will be collected per subject for the entire study. Routine hematology, chemistry, PK serum atacicept, PK anti-drug antibodies, PD immunoglobulins, PD Gd-IgA1, PD serum BLyS & APRIL, and exploratory biomarkers will be assessed from the blood samples for each subject visit as per the schedule of assessments and description in Table 2.

6.6.4.1. Clinical Safety and Screening Evaluations**Table 2: Phase 2b: Clinical Laboratory Assessments**

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	<u>RBC Indices:</u> MCV MCH %Reticulocytes	<u>WBC Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	██████████ Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range)	Calcium Serum creatinine (eGFR will be calculated from serum creatinine using the CKD-EPI equation)	Glucose Potassium Sodium Total protein Uric acid
Urine Sediment Analysis	Urine red blood cells and white blood cells/high powered field Casts Organisms Crystals		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal).		
Quantitative Analysis (24 -hour Urine Collection)	Total volume Total protein ██████████ Total creatinine UPCR ██████████		
Other Tests	Serum IgG, IgA, IgM Gd-IgA1 Complement (C3, C4) Serum BLyS and APRIL level (if assay is available) HBsAg, anti-HBc [total and IgM] (hepatitis B) <ul style="list-style-type: none"> If HBsAg negative and hepatitis B core antibody is positive, HBV-DNA will be performed and monitored monthly through safety follow up Anti-atacicept antibody titers (binding and neutralizing) anti-HCV (if anti-HCV positive with reflex testing for HCV RNA by PCR) anti-HIV 1 and 2 HbA1c TSH FSH (for women only) Serum pregnancy test (β-hCG) required only for WOCBP at Screening. Local urine testing will be standard all other visits unless serum testing is required by local regulation or IRB/IEC. Positive urine pregnancy test results will be confirmed by serum pregnancy testing. Quantiferon test for TB Urine drug screen for amphetamines, cocaine, methadone, and opiates		

β-hCG= beta human chorionic gonadotropin; antiHBc=anti-hepatitis B core; anti-HCV = anti-hepatitis C virus; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; HbA1c=hemoglobin-A1c; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; Ig=immunoglobulin; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid; TB=tuberculosis; TSH=thyroid stimulating hormone; ██████████; UPCR=urine protein albumin-to-creatinine ratio; WBC=white blood cell; WOCBP=woman of childbearing potential.

6.6.4.2. Urine Sampling and Testing

Urine samples need to be collected in different ways for different tests:

Quantitative proteinuria assessments: A 24-hour urine collection will be used to determine 24 hour total protein excretion, UPCR, [REDACTED]. Total volume of the 24-hour collection will be measured and an aliquot taken for determining protein, [REDACTED] and creatinine concentration to calculate the proteinuria and [REDACTED] assessments. Subjects will be provided with the materials for conducting their 24-hour urine collections and will have to bring the collection to the clinic; for remote study visits, transport of the sample will need to be arranged. At the Screening Visit, the subject will receive the collection materials and the 24 hour collection should be conducted and brought into the clinic as soon as complete within the Screening Period. At other visits requiring a 24-hour urine collection, the subject is advised to collect the urine starting the day prior to the visit and bring it to the visit.

24 hour urine collection: The 24-hour urine collection should begin 1 day before the study visit and should start with discarding the first morning void, and collecting all urine produced thereafter (through the day and night) up to 24 hours later (including the first morning void of the second morning).

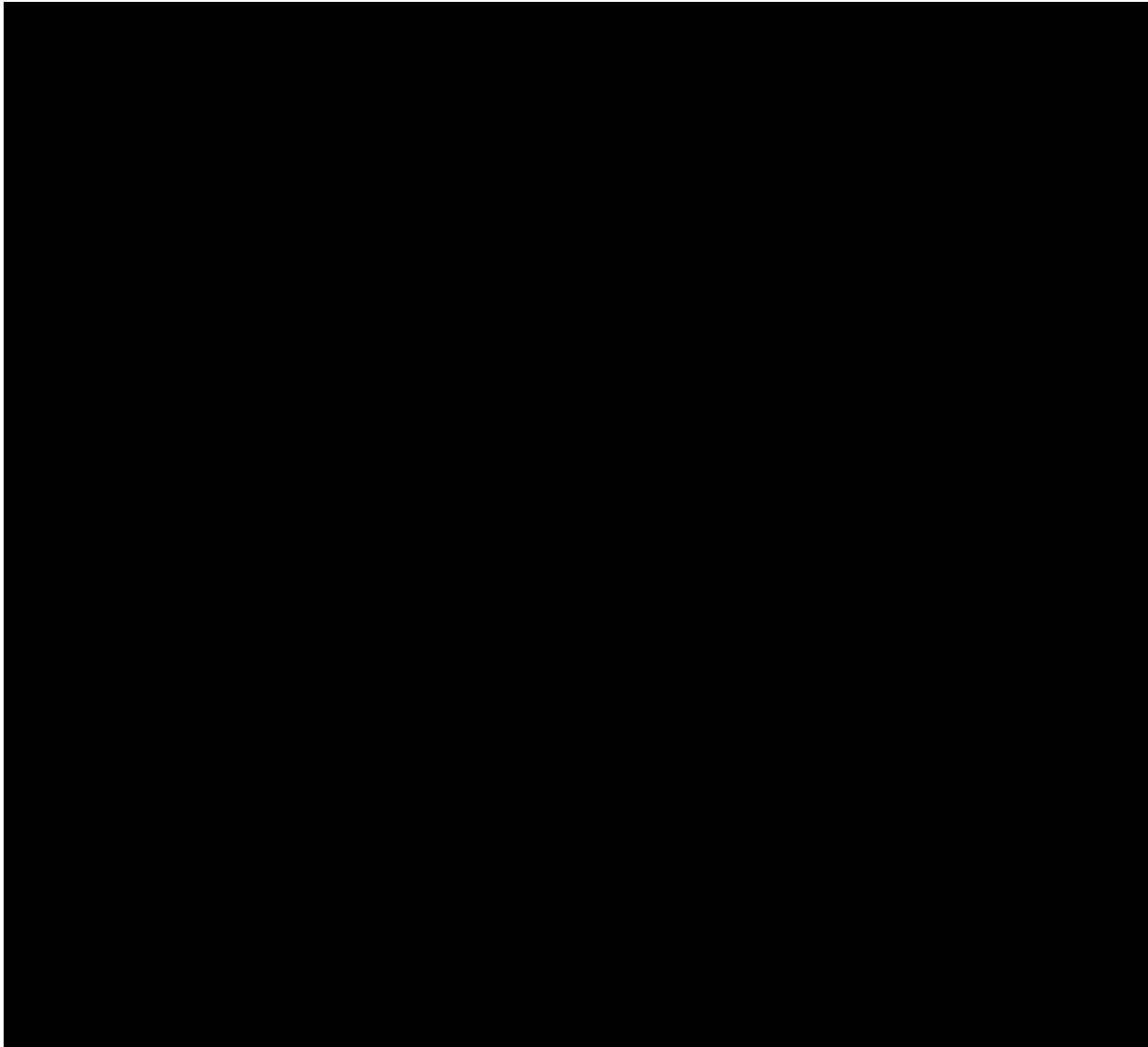
Urine collection: A urine sample from “fresh” urine will be collected during the scheduled clinic visit. Subjects will be provided a urine cup and instructions for a midstream collection to provide a clean catch specimen. The urine collection will be used for routine urinalysis and urine sediment analysis, and at specified visits, for sample storage for future exploratory biomarker analysis (see Section 6.8.1).

6.6.5. Local Tolerability (Injection Site Assessment)

Any local ISRs will be assessed by the Investigator or his/her designee and recorded as AEs in the eCRF, starting after first study drug administration and continuing through Part A and B or Early Termination (see Table 1).

Severity of the ISR reported on the AE form should reflect the highest severity of the manifestation (see below). For example, if the swelling is mild and the redness is moderate, then the AE should be reported as moderate.

The definition of ISR severity is the following:



If the subject experiences one or more of the above injection site symptoms, these should be reported with the AE verbatim term “injection site reaction”. These events will be captured on the AE page of the eCRF.

If the subject has any other injection site symptoms not included in the list above (e.g., injection site necrosis, injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (e.g., injection site necrosis, injection site abscess, injection site cellulitis) rather than the term “injection site reaction”.

Subjects who complete their last study visit with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required.

6.7. Pharmacokinetics

On Day 1, following first monitoring of ISR, a blood sample will be collected between 2-4 hours after first dose.

After Day 1 at PK timepoints in the Schedule of Assessments ([Table 1](#)) a blood sample will be collected prior to administration of study drug. Blood samples for PK analysis to assess trough levels of serum atacicept will be collected from all subjects. Instructions for collection, preparation and shipping these samples will be provided in a Laboratory Manual. Serum concentrations of atacicept will be assessed at trough as noted in the Schedule of Assessments. The actual date and time (24-hour clock time) of each sample will be recorded.

Blood samples for assessment of anti-drug antibodies, binding and/or neutralizing, will be collected at the visits specified in the Schedule of Assessments ([Table 1](#)). Samples will be tested first for binding activity, and those found to be positive will be tested for neutralizing activity when an assay is available.

6.7.1. Pharmacokinetic Sub-Study

At selected sites, a subgroup of subjects (approximately 32 subjects with 8 subjects per each Part A treatment arm) enrolled will have additional PK sampling visits that will be done at Day 2 and/or Day 3, approximately 24 and 48 hours after the first dose, respectively, in order to capture the drug's T_{max} . The exact time and date of blood sampling should be recorded.

6.8. Other Assessments

6.8.1. Biomarkers

Storage and analyses of samples will be handled according to the study Laboratory Manual, and described in the appropriate Informed Consent Form.

Serum Biomarkers

The following markers may be evaluated: predose serum BLyS and serum APRIL, and serum IgG, IgA, and IgM, serum Gd-IgA1.

Exploratory Biomarkers

[illegible]

The global coronavirus pandemic or outbreaks may impose difficulties with study conduct which may inhibit the subjects' ability of entering the study site. In cases of coronavirus limitations, it is the Investigator's responsibility to assure the safety of study subjects which should include phone or video contact to assess the subject's well-being including any adverse events, collection of study samples and clinical data as best as possible, and direct shipment of study drug to study subjects if necessary. These assessments can be performed at a scheduled or unscheduled study visit(s). Where available and appropriate, home health care may be considered to facilitate monitoring of subject safety and study continuity. Documentation of these cases and the site's management of subjects should be recorded in the Investigator study files.

Study drug may be stopped at any time at the Investigator's discretion.

Subjects who withdraw from, or are withdrawn from study drug early should remain in the study, completing an early termination visit and continuing in the 26-week Safety Follow up Period (see [Table 1](#)).

For such subjects who permanently discontinue study drug but remain in the study, the ET visit must be completed within 10 days of discontinuation, followed by the Safety Follow up visits as described in [Section 6.3.3](#).

For subjects who withdraw consent or are lost to follow-up or death, Safety Follow-up visits will not be possible. In such cases, the appropriate eCRF section must be completed.

If a subject is unblinded (Part A), the subject must be discontinued from the study drug and complete all assessments and procedures specified for the ET visit and complete the Safety Follow up period.

The subject must be withdrawn from study drug in the event of any of the following:

- Enrollment despite violation of an exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the subject necessary.
 - For Germany only – ineligible patients will not be enrolled and thus not discontinued
- Occurrence of an AE/SAE that makes discontinuation of study drug desired or considered necessary by the Investigator and/or the subject.
- Participation in any other interventional study during the duration of this study for which the Investigator considers discontinuation of the IMP necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to [Section 7.9](#)).
- If disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes ([Section 5.7](#)) is warranted in the view of the Investigator. Discussion with the Medical Monitor should occur prior to discontinuing IMP for this reason.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on Investigator judgment.
- Use of a nonpermitted medicine, as defined in [Section 5.7.2](#). This should first be confirmed with the Medical Monitor before discontinuation of study drug.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance to the required study considerations, as defined in [Section 5.6](#).
- Discontinuation of LTBI therapy before completion if present at the Screening Visit.
- If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart.
- Surgery considered by the Investigator or Sponsor to be major (see [Section 4.2](#)).
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Atacicept is contraindicated in subjects with a history of MS, ON, or any other demyelinating disease. Any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as, but not limited to, MS, ON, or transverse myelitis) should stop dosing of IMP.

The Schedule of Assessments specifies the data to collect at study drug discontinuation and follow-up, and any additional evaluations that need to be completed.

6.10.2. Study Drug Interruption

The Medical Monitor must be notified if the subject has missed 2 consecutive doses or 2 doses within a month period. If treatment has been interrupted for ≥ 4 consecutive weeks, the Investigator should discuss with the Medical Monitor whether to restart or discontinue treatment.

If the subject is unable to resume study drug, see Section 6.10.

6.11. Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent). Investigator or designee should make reasonable effort to obtain explanation for subject withdrawal and ask about the occurrence of any AEs. The subject will be asked to return for an ET visit per Schedule of Assessments (Table 1).

- The subject may be withdrawn by the Investigator due to participation in another clinical study
- The subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed
- A subject is considered withdrawn from the study due to death
- A subject must be withdrawn from the study in the event the subject is lost to follow up.
- Discontinuation of the study at the request of the sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC).

When a subject must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor.

If a subject is withdrawn from the study, the samples will be kept, and the subject may be asked to return for Safety Follow-up assessments. If the subject withdraws consent, the Sponsor may retain and continue to use any data collected prior to such withdrawal of consent; however, all samples not tested will be destroyed.

If there is a medical reason for withdrawal from the study, the subject will remain under the supervision of the Investigator until satisfactory health has returned or health has stabilized. The Investigator will inform the subject's primary health care provider as applicable and as agreed by the subject if the subject withdraws from the study, to ensure the subject receives the appropriate follow up and care.

Subjects who are withdrawn from the study for any reason after receipt of the study drug on or after Day 1 will not be replaced.

6.12. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). The Investigator reserves the right to discontinue the study should his/her judgment so dictate and should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

6.13. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study
- Before a subject is deemed “lost to follow-up”, the Investigator or designee must make every effort to regain contact with the subject:
 1. where possible, make 3 telephone calls, AND
 2. if necessary, send a certified letter (or an equivalent local method) to the subject’s last known mailing address.

These contact attempts should be documented in the subject’s medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

6.14. Medical Care of Subjects after End of Study

After a subject has completed the study including the Safety Follow- Up Period, or has withdrawn early, standard treatment should be administered, if required, in accordance with the study site’s SoC and generally accepted medical practice and depending on the subject’s individual medical needs.

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for patients with IgAN.

7. PHASE 2B: ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated and does not interfere with everyday activities.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out his or her usual activities. An AE that is assessed as severe should not be confused with an SAE. An event is defined as “serious” when it meets at least one of the predefined outcomes in the definition of SAE, and not when it is rated as severe.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study drug include, but may not be limited to, temporal relationship between the AE and the study drug, known side effects of study drug, medical history, concomitant medication, course of the underlying disease, and study procedures.

Investigators must also assess the causal relationship of AEs to the pre-filled syringe.

- Unrelated:** Not reasonably related to the study drug. AE could not medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol. A reasonable alternative explanation must be available.
- Related:** Reasonably related to the study drug. AE could medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Clinically significant abnormal laboratory or other examination (e.g., electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. If a laboratory abnormality fulfills these criteria, the

identified medical condition (e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., electrocardiogram abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

The severity of abnormal laboratory values should be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) and recorded per the Qualitative Toxicity Scale, as follows:

Mild:	CTCAE Grade 1
Moderate:	CTCAE Grade 2
Severe:	CTCAE Grade 3 and 4

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition(s); this may or may not be in agreement with the grading of the laboratory abnormality.

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization
Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are baseline conditions (e.g., pre-existing) and are not to be considered AEs. Situations where an untoward medical occurrence has not occurred are not to be considered AEs (e.g., hospitalization for elective surgery, social and/or convenience admissions).

Adverse Events of Special Interest

Adverse events of special interest must be reported on the SAE/AESI Report Form and will follow the procedure described below for reporting SAEs and AESIs.

Categories of AESIs include:

- Opportunistic infections considered to be medically significant by the Investigator, but do not meet at least one of the criteria for an SAE (infections meeting one or more of the seriousness criteria should be reported as SAEs)
- Hypersensitivity reactions
- Demyelinating disorders
- Cardiac events (cardiac failure, cardiac arrhythmias, and ischemic heart disease)

7.2. Time Period and Frequency for Collecting Adverse Event, Adverse Event of Special Interest and Serious Adverse Event Information

The AE/AESI/SAE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Safety FU Visit After informed consent, but prior to initiation of study drug, all SAEs and adverse events related to protocol-mandated procedures should be collected.

- Following initiation of study drug, collect all AEs, regardless of cause or relationship.

Any SAE assessed as related to study drug must be recorded and reported, whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Section 7.5.

7.3. Method of Detecting Adverse Events, Adverse Events of Special Interest and Serious Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, regardless if reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and AESIs must be additionally documented and reported using the appropriate report form as specified in Section 7.5.

7.4. Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 7.2, and are assessed for their outcome at the last Safety FU Visit. All SAEs ongoing at the last Safety FU Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow up procedures are performed.

7.5. Investigator Requirement and Instructions for Reporting Adverse Events, Serious Adverse Events, Adverse Events of Special Interest

Recording and Follow-Up of AEs

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study drug administration time), its severity, its causal relationship with the study drug, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All reports should be transmitted using the AE page and indicating the AE meets criteria for an SAE in eDC. Required information in eDC must be completed by the Investigator following specific completion instructions.

In exceptional circumstances (e.g., eDC is down), an SAE (or follow-up information) may be reported by fax or email; in these cases, a written report using the back-up paper SAE Reporting Form must be sent immediately by fax or email contacts listed below by any study site. Once eDC becomes accessible, the SAE needs to be entered into the system immediately.

IQVIA Safety (Back Up Contact Information):

Email (preferred): PhV_TZA74011_SO@IQVIA.com

Fax: refer to country specific fax numbers provide with paper forms

Additional documents will be provided by the Investigator, if requested by the Sponsor or its designee (e.g., laboratory results, hospital report, autopsy report) depending on the availability of the document.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports, by updating the (S)AE form in the eDC system and submitting any supporting documentation (e.g., subject discharge summary or autopsy report) to IQVIA via e-mail (preferred) or fax. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE information in the eDC and submit any supporting documentation as requested (e.g., subject discharge summary or autopsy report) to IQVIA Safety via e mail (preferred) or fax. If it is not possible to access the eDC system, refer to the procedures outlined above for initial reporting of SAEs.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will enter the AE into eDC and indicate the AE is an AESI in eDC in a timely manner. AESIs that meet the definition of an SAE must be reported in the same timely manner and process as SAEs as outlined above.

7.6. Regulatory Reporting Requirements for Serious Adverse Events

Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For atacicept, the reference safety information is included in the Investigator’s Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report where possible.

Regulatory Reporting

The Sponsor or designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the Independent Ethics Committee / Institutional Review Board (IEC/IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the Regulation (EU) No 536/2014, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.7. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are hypersensitivity reactions, opportunistic infections, cardiac disease/disorders (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and demyelination disorders.

7.7.1. Hypersensitivity Reactions

Atacicept is contraindicated in subjects with known hypersensitivity to the drug substance or to any of the excipients. If allergic angioedema or other serious hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions occur, administration of IMP should be discontinued immediately, and appropriate therapy initiated. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for resumption of IMP or permanent discontinuation.

Local ISRs may be treated as per Section [6.6.5](#).

7.7.2. Opportunistic Infections

Opportunistic infections are those due to bacteria, fungi, viruses, or parasites that normally do not cause a disease, but become pathogenic when the body's defense system is impaired.

Treatment of infections must be prompt and done in accordance with local SoC depending on considerations such as the nature and severity of the infection, patient's overall health status, etc.

- Subjects must be carefully examined for signs of infection and questioned about recent infective illnesses and recent vaccination(s)
- If laboratory findings raise concern, in the opinion of the Investigator, that there may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section 4.2, and may lead to study drug discontinuation
- Subjects will be instructed by study site personnel to monitor for early signs of infection, such as upper respiratory symptoms, fever, painful urination, productive cough, breathlessness, constitutional symptoms, etc. Subjects should inform the study site if any of these symptoms or signs are present and should be evaluated and treated in a timely manner according to the local SoC. At each study visit, monitoring for subject's symptoms and signs should also be done. Standard medical care will be provided at the study sites for all AEs occurring during the study. Any subject who experiences a chronic or recurrent significant infection, or opportunistic infection, should be re-evaluated (as per Investigator's clinical judgment and discussion with Medical Monitor) as to whether or not continued treatment with atacicept is appropriate. Serious infections will be reported as described in Section 7.5.

For infections associated with severe hypogammaglobulinemia (serum IgG < 3 g/L), consideration can be given to administration of Ig and discontinuation of study drug. If a subject has 2 consecutive serum IgG < 3 g/L at least 4 weeks apart, then the subject will be discontinued from study drug (see Section 6.10.1).

7.7.3. Cardiac Disease/Disorders

Treatment with atacicept must be temporarily discontinued in subjects who develop new onset or worsening of clinically significant symptomatic arrhythmias that require medical intervention (such as paroxysmal atrial tachycardia, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia, ventricular fibrillation or tachycardia), cardiac failure, or cardiac ischemic symptoms. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for discontinuation or resumption of study drug.

7.7.4. Demyelination Disorders

Based on the clinical trial results, MS patients who received atacicept developed significantly more relapses than patients in the placebo group. Therefore, any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as but not limited to MS, optic neuritis or transverse myelitis) should discontinue the study drug.

7.8. Management of Adverse Events Associated with Abnormal Laboratory Findings

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in [Appendix 3](#) and as outlined below.

Grades 1 (Mild) and 2 (Moderate) Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

Grade 3 (Severe) Laboratory Abnormality or Clinical Event

Study drug may be continued if the event is considered to be unrelated to study drug.

For clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to $\leq$ Grade 2.

If a laboratory abnormality recurs to $\geq$ Grade 3 following re-starting of study drug and is considered related to study drug and medically important by Investigator and/or Sponsor/designee, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

Grade 4 (Severe) Laboratory Abnormality or Clinical Event

For clinical event or Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug and medically important by Investigator and/or Sponsor/designee, study drug should be permanently discontinued and the subject managed according to local clinical practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to the study drug.

All subjects experiencing AEs must be monitored until symptoms subside and any abnormal laboratory values have resolved, returned to baseline levels, are considered irreversible, or have a reasonable explanation for the changes observed.

7.9. Pregnancy

Pregnancy should not be captured as an AE. However, pregnancies with an estimated conception date during the period defined in Section [7.2](#) must be recorded in the eCRF for both pregnancies in female subjects and pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Section [7.5](#).

Investigators must actively follow up, document and report on the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Reporting Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 7.2, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the study, the subject must be discontinued from study drug. The Sponsor/designee must be notified without delay and the subject must be followed as indicated above.

7.10. Special Situation Reports

Special situation reports include site-reported instances of overdose, misuse, abuse, medication error, and adverse reactions associated with product complaints.

- **Overdose:** For this study, any instance when IMP is given 3 times or more per week is considered an overdose. Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).

Note: The Sponsor does not recommend specific treatment for an overdose. The effects of an overdose of atacicept are unknown and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and appropriate supportive treatment should be given as needed per Investigator's clinical judgment.

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events should be reported as a protocol deviation and any associated events reported as an AE. Special Situations that are considered to meet SAE criteria will be managed per the same process as SAEs in Section 7.5.

8. PHASE 2B: STATISTICAL CONSIDERATIONS

The Phase 2b Statistical Analysis Plan (SAP) will be developed and finalized before the database lock for the first interim analysis and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary efficacy and safety endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Stratification factors will be described in the SAP.

All endpoints will be summarized using descriptive statistics. Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number. Statistical testing will be conducted for primary and secondary efficacy endpoints with no adjustments for multiple comparisons. For the purposes of this trial, a significance level of 0.05 will be utilized.

All statistical analyses will be conducted by the Sponsor or its agent using SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA 27513).

8.1. Stratification

Subjects will be stratified by screening eGFR, calculated by the central lab, between subjects who have values $\text{eGFR} \geq 30$ and $< 45 \text{ mL/min/1.73 m}^2$ and those subjects who have an $\text{eGFR} \geq 45 \text{ mL/min}$ as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Approximately 20% of subjects will be randomized that have an eGFR between 30 and $< 45 \text{ mL/min}$.

8.2. Statistical Hypotheses

The primary efficacy endpoint is the change from baseline to Week 24 in natural log transformed UPCR. The primary comparison of interest is a 2-sided test of superiority comparing the combined atacicept 75 mg and 150 mg doses (ATC75:150) to placebo.

$$H_0: \mu_{\text{placebo}} = \mu_{\text{ATC75:150}} \text{ VS } H_{13}: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

8.3. Sample Size Determination

Sample size and power are estimated for the primary efficacy endpoint, change from baseline to Week 24 in natural log transformed UPCR. It is assumed that the absolute difference (placebo – active) in the mean ratio of Week 24 UPCR to baseline UPCR is 0.28. The geometric mean ratio of Week 24 UPCR to baseline for placebo is expected to be 0.88. The coefficient of variation is estimated as 0.594 [i.e., pooled log SD of 0.55]. The expected placebo response and study intervention effect size are based on the analysis of the phase 2 study for atacicept and placebo in IgAN and placebo responses seen in other large IgAN studies. Based on these assumptions, 25 subjects in the placebo group and a combined total of 50 subjects in the atacicept 75 mg and 150 mg groups are considered sufficient to provide at least 80% power to detect a ratio of 1.47 when the ratio under the null hypothesis is 1 [PASS 2008: two-sided two Sample t-test for ratios, $\alpha=0.05$, coefficient of variation on the original scale is 0.594]. Adjusting for a 15% dropout rate, 30 subjects should be enrolled in each of the placebo, atacicept 75 mg, and atacicept 150 mg groups to ensure 25 subjects complete Week 24 in each of these groups. The sample size of 15 for the atacicept 25 mg group is chosen to provide preliminary safety and efficacy information and is not based on statistical considerations.

8.4. Populations for Analyses

The analysis populations are specified below. The final decision to exclude subjects from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Population	Description
Screening	All subjects who sign informed consent.
Intent-to-treat (ITT)	The ITT Population consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.
Full Analysis Set (FAS)	The FAS Population consists of all randomized subjects who have received at least 1 dose of treatment and have at least 1 post-baseline measurement of UPCR. Subjects will be analyzed according to randomized treatment.
Per-Protocol (PP)	The PP population consists of all subjects in the FAS who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the SAP, including exclusion of subjects who take prohibited medications. The PP Population will be used for supportive analyses on the primary and selected efficacy endpoints. Subjects will be analyzed according to treatment received.
Safety	The Safety Population consists of all randomized subjects who receive at least 1 dose of treatment. The Safety Population is the analysis population for the safety endpoints. Subjects will be analyzed according to treatment received.
Pharmacokinetics	The PK population consists of all randomized subjects who were administered at least 1 dose of treatment and have at least 1 evaluable PK sample. All PK evaluations will be based on this analysis set. Subjects will be analyzed according to treatment received.

Unless otherwise indicated, the Full Analysis Set (FAS) is the primary analysis population for efficacy endpoints and the Safety Analysis Set is the primary analysis population for safety endpoints.

8.5. Statistical Analysis

8.5.1. Efficacy Analyses

The primary analysis of proteinuria will assess UPCR data via a mixed-model repeated measures analysis. Change from baseline in natural log transformed UPCR will be the dependent variable.

8.5.2. Safety Analyses

Safety analyses will include the examination of vital signs, physical exam, 12 lead ECG, routine clinical laboratory tests (including hematology, blood chemistries, urinalysis), and AEs. All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

8.5.2.1. Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent adverse events (TEAEs) will be summarized using descriptive statistics by treatment group. Treatment-emergent adverse events are defined as AEs with onset dates occurring during the study period (i.e., from the first dose until the subject's last study visit) and will be assigned to the most recently received treatment at the start of the AE. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each MedDRA System Organ Class and MedDRA Preferred Term, by treatment group. Treatment-emergent adverse events will also be summarized by relationship to treatment and by severity within each treatment group, and by predefined AESIs.

8.5.3. Other Analyses

Laboratory data, vital sign data, and ECG data will be summarized by timepoint and treatment group with descriptive statistics.

8.5.4. Pharmacokinetic and Pharmacodynamic Analyses

Analyses of the PK substudy, serum BLYS, APRIL, Gd-IgA1, and other exploratory biomarkers will be summarized using descriptive statistics. Additional analyses may be detailed in the SAP.

9. PHASE 2B: RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the protocol, the Regulation (EU) No 536/2014, ICH E6(R2) addendum to its guideline for GCP, and applicable laws and regulations.

9.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

9.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions on the study.
- Subjects must be informed that their participation is voluntary.
- Subjects or their legal representative under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, subjects must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the subject.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

9.1.4. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study subject. The file must identify each subject, contain the following demographic and medical information for the subject, and should be as complete as possible:
 - Subject's full name, date of birth, sex, height, and weight
 - Medical history and concomitant diseases
 - Prior and concomitant therapies (including changes during the study)
 - Study identifier (i.e., the Sponsor's study number) and subject's study number
 - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
 - Any medical examinations and clinical findings predefined in the protocol
 - All AEs

- Date that the subject left the study, including any reason for early withdrawal from the study or study drug, if applicable
- All source data must be filed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] scan images, ECG recordings, and laboratory results). Each document must clearly identify the subject and the procedure date, ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. Investigators must notify Sponsor in advance if source documents are to be moved to another location, such as for archiving.

9.1.5. Data Protection

- The Sponsor will assign a unique identifier to subjects after obtaining their informed consent. All subject records or datasets transferred to the Sponsor will contain the identifier only; subject names or any identifiable information will not be transferred.
- The Sponsor must inform subjects that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain subjects' confidentiality.
- The Investigator will complete the subject registration using the IWRS (Section 5.1). If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject will be registered by IWRS. If the subject is ineligible for the study, a subject number will be allocated and documented.
- The Sponsor will ensure that data will be collected and processed in accordance with the General Data Protection Regulation (GDPR) EU 2016/679.

9.2. Sponsor Responsibilities

This clinical study will be Sponsored by: Vera Therapeutics, Inc.

The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

An iDMC will be formed in this study (see Section 3.2).

9.2.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
 - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study subjects. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
 - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
 - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

9.2.2. Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to subjects for use during the study. These provide the means for subjects to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the subject. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician (or designee). This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician (or designee) to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.2.3. Clinical Study Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

9.2.4. Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator.

9.2.5. Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.2.6. Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

9.3. Data Quality Assurance

- All subject study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of subjects are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

9.4. Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
 - Inadequate recruitment of subjects by the Investigator
 - Discontinuation of further development of the Sponsor's compound

10. IMPORTANT CLINICAL STUDY NOTE

It is important to note to all study investigators, regulators, competent authorities, ethics committees, institutional review boards, scientific committees, site staff, clinical research organizations, and individuals involved in the review or conduct of this study that the design of this protocol is a multi-part study as described below. Some study sites and countries will be participating in the Phase 2b component only, the Phase 3 component only, or both components.

This is a multi-part study comprising of the original Phase 2b study (Parts A and B) and the addition of a separate Phase 3 study (Parts C and D). The Phase 3 study has been added as a separate component to the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from the Phase 2b study have been used to inform the Phase 3 study design including selection of dose and determination of sample size.

The Phase 2b study is referred to as ORIGIN and the Phase 3 study is referred to as ORIGIN 3.

Phase 3:

- a. Synopsis: Pages [86](#) through [101](#)
- b. Protocol: Sections [11](#) through [19](#)

Key differences between the Phase 2b and Phase 3 studies are summarized in the table below and in [Appendix 4](#).

Key Differences Between Phase 2b and Phase 3 Studies

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
Objectives and Endpoints		
Primary endpoint	UPCR at Week 24	UPCR at Week 36
Secondary endpoint	UPCR at Week 36	Key: Change from baseline in eGFR at [REDACTED] Other: [REDACTED] <ul style="list-style-type: none"> UPCR [REDACTED] Gd-IgA1 [REDACTED] Achieving hematuria resolution [REDACTED] Time from first dose to the first occurrence of a $\geq 30\%$ decrease from baseline in eGFR that is sustained for a minimum of 30 days, through Week 104 Time to composite kidney disease progression event through Week 104
Exploratory endpoints	<ul style="list-style-type: none"> UPCR at Week 12 [REDACTED] eGFR at Week 12, 24, and 36 IgA, IgG, IgM levels, C3, C4, and Gd-IgA1 levels at Weeks 12, 24, and 36 PK of atacicept 	[REDACTED]
Study Design		
Randomization and treatment	2:2:1:2 to atacicept 150 mg, atacicept 75 mg, atacicept 25 mg, or matching placebo	1:1 to atacicept 150 mg or matching placebo
Stratification	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (≥ 30 to <45 mL/min/1.73 m² and ≥ 45 mL/min/1.73 m² by CKD-EPI) 	By: <ul style="list-style-type: none"> Screening eGFR values calculated by the central lab (<45 mL/min/1.73 m², or ≥ 45 to <90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI) Screening total urine protein excretion (<2 g/24h or ≥ 2 g/24h) Region (Asia or Other) Stable SGLT2 inhibitor use at screening (Yes or No)
Double-blind period duration	36 weeks	[REDACTED]

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
Study visits and assessments after premature study drug discontinuation in the double-blind period	Subjects who discontinue study drug prior to completion of the 96-week total treatment duration will complete an Early Termination (ET) Visit and have a 26-week follow-up period.	Subjects who prematurely discontinue study drug during the double-blind period are encouraged to continue with study visits and assessments per protocol through the end of the double-blind period.
Open-label extension duration	60 weeks	52 weeks
Duration of treatment	Up to 96 weeks	Up to 156 weeks
Number of sites / subjects	90 / 105	Up to 250 / 376
Eligibility Criteria – Inclusion criteria		
Screening proteinuria allowed	Total urine protein excretion > 0.75 g or UPCR > 0.75 mg/mg based on a 24-hour urine sample	Total urine protein excretion ≥ 1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 1.0 mg/mg based on a 24-hour urine sample
Criteria for RAASi use during Screening	On a stable prescribed regimen of RAASi (ACEi, ARB or MRA) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening.	On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1.
Eligibility Criteria – Exclusion criteria		
Systemic corticosteroids	Corticosteroids for the treatment of IgAN within 3 months prior to screening.	Corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening.
Use of blisibimod	Blisibimod is given as a prohibited medication at screening.	Blisibimod is implied as prohibited given it is a B-cell-direct biologic therapy. Only approved drugs are listed in the protocol.
Criteria for clinically significant or predefined abnormalities	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin > 1.5 × ULN. <ul style="list-style-type: none"> If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion. 	<ul style="list-style-type: none"> serum IgG below 7 g/L aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 × upper limit of normal (ULN) or total bilirubin > 1.5 × ULN. <ul style="list-style-type: none"> If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion. hemoglobin < 10 g/100 ml in men and hemoglobin < 9 g/100 ml in women platelets < 100 10⁹/L
Hepatitis C virus (HCV)	Subjects with any hepatitis C virus (HCV) are excluded	Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
History of malignancy	History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix	History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ), with no evidence of recurrence
Investigational Medicinal Product(s)		
Prefilled syringe	All study drug (atacicept and matching placebo) is provided in prefilled single-use syringe to the site	<p>The active dosage form and placebo will be supplied by the Sponsor as a ready-to-use, prefilled syringe or atacicept autoinjector combination (AAIC) product with 1.0 mL of drug product/placebo</p> <p>The Sponsor is currently developing an AAIC product. Contingent upon fulfilment of regional regulatory requirements for switching the device for use in this clinical study, the Sponsor may implement the AAIC in select countries and sites. When available, atacicept 150 mg may be self-administered SC via the AAIC.</p>
Permitted Medications		
Use of SGLT2 inhibitors and mineralocorticoid receptor antagonists	In subjects receiving SGLT2 inhibitors at the time of enrollment, the dose must be stable for at least 8 weeks prior to screening and is expected to be at a stable dose over the study period. The Investigator should discuss planned use of an SGLT2 inhibitor with the Medical Monitor prior to initiation for their awareness.	As with RASi medications, subjects prescribed SGLT2 inhibitors and/or mineralocorticoid receptor antagonists (MRAs; e.g. spironolactone, eplerenone or finerenone) are required to be on a stable dosing regimen for at least 12 weeks prior to screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes of SGLT2 inhibitors and/or MRAs. Introduction of SGLT2 inhibitors and/or MRAs during the double-blinded phase in subjects not on them previously at randomization is prohibited.
RAAS inhibitor changes during treatment period	It is recommended that changes in RAASi medication be avoided for the duration of the study.	To be eligible for randomization, all subjects who tolerate RASi (ACEi or ARB) medication are required to be on stable RASi treatment for at least 12 weeks prior to Screening that is at the maximum labeled or tolerated dose, which must be maintained through the screening period to Day 1. For subjects who are unable to tolerate RASi medication, management of IgAN will be SoC according to local practice. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
		<p>avoid dose changes and changes in type of RASi medication; every effort should be made to maintain subjects on their stable RASi dose, unless required for safety reasons. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non-RASi medications should have been considered before these specific drug classes. In certain instances (i.e. hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].</p>
Rescue medications	Not defined	<p>Defined as: Should the Investigator consider that rescue medication (steroids including oral budesonide and/or immunosuppressive treatment) be warranted, such treatment can be initiated at the discretion of the Investigator. However, in consideration of current guidelines (KDIGO 2021), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:</p> <ul style="list-style-type: none"> • Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] accompanied by eGFR < 60 mL/min/1.73 m²; and/or • Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., > 3.5 g/day] and hypoalbuminemia [albumin < 3.0 g/dL]) <p>Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. If rescue medication is required, it is the Investigator's decision to implement new treatment. In this case, the Medical Monitor must be notified within 48 hours after the initiation of rescue therapy, as continued dosing with IMP may, in this circumstance, be discontinued. If possible, it is encouraged that the Medical Monitor be informed prior to initiation of rescue medication. If possible, it is encouraged</p>

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
		that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of rescue medication, but this is at the investigator's discretion if feasible. Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 15.7.1.
Endothelin receptor antagonists	Prohibited during the study.	Permitted during the OLE period.
Prohibited Medications		
Systemic corticosteroids	No specific corticosteroid given	Includes oral budesonide
Endothelin receptor antagonists	Prohibited during the study.	Prohibited during the DB period only; permitted during the OLE period.
Schedule of Assessments		
Additional site visits not included in SOA table	N/A	Additional visits can be conducted at Weeks 1, 3, and 105.
AAIC	N/A	Potential to use AAIC added to schedule of assessments
Treatment with IMP		
Pulse and BP monitoring on Study Day 1	Pulse and BP will be recorded for 2 hours at approximately the following timepoints post administration: 5±2 minutes, 15±5 minutes and 30±5 minutes, 1 hour±10 minutes, 1.5 hours±10 minutes and 2 hours±10 minutes	Pulse and BP will be recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
Local Tolerability (Injection Site Assessment)		
Grading scales for severity of manifestations	Any local injection site reactions (ISRs) will be assessed by the Investigator and recorded as AEs. Severity of the ISR reported on the AE form should reflect the highest severity of the manifestation.	Any clinically significant ISR as per Investigator judgement will be reported as an AE. Severity of the ISR reported on the AE form based on grading scale provided in protocol Section 16.6.5.
Clinical Laboratory Assessments		
Amount of blood collected per subject per visit / total	14-16 mL / 552 mL	20-48 mL / 827.5 mL

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
Abnormal lab values	Adverse events related to abnormal lab values are graded based on CTCAE scale.	Adverse events related to abnormal lab values are graded based on the Toxicity Scale used for all other adverse events.
Adverse Events of Special Interest (AESI)		
Definition of AESI of infection	Defined as opportunistic infections considered to be medically significant but not meeting definition of serious adverse events (SAE) of infection	Defined as infection
Contraception		
Female subjects	Not defined	Invasive Methods defined as user-independent invasive contraceptive methods herein mentioned in this appendix is provided as a guidance. Women of childbearing potential who are already using one of these highly effective invasive contraceptive methods prior to inclusion OR who will begin using any of these highly effective contraceptive methods by their own decision will be eligible for inclusion.
Male subjects	Not included	It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

	Phase 2b (ORIGIN)	Phase 3 (ORIGIN 3)
Statistical Methods		
Statistical testing	Statistical testing will be conducted for the primary and secondary efficacy endpoints with no adjustments for multiple comparisons with a significance level of 0.05.	

PHASE 3 STUDY (ORIGIN 3)

1. Synopsis: Pages [86](#) through [101](#)
2. Protocol: Sections [11](#) through [19](#)

PHASE 3 (ORIGIN 3) PROTOCOL SYNOPSIS

Vera Therapeutics, Inc.
2000 Sierra Point Parkway, Suite 1200
Brisbane, CA 94005

Rationale: Atacicept (also known as VT-001) targets B-cells by inhibiting B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), and has been studied in a pilot Phase 2a clinical study for immunoglobulin A (IgA) Nephropathy (IgAN). The data from this study suggested clinical efficacy based on reduction in proteinuria and galactose-deficient IgA1 (Gd-IgA1), and stable estimated glomerular filtration rate (eGFR), which warrant further study of atacicept in this population. The Phase 2b clinical study results support clinical efficacy and safety as well as the best dose regimen for further evaluation. Based on the available clinical data, the targeted population for this Phase 3 study is subjects with IgAN with persistent proteinuria who remain at high risk of disease progression despite being on a stable prescribed regimen of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB). The objectives of the Phase 3 study will be to determine the effect of atacicept on proteinuria and preservation of renal function in subjects with IgAN.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Natural log-transformed UPCR ^a	Week 36
Key Secondary		
Evaluate the effect of atacicept compared to placebo on change from baseline in eGFR	Change from baseline in eGFR ^b	
Secondary		
Evaluate the effect of atacicept compared to placebo on annualized rate of change in eGFR	Annualized rate of change in eGFR ^b (i.e., annualized eGFR total slope)	
Evaluate the effect of atacicept compared to placebo on change in proteinuria	Natural log-transformed UPCR ^a	
Evaluate the effect of atacicept compared to placebo on change in Gd-IgA1	Natural log-transformed Gd-IgA1	
Evaluate the effect of atacicept compared to placebo on achieving hematuria resolution	Hematuria resolution	
Evaluate the effect of atacicept compared to placebo on time from first dose to the first occurrence of a sustained $\geq 30\%$ decline in eGFR	Time from first dose to the first occurrence of a $\geq 30\%$ decrease from baseline in eGFR that is sustained for a minimum of 30 days	Through Week 104
Evaluate the effect of atacicept compared to placebo on time from first dose to the first occurrence of composite kidney disease progression event	Time to composite kidney disease progression event defined as experiencing at least one of the following during the study: <ul style="list-style-type: none">• At least a 30% reduction in eGFR sustained for at least 30 days• eGFR < 15 mL/min/1.73m², sustained for at least 30 days• Chronic dialysis ≥ 30 days• Kidney transplantation• Death	Through Week 104

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Safety		
Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, AEs, serum trough PK, and ADAs	During the DB period

ADA = anti-drug antibodies; AE = adverse event; DB = double-blind; eGFR = estimated glomerular filtration rate; EQ = EuroQoL; FACIT-F = Functional Assessment of Chronic Illness Therapy - Fatigue; Gd-IgA1 = galactose-deficient IgA1; IgAN = immunoglobulin A nephropathy; PK = pharmacokinetics; PRO = patient-reported outcome; SF-36 = 36-Item Short Form Health Survey; [REDACTED] UPCR = urine protein to creatinine ratio.

a Based on 24-hour urine sample.

b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults.

Overall Design:

This is a multi-part study comprising the original Phase 2b study and the addition of a separate Phase 3 study. A Phase 3 study (i.e., Parts C and D) has been added as a separate component of the existing study to obtain study operational efficiency by keeping the original sites activated and modifying existing study systems and plans. The results from Phase 2b have been used to determine the dose selection and sample size for the Phase 3 study design.

The Phase 3 study is a multicenter, randomized, double-blind, placebo-controlled trial. In Part C, subjects will be randomized 1:1 to atacicept 150 mg or placebo for [REDACTED] followed by a 52-week open-label extension (Part D) in which subjects will be given 150 mg atacicept once weekly subcutaneous (SC) injections.

Subjects who have participated in Part A or B may not participate in Part C or D.

Subjects participating in the study will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/ 1.73 m², or ≥ 45 to <90 mL/min/ 1.73 m², or ≥ 90 mL/min/ 1.73 m²), total urine protein excretion (<2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (yes or no), and Region (Asia or Other). The use of SGLT2 inhibitors could impact the evaluation of clinical efficacy of the IMP. The Sponsor may cap the enrollment of these subjects.

The Phase 3 study is composed of a (up to) 4-week Screening Period, an [REDACTED] Double-Blind (DB) Treatment Period (Part C), a 52-week Open-Label Extension (OLE) (Part D), and a 26-week follow-up. Subjects who complete the DB period on treatment will be eligible for open-label atacicept 150 mg for an additional 52 weeks (OLE). Subjects who prematurely discontinue study drug prior to completion of the DB period should continue with study visits and assessments per protocol through the end of the DB period. After completion of the study treatment period, all subjects will have a 26-week follow-up period except if the subject discontinued study drug more than 26 weeks before the end of the DB period.

The ORIGIN 3 Week 36 interim analysis occurred as specified in the protocol and statistical analysis plan (SAP), Version 2. [REDACTED]

After regulatory and institutional review board (IRB)/independent ethics committee (IEC) approval of Protocol Amendment 8, all subjects on DB study drug will sign a revised informed consent form (ICF) and move to the OLE period at their next visit or an earlier, unscheduled visit, subject to study drug availability. At this visit, the assessments scheduled for Week 104 will be conducted. Subjects who are not on study drug will move to safety follow-up visits.

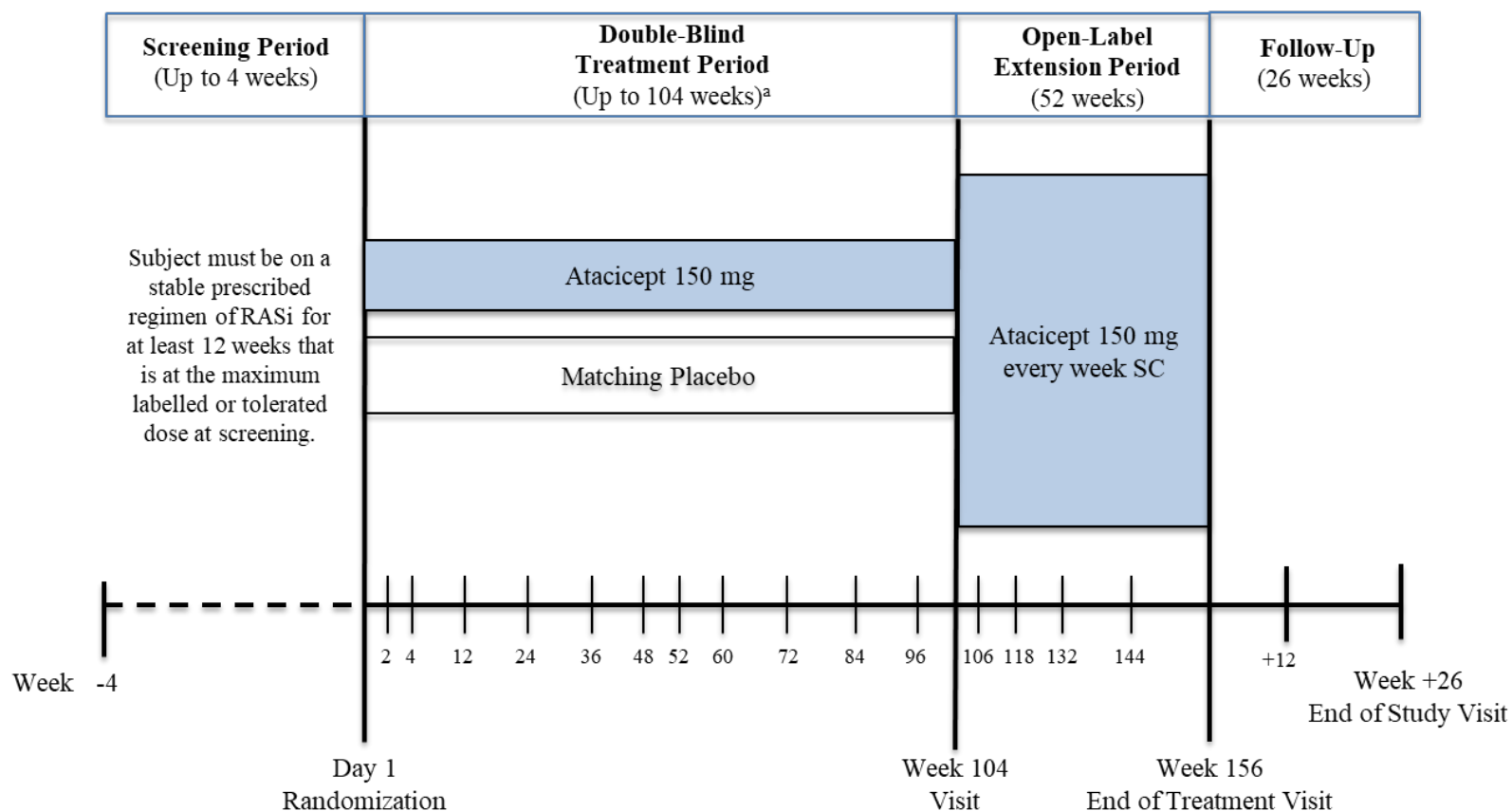
The study will be conducted on an outpatient basis.

Number of Study Sites: Approximately up to 250

Number of Subjects: Approximately 376 randomized

Involvement of Special Committee(s): An independent Data Monitoring Committee (iDMC) will review safety data on an ongoing basis.

Study Schema



DB = double-blind; ICF = informed consent form; IEC = independent ethics committee; IRB = institutional review board; OLE = open-label extension; RASi = renin-angiotensin system inhibitor; SC = subcutaneous

- a After regulatory and IRB/IEC approval of Protocol Amendment 8, all subjects on DB study drug will sign a revised ICF and move to the OLE period at their next visit or an earlier, unscheduled visit, subject to study drug availability. At this visit, the assessments scheduled for Week 104 will be conducted.

Target Population: Male or female patients with IgAN with persistent proteinuria who remain at high risk of disease progression despite being on a stable prescribed regimen of RASi for at least 12 weeks that is at the maximum labeled or tolerated dose.

Duration of Study Drug Treatment: Up to 156 weeks [REDACTED] + 52 weeks OLE)

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments.
2. Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments.
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit.
4. Total urine protein excretion ≥ 1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 1.0 mg/mg based on a 24-hour urine sample during the Screening Period
5. eGFR ≥ 30 mL/min/1.73 m² at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
6. On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1
 - The subject is eligible if they do not tolerate RASi, provided their management of IgAN is standard of care (SoC) per local practice. This intolerance must be documented by the Investigator and discussed with the Medical Monitor.
7. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening
8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

Exclusion Criteria:

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. Participation in the Phase 2b (Parts A and B) study or any previous treatment with atacicept.
2. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis.
3. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
4. Total urine protein excretion $\geq 5\text{g}$ per 24-hour or urine protein to creatinine ratio (UPCR) $\geq 5\text{ mg/mg}$ based on a 24-hour urine sample during the Screening Period
5. Evidence of nephrotic syndrome within 6 months of screening (serum albumin $< 3.0\text{ g/dL}$ in association with UPCR $> 3.5\text{ mg/mg}$)
6. Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants.
7. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
8. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $> 7.5\%$ at screening.
9. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

10. Prohibited medications:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or expected use during the study.
 - For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal, or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic, and intranasal.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 12 weeks prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for >1 week or average dose $> 0.5\text{ mg/kg/day}$ prednisolone or equivalent

- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or expected use during the study.
 - Use of traditional Chinese medications and/or Ayurvedic medications for IgAN within 12 weeks prior to screening, from screening to Day 1, or during the study period
 - Including but not limited to: Lei Gong Teng, Tripterygium Wilfordii Hook F, Caulis sinomenii, and Sinomenium acutum. Any other medications used to treat IgAN that are not listed should be discussed with the Medical Monitor.
 - Use of B-cell-directed biologic therapies including but not limited to belimumab, rituximab, ocrelizumab for any period of time.
 - Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time
 - Use of endothelin receptor antagonists (ERAs) for any period of time
 - Use of complement inhibitors including but not limited to iptacopan for any period of time
11. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:
- serum IgG below 7 g/L
 - aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level $> 2.5 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN.
 - If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
 - hemoglobin < 10 g/100 mL in men and hemoglobin < 9 g/100 mL in women
 - platelets $< 100 \times 10^9/L$
12. Administration of live and live-attenuated vaccinations within 30 days prior to randomization
13. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
14. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
15. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
16. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.

17. History of acute or chronic infection with human immunodeficiency virus, or hepatitis B virus.
 - Positive hepatitis B surface antigen (HBsAg) are excluded
 - Subjects who are HBsAg negative, hepatitis B core antibody (HBcAb) positive, hepatitis B surface antibody (HBsAb) positive, and with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow-up
18. Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
19. History of splenectomy
20. History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).
21. Known hypersensitivity to atacicept or any component of the formulated atacicept
22. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety FU Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull). Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)
23. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
24. Unwillingness or lack of capacity to follow all study procedures
25. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

Study Procedures/Frequency:

Study visits are planned to occur at Screening; Day 1; and Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, 96, and 104 in the DB period of the study.

At this visit, the assessments scheduled for Week 104 will be conducted. Subjects who are not on study drug will move to safety follow-up visits.

Note that for Weeks 4, 48, 84, 106, and 132, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP and home health care (if available). For the Phase 3 study, facilitation of optional remote visit(s) is the responsibility of the Investigator and site staff.

If, in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted at Weeks 1, 3, and 105. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

There will be a 26-week follow-up period after the subject's end of study visit. Subjects discontinuing study medication during the DB period are encouraged to continue with study visits and assessments per protocol through the end of the DB period. If the subject discontinues study drug more than 26 weeks before the end of the DB period, the subject does not need to complete a further 26 weeks of follow-up. If the subject discontinues less than 26 weeks before the end of the DB period, the subject should complete all DB visits and continue into the 26-week safety follow-up period for the appropriate amount of time to ensure 26 weeks of safety follow-up data are collected after the last dose of study drug. Subjects who discontinue during the OLE period will require a 26-week follow-up period.

Assessments to be done at each visit can be found in the Schedule of Assessments ([Table 3](#)).

Test Product, Dose, Mode of Administration, and Reference Therapy:

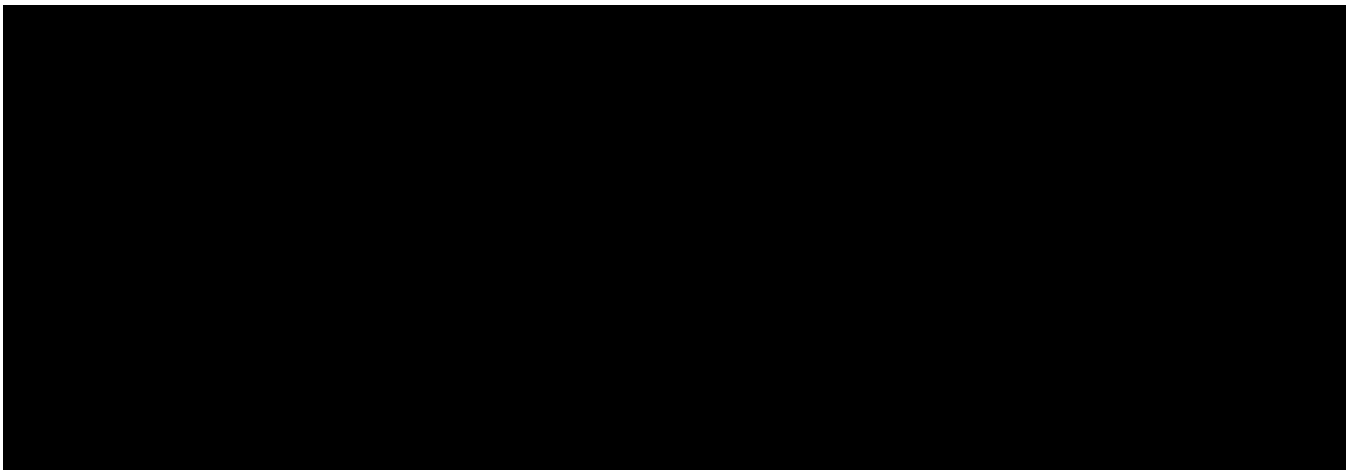
In a blinded fashion, 150 mg atacicept or placebo, given as once-weekly subcutaneous (SC) injections for [REDACTED] by prefilled syringe. For OLE, open-label 150 mg atacicept, given as once-weekly SC injections for 52 weeks by prefilled syringe. It is strongly recommended that changes in RASi medication be avoided for the duration of the double-blind study.

The Sponsor is currently developing an atacicept autoinjector combination (AAIC) product. Contingent upon fulfilment of regional regulatory requirements for switching the device for use in this clinical study, the Sponsor may implement the AAIC in select countries and sites. When available, atacicept 150 mg may be self-administered SC via the AAIC.

Statistical Methods:

This section summarizes analyses of the primary and secondary endpoints for the completed Week 36 interim analysis and [REDACTED]. Analyses of additional measurements collected as part of this protocol will be fully described in the SAP. Any deviations from this plan will be noted in the corresponding clinical study report.

Multiple Testing Hierarchy



Sample size and power calculations

Planned Analyses

The primary analysis of UPCR was performed after the first 203 subjects completed the Week 36 visit or prematurely discontinued from the study.

Analysis Population

All randomized subjects receiving at least one dose of study intervention will be included in the Full Analysis Set (FAS) Population and Safety Analysis Population.

The Interim Analysis Set (IAS) Population consisted of a subset of subjects in the FAS Population who completed or prematurely discontinued from the study, or otherwise had the potential to complete the Week 36 visit at the time of the data cut date for the Week 36 interim analysis. Unless otherwise indicated, the IAS was the primary analysis population for efficacy endpoints in the Week 36 interim analysis. Subjects were analyzed according to randomized treatment.

[REDACTED]

[REDACTED]

Other analysis populations are defined in Section 18.

Primary and key secondary efficacy endpoint analysis

The primary efficacy endpoint is the change from baseline in natural log-transformed UPCR at Week 36, and was analyzed by a mixed-effected model for repeated measures (MMRM) including UPCR data up to Week 36 for the IAS Population. Effects for stratification factors, baseline natural log-transformed UPCR, randomized treatment, visit, and treatment-by-visit interaction were included as fixed effects. The primary comparison tested the mean difference in change from baseline in natural log-transformed UPCR between the atacicept and placebo groups at Week 36. This statistical comparison was based on linear contrasts of the least-squares means estimated by MMRM. Least-squares mean difference was exponentiated to obtain the mean ratio.

[REDACTED]

More details regarding estimand, intercurrent events, and missing data handling are discussed in Section 18.

Other efficacy endpoint analyses

For both the Week 36 and [REDACTED]

[REDACTED]

Continuous efficacy endpoints of change from baseline will be analyzed using a similar MMRM model as for the primary efficacy endpoint of UPCR. A mixed-effects model with random intercept and random slope will be used to analyze the annualized rate of change in eGFR.

Binary efficacy endpoints will be presented as the number and percentage of responders by treatment group. The population-level summary measure is the odds ratio comparing the odds of being a responder in the atacicept vs. placebo group, which will be evaluated by a logistic regression model controlling for stratification factor(s), randomized treatment, and the appropriate baseline value. The odds ratio for the treatment effect, 95% CIs, and p-value will be estimated from the model.

Time-to-event efficacy endpoints will be displayed using Kaplan-Meier methodology. The population level summary measure is the ratio of the hazard rates of the atacicept vs. placebo group for the corresponding endpoint. The population-level study measure will be evaluated using the Cox proportional hazard model with effects for stratification factor(s), randomized treatment, and the appropriate baseline value. Subjects who do not have an endpoint of interest will be censored at the last assessment of the endpoint. The adjusted hazard ratio of the risk of the event between the atacicept and the placebo group, the corresponding 95% CIs, and p-value will be estimated from this model.

Safety endpoint analyses

All safety evaluations will be conducted based on the Safety Analysis Population and the safety data of each treatment group will be summarized by descriptive statistics.

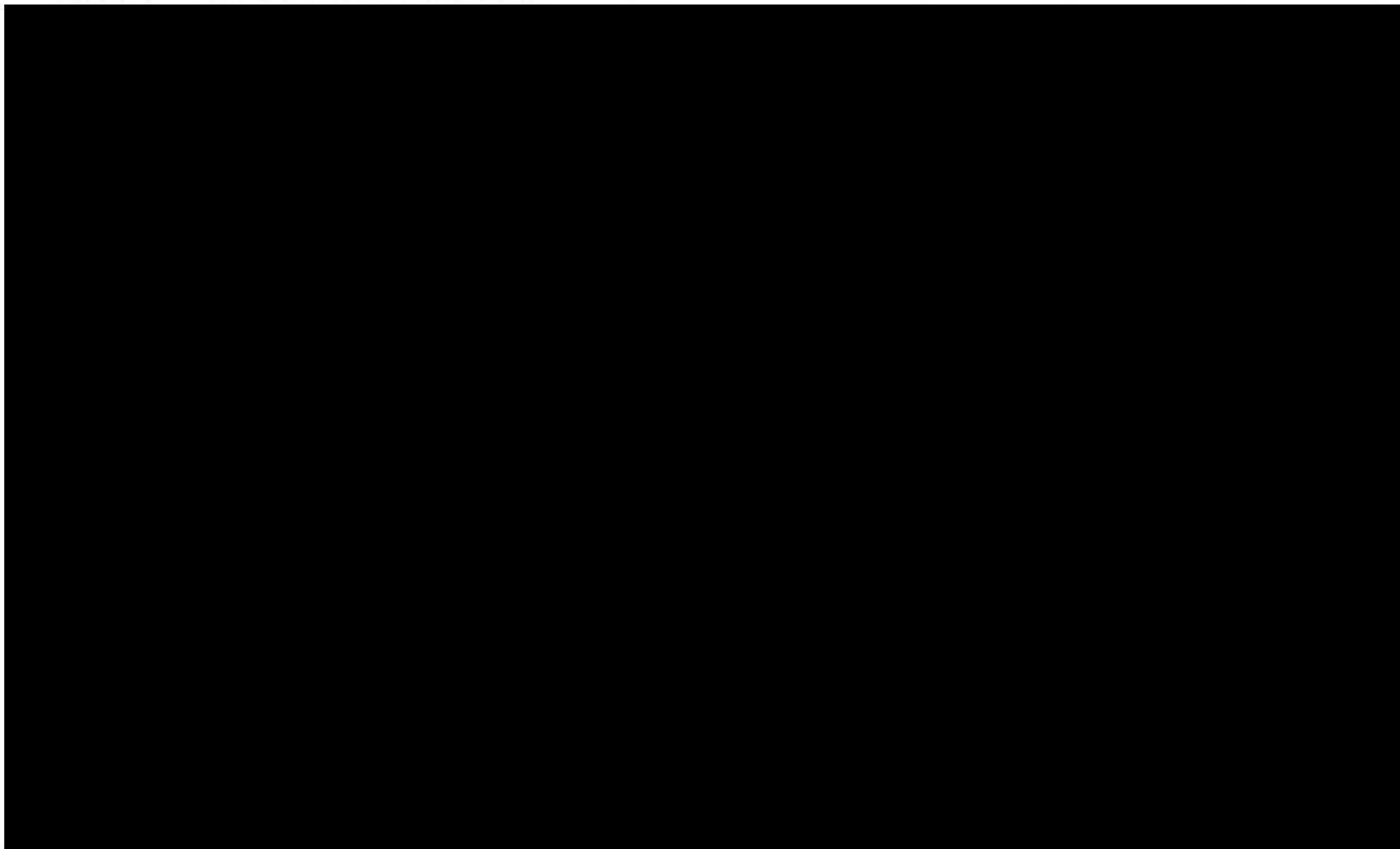
Blinding and unblinding considerations

Subjects will be randomly assigned to a treatment group based on a predefined randomization code via the interactive web response system (IWRS) at the Day 1/Randomization visit. The site staff, Sponsor, and contract research organization (CRO) will be blinded to the subject's treatment allocation, with the exception of the selected study drug supply, iDMC, and serious adverse event (SAE) reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of interim analyses. A data access plan and 2 blinding plans were developed to outline the study-specific approaches to protect the study blind and data integrity. For emergency unblinding only, corresponding treatment assignments will be made available to the Investigator through the IWRS.

Compliance

The study will be conducted in compliance with the protocol, with the Regulation (EU) No 536/2014, and with the guidelines of Good Clinical Practice (GCP).

Table 3: Phase 3: Schedule of Assessments



11. PHASE 3: INTRODUCTION

Atacicept (also known as VT-001) is a novel immunomodulator, administered by subcutaneous (SC) injections, dual-blocking the activity of B-cell activating factor (BAFF, also known as B lymphocyte stimulator) and a proliferation-inducing ligand (APRIL). Inhibition of BAFF and APRIL leads to a decrease in the maturation, differentiation, and effector function of B cells and plasma cells (Dillon 2006, Dillon 2010, Moore 1999, Ramanujam 2004, Schneider 1999). Atacicept is being developed for the treatment of patients with IgA Nephropathy (IgAN).

Complete information on the atacicept nonclinical and clinical program, and summaries of key chemistry, pharmacology, efficacy, and safety data of atacicept are provided in the Investigator's Brochure (IB).

11.1. Background

Immunoglobulin (Ig) A nephropathy (IgAN) or Berger's disease, is the most frequent biopsy-proven primary glomerular disease, but with widely variable geographic distribution (Lai 2016, Schena 2018). The prevalence of IgAN can be difficult to ascertain because of regional variability in screening and renal biopsy practices, however; a 15-year retrospective study of the United States (US) Renal Data System found that of over 84,000 end stage renal disease (ESRD) patients with glomerulonephritis (GN) etiology, around 15% were attributed to IgAN (O'Shaughnessy 2015). The global incidence of primary GN ranges from 2 to 25 per million people (pmp) per year, with a worldwide IgAN incidence of at least 25 pmp per year in adults (McGrogan 2011), and an age adjusted US incidence of approximately 21 pmp per year (Swaminathan 2006). Consistent with differences in incidence based on ethnicity and genetic predisposition, biopsy data from autopsy and donor registries support a higher prevalence of IgAN in East and Pacific Asian countries (Rodrigues 2017), as compared to Southern Europe and Africa (Kiryuk 2012).

Immunoglobulin A nephropathy (IgAN) is highly variable, both clinically and pathologically. The classic presentation of IgAN is visible hematuria following an infection, but, more typically, IgAN presents as asymptomatic non-visible hematuria, with or without proteinuria. Renal impairment and hypertension are often present in subjects with older age at presentation (Barratt 2005). Up to 40% of all subjects with IgAN will progress to ESRD over 30 years (D'Amico 2000). In the US, IgAN accounted for 1.8% (10,557) of all prevalent subjects on dialysis at the end of 2011 (Collins 2014), with 5,044 incident subjects during the 5-year period from 2007 to 2011, or approximately 1000 subjects per year (Collins 2014). The annual incidence of ESRD due to IgAN can be estimated as 0.32/100,000 using the US population estimate from the US Census of 309 million people undertaken in 2010 (Mackun 2010).

A histopathological hallmark of IgAN is accumulation of poorly O-galactosylated IgA1 (Gd-IgA1) in the glomerular mesangium, either alone or in combination with IgG and/or IgM (Wyatt 2013). Sampling of the serum and plasma of subjects with IgAN has confirmed the presence of elevated levels of IgA containing immune complexes containing Gd-IgA1 (Czerkinsky 1986). Circulating Gd-IgA1 containing immune complexes were later shown to be the target antigens for IgG antibodies with specificity for the O-glycans of the IgA1 hinge region (Suzuki 2009). Hence, IgAN is a unique autoimmune disease whereby the pathogenesis is driven by an autoantigen (Gd-IgA1) eliciting an autoantibody (IgG anti-glycan) response.

11.1.1. Medical Need in IgA Nephropathy

The level of 24-hour protein excretion is a risk indicator for morbidity and mortality in patients with renal disease. Patients with IgAN with persistent proteinuria > 1 g/day are at increased risk of progression to ESRD ($> 60\%$ over 20 years) (Berthoux 2011, Lee 2012, Moriyama 2014, Reich 2007). They are also at increased risk of cardiovascular mortality; up to 50% experience a cardiovascular event prior to reaching ESRD and their mortality risk is 43% higher compared with age/sex-matched controls in the general public (Lee 2012). By contrast, subjects with IgAN with proteinuria < 1 g/day have mortality rates similar to those of the general public.

Furthermore, in the STOP-IgAN study which recruited IgAN patients with proteinuria (urine protein to creatinine ratio [UPCR] ≥ 0.75 mg/mg), $> 50\%$ of patients progressed to death, ESRD, or eGFR decline of over 40% after 7.4 years, and use of immunosuppression, including corticosteroids, made no difference to outcome (Rauen 2020).

Since first being described in 1968, there have been limited advances in the treatment for IgAN. The central component of supportive care consists of appropriate blood pressure (BP) control and proteinuria management using Angiotensin Converting Enzyme Inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis (KDIGO 2012). The use of renin-angiotensin-aldosterone system inhibitor (RAASi) has been shown in randomized controlled studies to decrease proteinuria and correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day (Descamps-Latscha 2004).

Other treatments, such as corticosteroids (CS) and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is cautiously suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate blood pressure control and treatment with ACEis (KDIGO 2012), a recent review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist particularly in light of the prematurely halted TESTING study (Lv 2012, Lv 2017).

There is a significant unmet medical need for the treatment of IgAN, as there are currently no therapies proven effective in large randomized controlled trials. Current management includes BP control, renin-angiotensin system (RAS) blockade (with ACEi/ARB) and in rare instances combination immunosuppression with cyclophosphamide and corticosteroids for rapidly progressive IgAN (KDIGO 2012). In Japan, tonsillectomy is sometimes performed (Liu 2015). There are insufficient data supporting the use of most of the above listed therapies for IgAN, with the exception of RASi. Reviews of randomized controlled trials suggest benefit from RAS blockade in reducing proteinuria and improving renal outcomes, but it is unclear whether this latter outcome is beyond the benefit expected from the control of hypertension alone (Cheng 2009, Hotta 2013, Reid 2011). The benefits of corticosteroid therapy and tonsillectomy for IgAN remain unclear (Lv 2012, Zhou 2011). The IgAN therapies granted conditional approval still have concerns regarding safety. Development of medicines that can affect the pathophysiology of disease by reducing immune complexes may potentially offer long term clinical benefit.

Thus, available treatments for IgAN are currently inadequate. Given that outcomes in subjects with IgAN remain poor, particularly with respect to development of ESRD and overall mortality, IgAN cannot be considered an indolent disease and better treatments are required.

11.2. Scientific Rationale for Study Design

This Phase 3 study will evaluate the efficacy and safety of the planned commercial dose of atacicept (150 mg) compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria despite being on a maximally tolerated dose (MTD) of a RASi. High risk of progression in IgAN is currently defined as proteinuria > 0.75-1 g/d despite optimized supportive care ([KDIGO 2021](#)).

Atacicept is capable of binding to all known conformations of BAFF and APRIL and is thus expected to inhibit the maturation, differentiation, and effector function of B cells. These mechanisms are consistent with the known pharmacological effects of atacicept, which include depletion of peripheral B cell subsets, naïve follicular, marginal zone and long lived plasma cell B cell subsets, impeded germinal center reaction, and reduced immunoglobulins, while leaving immature B cells and memory B cells intact ([Dillon 2006](#), [Dillon 2010](#), [Gross 2001](#), [Moore 1999](#), [Schneider 1999](#), [Schneider 2005](#)). These effects are predicted to reduce the production and subsequent deposition of Gd-IgA1-containing immune complexes in kidney glomeruli, and thus reduce the extent of kidney injury in IgAN patients.

Atacicept has been studied in a pilot Phase 2a clinical study for IgAN (JANUS; MS700461-0035). The data from this study suggested clinical efficacy based on reduction in proteinuria and Gd IgA1, and stable estimated glomerular filtration rate (eGFR), which warranted further study of atacicept in this population. Further evaluation of atacicept was performed through a dose ranging Phase 2b study for IgAN (ORIGIN; VT-001-0050). Results from this positive study showed a statistically significant difference in reduction of proteinuria with atacicept 150 mg compared with placebo at 24 weeks (see Section 11.3). Estimated GFR (eGFR) stabilization and reduction in galactose-deficient IgA1 (Gd-IgA1) were also seen in subjects on atacicept 150 mg while eGFR declined and Gd-IgA1 remained stable with placebo. Based on the available clinical data, the targeted population for this Phase 3 study is subjects with IgAN with persistent proteinuria who remain at high risk of disease progression despite being on a stable and maximal supportive care regimen. The objectives of the study will be to determine the effect of atacicept versus placebo on proteinuria and preservation of renal function in subjects with IgAN.

Use of ACEis and ARBs:

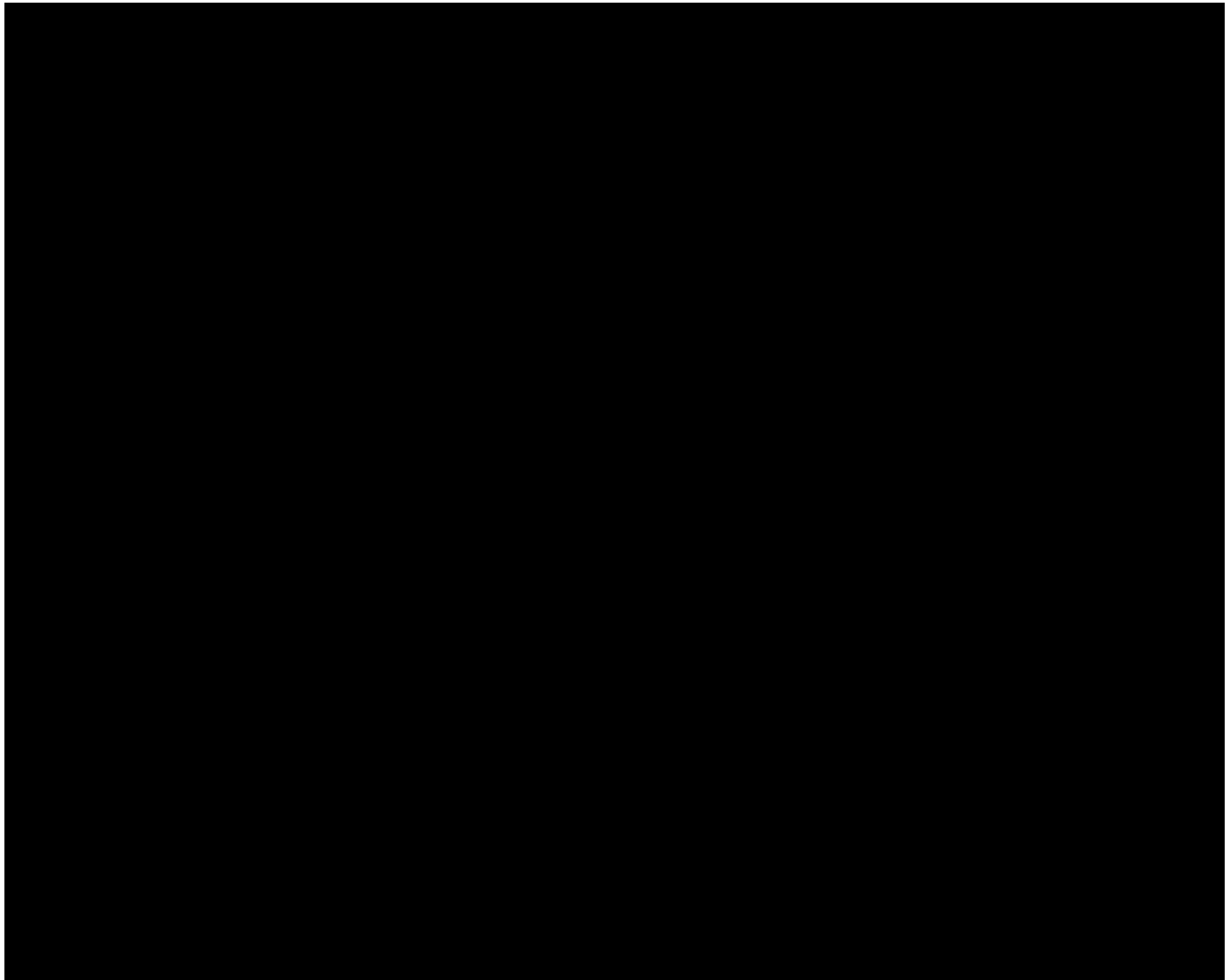
The central component of supportive care in IgAN consists of appropriate BP control and proteinuria management using RASi as outlined in the KDIGO Clinical Practice Guideline for Glomerulonephritis ([KDIGO 2021](#)). The use of ACEis has been shown in randomized controlled studies to decrease proteinuria, and this correlates with improved renal survival, particularly in subjects with proteinuria > 1 g/day ([Descamps-Latscha 2004](#)). Therefore, in this study, subjects at the Screening Visit will be required to be on a stable prescribed regimen of RASi for at least 12 weeks that is at the maximum labeled or tolerated dose (as determined by the Investigator), according to standard of care (SoC). Stable SoC background of RASi medication is likely to decrease potential confounding of the study results and may help to better capture the effect of atacicept in this population. Therefore, subjects in all treatment groups will receive optimized, unchanged RASi therapy 12 weeks prior to screening and throughout the duration of the study, thus providing a stable background SoC during this trial. Subjects who are unable to tolerate either RASi medication may be eligible for participation in the study provided their management of IgAN is SoC according to local practice and intolerance of RASi is documented by the investigator and discussed with the Medical Monitor.

Use of Placebo:

Subjects in atacicept and placebo groups will continue to receive stable background SoC during this trial. Other treatments, such as CS and immunosuppressants, have not been shown to definitively improve renal outcomes (Floege 2011). Although a short course of CS is suggested for subjects with preserved kidney function who have persistent proteinuria despite adequate BP control and treatment with ACEis (KDIGO 2012), a review of published clinical trials suggests that CS may only improve renal survival in selected situations, and questions about safety persist (Lv 2012, Lv 2017). Therefore, in this trial, the inclusion of a placebo group will allow differentiation of the effect of atacicept treatment from the effect of SoC therapy alone, without potential confounding by other immunosuppressant use.

In conclusion, based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

11.3. Justification for Dose Selection



11.4. Risk Benefit Assessment

The Phase 2b ORIGIN and Phase 2a JANUS IgAN studies support that the safety data available for atacicept in patients with IgAN are well-tolerated and consistent with those reported in an integrated safety analysis of atacicept in randomized, DB, placebo-controlled clinical trials ([Gordon 2019](#)). The UPCR, eGFR, and Gd-IgA1 data from the ORIGIN trial support further evaluation in IgAN patients with atacicept 150 mg, a dose regimen which has also been shown to be promising regarding efficacy and an acceptable safety profile for the SLE HDA subpopulation ([Isenberg 2015](#), [Merrill 2018](#), [Morand 2020](#)). The risk benefit assessment remains positive for atacicept in IgAN patients.

COVID Pandemic Risk/Benefit

Atacicept is an immune-modulator which may impact a patient's innate immune response to infection. In a patient receiving an immune-modulator, there may be a potential for limited or compromised immune response leading to more severe/serious complications of the SARS CoV 2 infection. However, in an integrated safety analysis ([Gordon 2019](#)) of over 1500 patients in previous atacicept clinical studies, serious infection rates were similar for atacicept and placebo. In addition, in the ADDRESS II study of SLE patients treated with atacicept 150 mg and 75 mg, titer status for both tetanus toxoid and diphtheria vaccinations remained protective from Day 1 to Week 72 ([Wallace 2021](#)). Finally, the Week 36 results from the Phase 2b (ORIGIN) study support that number of subjects with COVID-19 AEs was not disproportionate between arms (atacicept 26%, 21 subjects; placebo 18%, 6 subjects). Risk mitigation includes excluding patients with active infection from study participation and recommendation to have up-to-date vaccinations as per local guidelines within 30 days of screening and to remain up to date with all non-live vaccination as per local guidelines during the study. Live and live-attenuated vaccines are not permitted during the study. In the setting of a pandemic or epidemic, the Investigator should evaluate the best option of care for the patient including the screening for active infections prior to and during study participation according to the protocol, should this study be considered as an option.

IgAN patients continue to have too few approved therapies with a high unmet need given the risk for progression to end stage renal disease. Atacicept has promising potential to have clinical benefit for IgAN patients, while being supported with an acceptable safety profile.

12. PHASE 3: OBJECTIVES AND ENDPOINTS

The objectives, endpoints, and endpoint timelines are defined in the table below.

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Primary		
Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN	Natural log-transformed UPCR ^a	Week 36
Key Secondary		
Evaluate the effect of atacicept compared to placebo on change from baseline in eGFR	Change from baseline in eGFR ^b	
Secondary		
Evaluate the effect of atacicept compared to placebo on annualized rate of change in eGFR	Annualized rate of change in eGFR ^b (i.e., annualized eGFR total slope)	
Evaluate the effect of atacicept compared to placebo on change in proteinuria	Natural log-transformed UPCR ^a	
Evaluate the effect of atacicept compared to placebo on change in Gd-IgA1	Natural log-transformed Gd-IgA1	
Evaluate the effect of atacicept compared to placebo on achieving hematuria resolution	Hematuria resolution	

Objectives	Endpoints (Outcome Measures)	Timeframe of Evaluation
Evaluate the effect of atacicept compared to placebo on time from first dose to the first occurrence of a sustained $\geq 30\%$ decline in eGFR	Time from first dose to the first occurrence of a $\geq 30\%$ decrease from baseline in eGFR that is sustained for a minimum of 30 days	
Evaluate the effect of atacicept compared to placebo on time from first dose to the first occurrence of composite kidney disease progression event	Time to composite kidney disease progression event defined as experiencing at least one of the following during the study: <ul style="list-style-type: none">• At least a 30% reduction in eGFR sustained for at least 30 days• eGFR < 15 mL/min/1.73m², sustained for at least 30 days• Chronic dialysis ≥ 30 days• Kidney transplantation• Death	
Exploratory		

Safety

Evaluate the safety and tolerability of atacicept	Routine clinical and laboratory tests, AEs, serum trough PK, and ADAs	During the DB period
---	---	----------------------

ADA = anti-drug antibodies; AE = adverse event; DB = double-blind; eGFR = estimated glomerular filtration rate;

Gd-IgA1 = galactose-deficient IgA1;

IgAN = immunoglobulin A nephropathy; PK = pharmacokinetics;

UPCR = urine protein to creatinine ratio.

a Based on 24-hour urine sample.

b eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for adults.

13. STUDY DESIGN

13.1. Overall Design

This Phase 3 study is a multicenter, randomized, DB, placebo-controlled study.

The target study population includes male or female subjects with IgAN who continue to have persistent proteinuria and remain at high risk of disease progression despite being on a stable prescribed regimen for at least 12 weeks with a RASi that is at the maximum labeled or tolerated dose. The use of SGLT2 Inhibitors could impact the evaluation of clinical efficacy of the IMP. The sponsor may cap the enrollment of these subjects.

Approximately 376 subjects will be randomized 1:1 to atacicept 150 mg or placebo:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly subcutaneous (SC) injections (N=188)

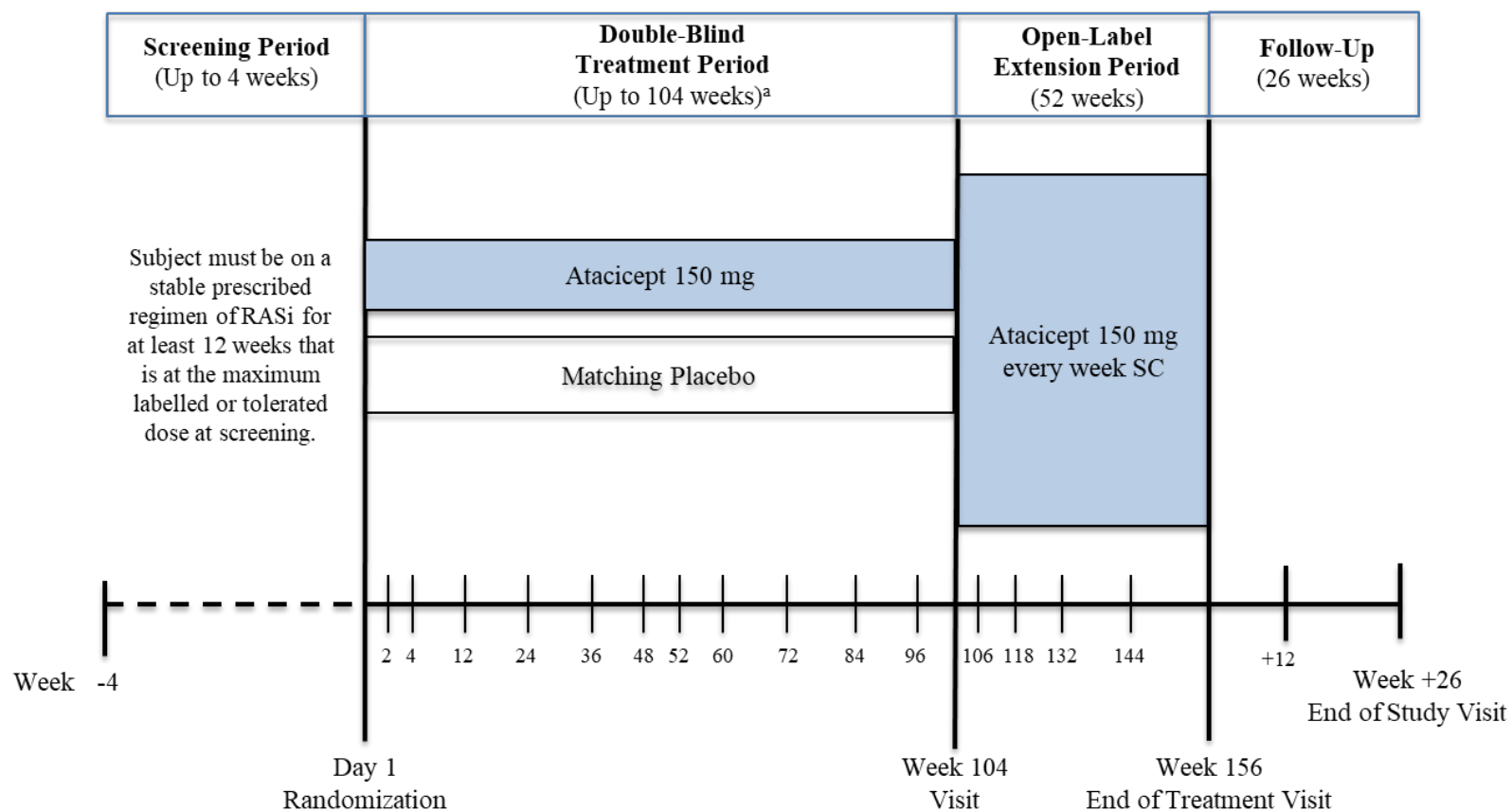
The Phase 3 study is composed of a (up to) 4-week Screening Period, [REDACTED] a 52-week Open-Label Extension (OLE) (Part D), and a 26-week follow-up. Subjects who complete the DB period on treatment will be eligible for open-label atacicept 150 mg for an additional 52 weeks (OLE). Subjects who prematurely discontinue study drug prior to completion of the DB period should continue with study visits and assessments per protocol through the end of the DB period. After completion of the study, all patients will have a 26-week follow-up period except if the subject discontinued study drug more than 26 weeks before the end of the DB period.

The ORIGIN 3 Week 36 interim analysis occurred as specified in the protocol and statistical analysis plan (SAP), Version 2. [REDACTED]

After regulatory and institutional review board (IRB)/independent ethics committee (IEC) approval of Protocol Amendment 8, all subjects on DB study drug will sign a revised informed consent form (ICF) and move to the OLE period at their next visit or an earlier, unscheduled visit, subject to study drug availability. At this visit, the assessments scheduled for Week 104 will be conducted. Subjects who are not on study drug will move to safety follow-up visits.

The study will be conducted on an outpatient basis.

Subjects who participated in the Phase 2b portion may not participate in the Phase 3 portion of the study.

Figure 3: Phase 3: Study Schema

DB = double-blind; ICF = informed consent form; IEC = independent ethics committee; IRB = institutional review board; OLE = open-label extension; RASi = renin-angiotensin system inhibitor; SC = subcutaneous

- a After regulatory and IRB/IEC approval of Protocol Amendment 8, all subjects on DB study drug will sign a revised ICF and move to the OLE period at their next visit or an earlier, unscheduled visit, subject to study drug availability. At this visit, the assessments scheduled for Week 104 will be conducted.

13.2. End of Study Definition

A subject has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in the Schedule of Assessments ([Table 3](#)).

The end of the study is defined as the date of last contact with the last subject who participates in the study (i.e., last subject's last visit); see Section [19.4](#) for details on study and site closures.

13.3. Independent Data Monitoring Committee

An independent data monitoring committee (iDMC) will monitor the safety and welfare of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority on all aspects. Details regarding the role, responsibilities and data review requirements of the iDMC will be outlined in a separate iDMC charter.

14. PHASE 3: STUDY POPULATION

The eligibility criteria in Sections [14.1](#) (Inclusion Criteria) and [14.2](#) (Exclusion Criteria) are designed to enroll only subjects who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a subject is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the subject's routine medical care, the Investigator will confirm that the subject has provided written informed consent, as indicated in Section [19.1.3](#).

Subject eligibility (based on Screening Visit assessments of the inclusion and exclusion criteria) must be reviewed again by the Investigator on Day 1 prior to randomization. Once a subject meets eligibility requirements, the subjects will be randomized to treatment with atacicept or placebo through a central randomization process. The interactive web response system (IWRS) will be used to randomize a subject to study drug assignment.

14.1. Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study assessments
2. Adult male or female of ≥ 18 years of age, or as per country specific legally or nationally recognized adult age, who provide written informed consent prior to performing any study assessments
3. Diagnosis of IgAN as demonstrated by renal biopsy conducted within 10 years of the Screening Visit.

4. Total urine protein excretion ≥ 1.0 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 1.0 mg/mg based on a 24-hour urine sample during the Screening Period
5. eGFR ≥ 30 mL/min/1.73 m² at screening, as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
6. On a stable prescribed regimen of RASi (ACEi or ARB) for at least 12 weeks that is at the maximum labeled or tolerated dose at screening and from screening to study Day 1.
 - The subject is eligible if they do not tolerate RASi, provided their management of IgAN is standard of care (SoC) per local practice. This intolerance must be documented by the Investigator and discussed with the Medical Monitor.
7. Systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg at screening
8. A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period, a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1), not breastfeeding (for at least 3 months prior to screening), and at least one of the following conditions applies:
 - Is not a woman of childbearing potential (WOCBP), as defined in [Appendix 2](#).OR
 - Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in [Appendix 2](#), at least 7 days prior to randomization, through 175 days after the last dose of study drug. See [Appendix 2](#) for further details.

14.2. Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria at the Screening Visit or during the Screening Period:

1. Participation in the Phase 2b (Parts A and B) study or any previous treatment with atacicept
2. IgAN secondary to another condition (e.g., liver cirrhosis), or other causes of mesangial IgA deposition including IgA vasculitis (i.e., Henoch-Schonlein purpura), systemic lupus erythematosus (SLE), dermatitis herpetiformis, ankylosing spondylitis
3. Evidence of rapidly progressive glomerulonephritis (loss of $\geq 50\%$ of eGFR within 3 months of screening)
4. Total urine protein excretion ≥ 5 g per 24-hour or urine protein to creatinine ratio (UPCR) ≥ 5 mg/mg based on a 24-hour urine sample during the Screening Period
5. Evidence of nephrotic syndrome within 6 months of screening (serum albumin < 3.0 g/dL in association with UPCR > 3.5 mg/mg)
6. Renal or other organ transplantation prior to, or expected during, the study, with the exception of corneal transplants
7. Concomitant chronic renal disease in addition to IgAN (e.g., diabetic nephropathy, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, C3 glomerulopathy, lupus nephritis)
8. Uncontrolled diabetes, defined as hemoglobin-A1c (HbA1c) $> 7.5\%$ at screening

9. History of tuberculosis (TB), untreated latent TB infection (LTBI), or evidence of active TB determined by a positive Quantiferon test at the Screening Visit.

If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to the Screening Visit without evidence of re-exposure to be eligible for this study. If on LTBI treatment at the Screening Visit, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.

- Subjects with current household contacts with active TB will be excluded unless prophylaxis treatment has been completed, and evidence that household contacts have completed treatment is provided.
- Indeterminate Quantiferon tests may be repeated once by the same test and will be considered positive if retest results are positive or indeterminate.

10. Prohibited medications:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or expected use during the study.
- For glucocorticosteroids (GCS), “Systemic” is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic, and intranasal. For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
 - Within 12 weeks prior to randomization: Use of systemic corticosteroids or immunosuppressive medications for >1 week or average dose >0.5 mg/kg/day prednisolone or equivalent
- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or expected use during the study.
- Use of traditional Chinese medications and/or Ayurvedic medications for IgAN within 12 weeks prior to screening, from screening to Day 1, or during the study period.
 - Including but not limited to: Lei Gong Teng, Tripterygium Wilfordii Hook F, Caulis sinomenii, and Sinomenium acutum. Any other medications used to treat IgAN that are not listed should be discussed with the Medical Monitor.
- Use of B-cell-directed biologic therapies including but not limited to belimumab, rituximab, ocrelizumab for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time
- Use of endothelin receptor antagonists (ERAs) for any period of time
- Use of complement inhibitors including but not limited to iptacopan for any period of time

11. Clinically significant or predefined abnormalities per central laboratory tests, at the Screening Visit, meeting any of the criteria below:

- serum IgG below 7 g/L

- aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level $> 2.5 \times$ upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ ULN.
 - If subject has a known history of Gilberts (history of isolated increase in total bilirubin without increase in liver transaminases), contact the Medical Monitor for further discussion.
 - hemoglobin < 10 g/100 mL in men and hemoglobin < 9 g/100 mL in women
 - platelets $< 100 \times 10^9/L$
12. Administration of live and live-attenuated vaccinations within 30 days prior to randomization
 13. History or current diagnosis of any demyelinating disease such as, but not restricted to, multiple sclerosis (MS) or optic neuritis (ON)
 14. Patients with history of unstable angina, Class III and IV congestive heart failure and/or clinically significant arrhythmia, as judged by the Investigator.
 15. Any condition, including any uncontrolled disease state other than IgAN, that in the opinion of the Investigator or the Sponsor/designee constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation
 16. Active clinically significant viral, bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks prior to, or during the Screening Visit, or completion of oral anti-infectives within 2 weeks prior to, or during the Screening Visit or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled are not exclusionary.
 17. History of acute or chronic infection with human immunodeficiency virus, or hepatitis B virus.
 - Subjects with positive hepatitis B surface antigen (HbsAg) are excluded
 - Subjects who are HbsAg negative, hepatitis B core antibody (HbcAb) positive, hepatitis B surface antibody (HbsAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring through safety follow up
 18. Subjects with positive hepatitis C (HCV) RNA are excluded, however, subjects who are HCV antibody positive with no detectable HCV RNA at least 24 weeks after completion of antiviral therapy are eligible.
 19. History of splenectomy
 20. History of malignancy (hematologic or solid tumor) within 5 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix.
 21. Known hypersensitivity to atacicept or any component of the formulated atacicept
 22. Major surgery within 6 weeks prior to the Screening Visit or planned/expected major surgery during the study period (including the Safety Follow-up Period)
 - Major surgery often involves opening one of the major body cavities (abdomen, chest, and skull). Types of surgery that have the highest risk include heart or lung, liver, abdomen, or major operations on the bones and joints (for example, hip replacement)

23. Clinically significant history of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion
24. Unwillingness or lack of capacity to follow all study procedures
25. Treatment with other investigational agents within the last 4 weeks or 5 half-lives, whichever is longer, prior to the Screening Visit.

14.3. Screen Failures

Repeat testing: Aside from the TB testing as delineated above, tests that do not meet the above inclusion/exclusion criteria may be repeated once within the 28-day Screening Period if the results are thought to represent a laboratory error or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values. If eligibility criteria are not met at the end of the 28-day Screening Period, the subject should be considered a screen failure.

Re-Screening: Subjects who do not meet the above eligibility criteria (in Sections 14.1 and 14.2) within the screening period and screen fail may undergo re-screening upon approval by the Medical Monitor. If the subject is re-screened, then the subject will receive a new subject identification number (Subject ID). The second screening is a new 28-day screening episode.

15. PHASE 3: INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational Medicinal Product (IMP) or study drug is atacicept or placebo intended to be administered to a study subject per the study protocol.

15.1. Randomization, Blinding, and Measures to Minimize Bias

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessments (Table 3).

Before the study is initiated, the login information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study drug administration for each subject.

15.1.1. Blinding of Investigational Medicinal Product

This study will be double-blinded for all subjects and Investigators through Part C. Investigational Medicinal Product (IMP) packaging and labeling will be prepared to protect the blinded nature of the study. Study drugs will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part D of the study will be conducted in an open-label fashion.

15.1.2. Procedures for Breaking the Treatment Codes

If, at any time during Part C of this study, any site personnel are unblinded to the treatment code for any reason, the circumstances and reason must be documented. The Sponsor and clinical research organization (CRO) study staff will be blinded to the study group assignment with the exception of the selected study drug supply vendor, iDMC (if applicable) and SAE reporting contact personnel. A separate cross-functional team, independent from the study management team, will be unblinded at the time of analysis of the primary endpoint. A blinding plan will be developed to outline the study-specific approaches to protect the study blind and data integrity.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study drug discontinued.

In a medical emergency, the Investigator is solely responsible for determining if unblinding of a subject's study drug assignment is warranted. Subject safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted in cases of suspected serious infection or where breaking the blind is required to provide medical care, the Investigator should contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study drug, except to the designated drug safety representative, as appropriate. The date of and reason for unblinding must be recorded in the source documents and electronic case report form (eCRF). Contact information for unblinding in an emergency is given on the subject emergency card provided to each subject, as noted in Section 19.2.2 (Emergency Medical Support).

The Sponsor (or delegate) will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

In the case of emergency unblinding, the subject must be discontinued from the study drug and complete all assessments and procedures specified for the Early Treatment Discontinuation Visit and should remain in the study and continue the study visits through the end of the DB period.

Causality assessments if emergency unblinding is for an AE/SAE should be documented for the AE/SAE prior to unblinding. Further details on expedited reporting and SAEs are in Section 17.

15.1.3. Other Blinding Parameters

Laboratory results:

After Day 1, certain laboratory results can reveal the PD effects of atacicept. These laboratory/analyte results (serum Gd-IgA1, IgG, IgA, IgM, APRIL, and BAFF) that could be indicative of treatment allocation will not be reported to investigative sites or other blinded personnel.

Lymphocyte counts as assessed by routine, complete blood counts will not be blinded; these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5% to 20%).

Independent Data Monitoring Committee (iDMC):

The iDMC will review available safety data in a blinded manner with the capability to review unblinded data in case of a safety concern. See Section 13.3 for further information on the iDMC.

Unblinding Clinical Studies for Sample Analysis of Special Data:

Bioanalysis and PK scientists may be unblinded to study treatment information in order to perform sample analysis and preliminary PK and PK /PD analysis activities. Anyone who will be unblinded prior to database lock will be named with clear instruction on how to ensure the integrity of the clinical study.

15.2. Investigational Medicinal Product(s)

The atacicept protein is a soluble glycoprotein containing [REDACTED], resulting from the fusion of human IgG1-Fc and the extracellular domain of the BAFF and APRIL receptor TACI (Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor), with a predicted mass of [REDACTED] kilodaltons. [REDACTED]

[REDACTED]

[REDACTED]

15.2.1. Formulation

Atacicept is the active ingredient in the drug product. [REDACTED]

[REDACTED]

15.3. Packaging and Labeling

The drug product/placebo is manufactured, packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released under Good Manufacturing Practice conditions. [REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED] the labeling configuration of the pre-filled syringes results in the active and placebo being identical in appearance. Full re-traceability is provided from the unique medication number on the labels together with the packaging documentation, according to the current Good Manufacturing Practice guidelines.

15.4. IMP Administration

Study drug dosing is a single injection of 1.0 mL, once weekly from Day 1 to up to Week 156, subcutaneous (SC) administration by pre-filled syringe or AAIC. Subjects will contact the Investigator any time they have any injection administration product complaint.

Participants or family members/caregivers who receive appropriate training will be permitted to administer medication in this study and will be trained at the investigational site on the appropriate use of the pre-filled syringe or AAIC and storage of the IMP. The initial training will occur on the day of randomization and as required. The first injection will be performed under supervision. Subcutaneous injection site location data will be collected and made available for analysis. The Day 1 visit should be performed no later than 3 days after randomization. For the injection on Day 1 and Week 104, pulse and BP will be recorded before the dosing and will be recorded as clinically indicated. The study staff monitor for injection site reactions (ISRs) (local tolerability) (see Section 16.6.5).

It is recommended that the weekly dose of IMP be taken on the same day of the week as the original dose. For missed dose(s) of study drug, subjects should be instructed to take the missed dose(s) as soon as possible. If necessary, a dose can be given ± 3 days from the scheduled dose day as long as there is an interval of at least 4 days from the previous injection, with subsequent doses resumed to be taken on the original day of the week.

At the Week 104 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 104 will be the first OLE dose.

When the AAIC is available in select countries, subjects will switch from PFS to AAIC. When switching, the subject should return to the site at a scheduled study visit to receive training on the proper technique of self-administration using the AAIC. The study staff will demonstrate the technique by administering the allocated study drug to the subject and will monitor for ISRs as per the Pharmacy Manual.

15.5. IMP Preparation, Handling, Storage, and Accountability

All study drug (atacicept and placebo) is provided in prefilled single-use syringe or AAIC to the site via cooled transport. No additional preparation will be required at the site.

Storage

All study drug supplied to each site must be stored in their original containers carefully, safely, and temperature controlled. The storage facility at the study site must be locked and accessible only to authorized site personnel. The study drug must be stored under refrigeration at 2°C to

8°C (36°F to 46°F) and protected from light. The study drug temperature will be monitored and documented per the site's standard process for refrigerated medication. Atacicept and placebo must NOT be frozen.

To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the study drug back home and instructed not to leave their medicine unattended or in a place that might get too hot, e.g., inside a car, or exposed to light. Subjects should have access to refrigeration to store the study drug.

Dispensation

Site staff will dispense kits as per the kit number assigned by IWRS. At randomization, drug should be administered no later than 3 days after a subject is randomized.

During the study, if needed, an extra drug kit may be provided in order to allow subjects to have back up study drug in the event a syringe is left out for over 60 minutes, or a visit is conducted late in the visit window.

Handling

Each study drug syringe or AAIC should be removed from the refrigerator and kept at room temperature per the Pharmacy Manual (e.g., for at least 30 minutes) prior to SC injection. The product should not be left out at room temperature for more than 60 minutes. Additional details on the instructions for handling and storage will be provided to subjects as required for home injection.

Accountability

Information on the time of each dose will be recorded by the subject or by the study staff and collected in the eDC system. At visits where new drug kits are dispensed, subjects should return all cartons and any unused syringes.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study drug(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Only subjects enrolled in the study may receive study drug(s) and only authorized site staff may supply it.
- Study drug(s) accountability records at the study site will include the following:
 - Confirmation of receipt, in good condition and in the defined temperature range
 - The number of dose(s) each subject used during the study
 - The disposition (including return, if applicable) of any unused study drug(s)
 - Dates, quantities, study drug number, expiry dates, and the subject numbers
- The Investigator site will maintain records which adequately document that subjects were provided the doses specified in this protocol and all study drug(s) provided were fully reconciled
- Unused study drug(s) must not be discarded or used for any purpose other than the present study. No study drug that is dispensed to a subject may be re-dispensed to a different subject.

- A Study Monitor will periodically collect the study drug(s) accountability forms
 - Further guidance and information for the final disposition of unused study drug(s) are provided in the Pharmacy Manual.
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

15.6. Study Drug Compliance

The study drug will be administered by the subject under supervision as defined in the Schedule of Assessments. All other dosing will be done by the subject, subject's caregiver, or home health nurse (if available) at home throughout the rest of the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient study drug for at-home dosing until the next scheduled visit. Subjects will be provided with an Injection Diary to enter information regarding administration of each dose.

Compliance will be determined based on the Injection Diary entries. Acceptable compliance for the study is defined as 80%-100% (inclusive) of study drug compliance based on drug accountability calculated for the blinded period and open-label extension period. If dosing is interrupted for any reason, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures.

Consequences of noncompliance will lead to retraining and/or discontinuation of study drug as described in Section 16.10.1. In case of overdose see Section 17.9.

15.7. Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines) used from the time the subject signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, date(s) administered, and dosing information (as applicable).

Contact the Medical Monitor for any questions on concomitant or prior therapy.

15.7.1. Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study drug may be given at the Investigator's discretion.

Permitted medications are any medications that are required by the subject during the course of the study and which are not specifically prohibited by the protocol (see Section 15.7.2). Any such medications prescribed or used should be recorded in the eCRF.

Use of RASi and anti-hypertensive medications

To be eligible for randomization, all subjects who tolerate RASi (ACEi or ARB) medication are required to be on stable RASi treatment for at least 12 weeks prior to Screening that is at the maximum labeled or tolerated dose, which must be maintained through the screening period to Day 1. For subjects who are unable to tolerate RASi medication, management of IgAN will be SoC according to local practice. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes and changes in type of RASi medication; every effort should be made to maintain subjects on their stable RASi dose, unless required for safety reasons. In the case of ACEi specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non-RASi medications should have been considered before these specific drug classes. In certain instances (i.e., hyperkalemia), it will be in the best interest of the subject to have their RASi medication adjusted and in such cases Investigators should follow the principles of ICH GCP [see Guideline for Good Clinical Practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)].

All other antihypertensive medications, including diuretics, calcium channel blockers and β blockers, can be used at any timepoint during the study per the Investigator and following current guidelines.

Use of SGLT2 inhibitors and mineralocorticoid receptor antagonists

As with RASi medications, subjects prescribed SGLT2 inhibitors and/or mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone, eplerenone or finerenone) are required to be on a stable dosing regimen for at least 12 weeks prior to screening and from screening to Day 1. Following randomization, and throughout the double-blind treatment period, it is strongly recommended to avoid dose changes of SGLT2 inhibitors and/or MRAs. Introduction of SGLT2 inhibitors and/or MRAs during the double-blinded phase in subjects not on them previously at randomization is prohibited.

Use of statins and dipyridamoles

Statins and dipyridamoles are permitted, but it is recommended to keep doses stable.

Use of endothelin receptor antagonists

Endothelin receptor antagonists are permitted during the OLE period only.

15.7.1.1. Rescue Medications

Should the Investigator consider that rescue medication for IgAN (systemic steroids including oral budesonide and/or immunosuppressive treatment) be warranted, such treatment can be initiated at the discretion of the Investigator. However, in consideration of current guidelines (KDIGO 2021), subjects should continue to have a proteinuria level greater than 1 g per 24 hours (or the equivalent 1 g/g per UPCR) and any of the following:

- Rapidly progressive non-reversible decline in kidney function [i.e., $\geq 50\%$ decline in GFR over ≤ 3 months] accompanied by $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$; and/or
- Development of nephrotic syndrome (i.e., including edema and both nephrotic range proteinuria [i.e., $> 3.5 \text{ g/day}$] and hypoalbuminemia [albumin $< 3.0 \text{ g/dL}$])

Additionally, in such instances, a kidney biopsy may be considered to confirm underlying pathology to support rescue treatment. If rescue medication is required, it is the Investigator's decision to implement new treatment. In this case, the Medical Monitor must be notified within 48 hours after the initiation rescue therapy, as continued dosing with IMP may, in this circumstance, be discontinued. If possible, it is encouraged that the Medical Monitor be informed prior to initiation of rescue medication. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24-hour UPCR is not possible), prior to the initiation of rescue medication, but this at the Investigator's discretion if feasible.

Investigators are not bound by the opinion of third parties in making medical management decisions for their study subjects. Investigators should follow the principles of ICH GCP [see Guideline for good clinical practice E6 (R2) 2.3 (The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society)]. Information related to determination of a subject's clinical condition that may warrant initiation of rescue therapy or not is provided under Protocol Section 15.7.1.

15.7.2. Prohibited Medicines

The following treatments are not permitted during the study:

- Use of systemic corticosteroids (including oral budesonide) for the treatment of IgAN within 6 months prior to screening, from screening to Day 1 or during the study.
 - For GCS, "Systemic" is defined as oral, rectal or injectable (intravenous or intramuscular) routes of administration. Other routes of administration are allowed, including intra-articular, inhaled, topical, ophthalmic, otic and intranasal.
- Immunosuppressive medications (e.g., MMF, azathioprine, cyclophosphamide, hydroxychloroquine) for the treatment of IgAN within 12 weeks prior to screening, from screening to Day 1 or during the study.
- For non-IgAN indications (e.g., gout flare, exacerbation of asthma, severe rash, etc.):
- Use of systemic GCS is prohibited except for a maximum of 3 periods of 2 weeks duration with the equivalent of 0.5 mg/kg/day prednisolone or less
- Use of traditional Chinese medications or Ayurvedic medications for IgAN within 12 weeks prior to screening, from screening to Day 1 or during the study period.
 - Including but not limited to: Lei Gong Teng, Tripterygium Wilfordii Hook F, Caulis sinomenii, and Sinomenium acutum. Any other medications used to treat IgAN that are not listed should be discussed with the Medical Monitor.
- Use of B-cell directed biologic therapies including belimumab, rituximab, ocrelizumab, and sibeprenlimab, for any period of time
- Use of other biologics (e.g., anti-TNF, abatacept, anti-IL-6) and investigational biologics for any period of time

- Use of endothelin receptor antagonists (ERAs) for any period of time during the DB period. ERAs are permitted during the OLE.
- Use of complement inhibitors including but not limited to iptacopan for any period of time

Note: Intravenous (IV) hydrocortisone is permitted for stress dosing in emergency situations only, e.g., traumatic event requiring hospitalization. If administered, the event should be discussed with the Medical Monitor to ensure IMP does not need to be discontinued.

- Introduction of SGLT2 inhibitors and/or MRAs during the double-blinded phase in subjects not on them previously at randomization is prohibited.

If the Investigator believes that treatment with a medication within the categories described above is required, and the potential benefits outweigh the possible risks, the Medical Monitor must be notified within 48 hours of initiation of treatment, as continued dosing with IMP may, in this circumstance, be discontinued (see Section 16.10.1). If possible, it is encouraged that the Medical Monitor be informed prior to initiation of prohibited medication. If possible, it is encouraged that the subject completes an unscheduled visit to collect eGFR and 24-hour UPCR (or spot UPCR, if 24 hour UPCR is not possible), prior to the initiation of prohibited medication, but this at the Investigator's discretion if feasible.

Refer to the inclusion and exclusion criteria (Sections 14.1 and 14.2) for prohibited medications before and during the study.

15.7.3. Other Interventions

Planned/expected major surgery during the entire study period is exclusionary. Unplanned major surgeries should be discussed in advance with the Medical Monitor with respect to whether the subject may continue on study treatment.

15.7.3.1. Vaccinations

It is recommended that subjects have up-to-date vaccinations, as per local guidelines, within 30 days of screening and during the study. Investigators should review the subject's vaccine status, and ensure they remain up to date with all non-live vaccinations throughout the treatment period as per local guidelines. Live and live-attenuated vaccinations will not be permitted during the study period.

15.8. Special Precautions

- Women of childbearing potential must be willing to use a form of highly effective contraception at least 7 days prior to randomization through 175 days after the last dose of study drug ([Appendix 2](#))
- Male subjects with female partners of childbearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the highly effective methods of contraception as well. ([Appendix 2](#)) Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

- Caution should be exercised when administering atacicept to subjects with underlying conditions that may predispose them to infections (see Section 17.7.2)
- Good hygiene practice should be employed: Subjects should be consistently reminded of the importance of good hygiene practices such as hand washing for their care providers and/or social contacts, especially if they are suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. It is recommended they be vaccinated according to local recommendations for individuals with a chronic disease and/or immunosuppression. They should be advised to promptly report to the Investigator any signs or symptoms suggestive of an infection.

16. PHASE 3: STUDY ASSESSMENTS AND PROCEDURES

The following assessments will be conducted during screening and at selected timepoints specified in the Schedule of Assessments (Table 3). Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the Investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate eCRF. General considerations for study visits include, but are not limited to:

- No protocol waivers or exemptions are allowed
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the subject's routine medical care, the Investigator will obtain written informed consent as specified in Section 19.1.3 (Informed Consent Process). Upon subject's agreement, their primary health care provider should be informed about the subject's enrollment in the study.
- Recommended Order of Procedures:
 - Vital signs should be collected prior to blood draws.
 - [REDACTED]
 - Pharmacokinetic sampling should be collected according to Section 16.7 Laboratory samples must be collected prior to dosing for Day 1 and Week 104 only.
 - All other study assessments should also be performed, according to the Schedule of Assessments (Table 3).
- **Unscheduled visits:** may occur at any time during the study; assessments to be performed according to the Investigator's judgment.

16.1. Screening Period and Confirmation of Eligibility

The subject's eligibility will be assessed at the Screening Visit that will occur up to, at most, 4 weeks (28 days) before the Randomization Visit (Day 1). Demographic data will be collected at screening.

Subjects will arrive at the site and the following procedures will be done to determine the subject's eligibility to participate in the study:

- Obtain written informed consent prior to screening procedures
- The physical examination will be performed at the discretion of the site investigator if deemed necessary as per SoC.
- Review inclusion and exclusion criteria
- Collect demographic data
- Complete medical and disease history
- Document the criteria for IgAN diagnosis for eligibility
- Assess vital signs: seated systolic and diastolic BP, pulse rate, temperature (oral or body – with same method to be used throughout the study), height and weight measurements (see Section 16.6.2 for details)
- Perform standard, single, 12-lead electrocardiogram (ECG) (see Section 16.6.3)
- Complete physical examination as specified in the schedule of events
- Collect blood and fresh clean catch urine samples for routine laboratory tests (see Table 4).

The laboratory tests will include:

- Clinical chemistry and hematology
- HbA1c
- Thyroid stimulating hormone (TSH)
- Follicle stimulating hormone (FSH) for woman only
- Immunoglobulin (IgG)
- Serum virology
- Quantiferon test for TB assessment
- Urinalysis and urine sediment from fresh, clean-catch, mid-stream specimen obtained in the clinic
- Dispense:
 - Two 24-hour urine collection containers (one for Screening and one for the Day 1 Visit)
- Serum pregnancy test (β -hCG) required only for WOCBP. Any woman with a positive pregnancy test will be ineligible for the study. [NOTE: It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 12 months or who are surgically sterile]
- If an archival kidney biopsy (within 10 years of Screening Visit) is unavailable, a pre treatment kidney biopsy is required to confirm subject eligibility but is to be performed at the discretion of the Investigator.

- Safety
 - Record AEs beginning after the informed consent form (ICF) has been signed.
 - Review/record prior and concomitant medications
 - Review/record vaccinations. Administration of a vaccine is acceptable within 30 days of screening or planned during the study.

Subjects who meet the screening criteria and are to be randomized will be given instructions as to the date and time they are due back at the site for Day 1 (randomization/first day of dosing).

Subjects who do not meet the screening criteria can be re-screened upon approval of the Medical Monitor. In specific circumstances, repeat testing of screening testing may be allowed. See Section 14.3 for further details.

16.2. Randomization/First Administration IMP (Day 1)

The following assessments will be conducted on Day 1. All subjects will return to the site in the morning up to at most 4 weeks (28 days) after the Screening Visit. At this visit, subjects or caregivers will be provided with training to properly store and perform self-injection of IMP at home from Week 1 onwards. Retraining can be provided by the site at the Week 2 Visit as required.

These dosing instructions will be reviewed with the subject/caregiver before leaving the site. At each of these visits, site staff will contact the IWRS to obtain appropriate kit numbers and the specified kit will be dispensed.

Predose Assessments

Predose assessments on Day 1 are considered baseline measurements prior to first dose of study drug. The results of all assessments and procedures performed at the Screening Visit will be reviewed to assess the subject's eligibility. All eligible subjects will undergo the following procedures before IMP administration (unless stated otherwise):

- Review inclusion and exclusion criteria
- Record archival kidney biopsy (if obtained)
- Vital signs: BP, pulse rate, temperature (oral or body – with same method to be used throughout the study) (see Section 16.6.2 for details)
- Standard, single, 12-lead ECG (see Section 16.6.3)
- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, urinalysis, and spot urine) (see Table 4)
- Urine:
 - 24 hour collection for UPCR, [REDACTED]

PK (see Section 16.7)

- Blood samples will be collected per schedule of assessments. The exact time and date of the last dose of study drug and of blood sampling should be recorded.
- Anti-drug antibodies (binding and neutralizing)

Other analyses (see Section 16.8)

- Blood samples will be collected to assess serum BAFF and APRIL prior to the first dose of IMP (predose).
- Serum immunoglobulins: IgG, IgA, and IgM
- Serum Gd-IgA1
- Blood and urine samples for storage and future testing

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Randomization

Eligible subjects will be randomized in a 1:1 ratio to atacicept or placebo by the IWRS. The baseline visit should occur no later than 3 days of randomization.

Treatment with IMP

- The study staff will instruct the subject (or caregiver) in proper technique of SC administration and demonstrate it by administering the allocated IMP to the subject via SC injection.
- The first dose (on Day 1 and Week 104) will be given at the study site. After the first dose, subjects or caregivers will be permitted to administer the medication following instruction in injection technique and verification of satisfactory technique.
- On Day 1 and Week 104, the study staff will record the exact time and location of dosing and monitor the following:
 - Injection site reactions (ISRs) (local tolerability) (see Section 16.6.5).
 - Pulse and BP will be recorded before the dosing. After dosing pulse and BP will be recorded as clinically indicated.
- If suspected hypersensitivity reaction occurs at any time, the subject will be treated symptomatically (see Section 17.7.1).
- At the Week 104 visit, the subject is expected not to dose until after the completion of the study visit assessments for that scheduled visit. The dose given in clinic at Week 104 (Part C) will be the first OLE dose.

PK sampling (post-first dose)

- On Day 1, following ISR monitoring, a blood sample will be collected 2-4 hours after the first study dose. A blood sample will also be collected 2-4 hours after the first OLE dose, given at Week 104.
- After Day 1, at PK timepoints, a blood sample for PK analysis will be collected to assess levels of serum atacicept.

Completion of Day 1

Following completion of all Day 1 procedures described above, the following additional procedure should be completed before the subject leaves the site:

- Provide subjects with emergency contact numbers (see Section 19.2.2).

16.3. Post-Randomization Visits

16.3.1. Treatment Periods

Following completion of Randomization (Day 1), study visits are planned to occur at Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, 96, and 104 in the DB period of the study. After regulatory and IRB/IEC approval of Protocol Amendment 8, all subjects on DB study drug will sign a revised ICF and move to the OLE period at their next scheduled visit or an earlier, unscheduled visit, subject to study drug availability. At this visit, the assessments scheduled for Week 104 will be conducted. Subjects who are not on study drug will move to safety follow-up visits.

Note that for Weeks 4, 48, 84, 106, and 132, the study visit can be performed in-clinic or via optional remote visit, at Investigator's discretion. The optional remote visit(s) will include alternative methods for assessing safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery and administration of IMP. For the Phase 3 study, facilitation of optional remote visit(s) is the responsibility of the investigator and site staff.

If in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted at Weeks 1, 3, and 105. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

16.3.2. End of Treatment or Early Treatment Discontinuation

Criteria for discontinuation are provided in Section 16.10. Subjects who are discontinued from IMP will complete the Early Treatment Discontinuation visit as soon as possible (within 10 days) after IMP discontinuation. These subjects should receive a 24-hour urine collection container in advance (e.g., at the prior visit), but no later than 2 days before the scheduled ETD visit. Subjects who prematurely discontinue study drug prior to completion of the DB treatment period should continue with study visits and assessments per protocol through the end of the DB period.

End of treatment is defined as subjects who complete Part C and D for a total of up to 156 weeks of study drug. The ETD Visit follows the same schedule of assessments as Week 156.

16.3.3. Safety Follow-up Period

After the last dose of the IMP (whether subjects complete planned treatment or are discontinued prematurely from IMP), all subjects are required to be followed for safety for at least 26 weeks either as part of the 26-week Safety FU period or continuing in the DB treatment period (Section 16.10.1).

The Safety FU period will consist of visits at Weeks +12 and +26.

Subjects completing Part D (Week 156) and continuing on to study VT-001-0051 will not be expected to complete the 26-week Safety FU period.

16.4. Demographic and Other Baseline Characteristics

Demographic data such as date of birth, self-reported race and ethnic origin, gender, weight, height, and body mass index (to be calculated by CRO/Sponsor) will be assessed at screening. Information about previous and concomitant medications will also be recorded.

Complete medical and disease history will be recorded. This includes history of disease treatments, including but not limited to conditions that may affect eligibility (herpes zoster, cytomegalovirus, Epstein Barr virus, TB, cancer, infections [current active infections, recent serious infections, opportunistic infections, chronic or recurrent infections], congestive heart failure, hypersensitivity to drugs and other significant illnesses, smoking history, alcohol or drug abuse). In addition, a history and status of medications will be recorded, including surgeries and other procedures, with particular attention to current and previous treatments for IgAN.

Other baseline measurements such as physical examination, safety laboratory parameters, ECG, and vital signs will be assessed as specified below.

16.5. Efficacy Assessments and Procedures

Assessments for the endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 3).

Clinical renal disease assessments:

- UPCR, 24-hour total protein excretion, [REDACTED]
- Active urinary sediments by urinalysis, including spot UPCR [REDACTED]
- Renal function by eGFR will be calculated by the central lab as follows: (Levey 2009)
$$\text{CKD-EPI: eGFR} = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$$

(if female) $\times 1.159$ (if black)
Scr is serum creatinine in mg/dL; κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicated the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1

Blood assessments:

- Predose Ig levels (i.e., IgG, IgA, and IgM), Gd-IgA1.
- Predose levels of free BAFF and free APRIL.

16.6. Safety Assessments and Procedures

Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, and evaluation of AE/SAEs, with attention given to infections (serious), cardiovascular events, local tolerability (ISRs) and hypersensitivity reactions.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

Adverse events of special interest (AESIs) are infections, hypersensitivity reactions, demyelinating disorders and cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease).

16.6.1. Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A complete physical examination will include, at a minimum, assessment of the general appearance, skin, lymph nodes (cervical), head, ears, eyes, nose, throat (HEENT), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems. Height (at Screening Visit) and weight will also be measured and recorded.

At selected visits, a symptom-driven physical examination will be performed, and will include assessment of any new subject complaints or changes from baseline.

16.6.2. Vital Signs

Vital sign measurements (BP, pulse, respiratory rate, temperature), weight and height (at screening only) should be measured prior to any other study-related procedures, at the visits specified in the Schedule of Assessments ([Table 3](#)).

- Temperature, pulse rate, respiratory rate
- Blood pressure and pulse measurements should be done before any blood sampling using a standardized cuff adapted to the size of the patient's arm after the patient has been sitting and resting for least 5 minutes. Manual techniques will be used only if an automated device is not available.
 - During the Screening Period, blood pressure will be measured up to 3 times with each measurement separated by up to 2 minutes (all values will be recorded on the eCRF).
 - On Day 1 and at Week 104, pulse and BP will be recorded before the dosing of study drug. After dosing, pulse and BP will be recorded as clinically indicated during ISR monitoring.
- Vital signs to be taken before blood collection for laboratory tests
- Height will be measured at Screening only. Body weight will be measured with a balance beam scale if possible.

16.6.3. Resting Electrocardiogram (ECG)

Digital ECGs for all subjects will be recorded at the site using an appropriate ECG machine.

- A standard, single, digital 12-lead ECG will be obtained as outlined in the Schedule of Assessments after the subject has been resting in the supine position for 5 minutes.

All digital ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The Investigator will judge the overall interpretation as normal or abnormal. Clinical significance and the reason for the abnormality will be recorded on the eCRF.

Any changes in ECG values that are abnormal that are determined to be clinically significant by the Investigator will be recorded as AEs.

16.6.4. Clinical Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in the following table, at the timepoints listed in the Schedule of Assessments.

- All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations
- The tests will be performed by the central laboratory
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- Non-fasting blood samples are acceptable for this study.
- Repeat laboratory testing may be required during the study for various reasons, e.g., loss of sample en route to the central laboratory. Any testing which is required to be repeated should be repeated as soon as possible after a visit.

For information on blinded laboratory results see Section [15.1.3](#). Between 20–48 mL of blood will be collected per subject for each study visit. Approximately 827.5 mL of blood will be collected per subject for the duration of the blinded, open label and follow up periods. Blood and urine samples collected will be used to assess routine hematology, chemistry, PK serum atacicept, PK anti-drug antibodies, PD immunoglobulins, PD Gd-IgA1, PD serum BAFF and APRIL, and exploratory biomarkers for each subject visit as per the schedule of assessments.

16.6.4.1. Clinical Safety and Screening Evaluations

Table 4: Phase 3: Clinical Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	<u>RBC Indices:</u> MCV MCH %Reticulocytes	<u>WBC Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	██████ Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range)	Calcium Serum creatinine (eGFR will be calculated from serum creatinine using the CKD-EPI equation)	Glucose Potassium Sodium Total protein Uric acid
Urine Sediment Analysis	Urine red blood cells and white blood cells/high powered field Casts Organisms Crystals		
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal). Spot urine (including spot UPCR and ████████)		
Quantitative Analysis (24 -hour Urine Collection)	Total volume Total protein ██████ Total creatinine UPCR ██████		

Laboratory Assessments	Parameters
Other Tests	Serum IgG, IgA, IgM Gd-IgA1 Serum BAFF and APRIL level (if assay is available) HBsAg, HBcAb [total and IgM], HBsAb (hepatitis B) <ul style="list-style-type: none">if HBsAg negative, HBcAb positive, and HBsAb positive, then HBV-DNA will be performed to determine eligibility. HBV-DNA will be monitored monthly through safety follow up in those randomized Anti-drug antibody titers (binding and neutralizing) anti-HCV (if anti-HCV positive with reflex testing for HCV RNA by PCR) anti-HIV 1 and 2 HbA1c TSH FSH (for women only) Serum pregnancy test (β -hCG) required only for WOCBP at Screening. Local urine testing will be standard all other visits unless serum testing is required by local regulation or IRB/IEC. Positive urine pregnancy test results will be confirmed by serum pregnancy testing. Quantiferon test for TB Urine drug screen for amphetamines, cocaine, methadone, and opiates

β -hCG= beta human chorionic gonadotropin; antiHBc=anti-hepatitis B core; anti-HCV = anti-hepatitis C virus; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; HbA1c=hemoglobin-A1c; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; Ig=immunoglobulin; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell; RNA=ribonucleic acid; TB=tuberculosis; TSH=thyroid stimulating hormone; [REDACTED] UPCR=urine protein albumin-to-creatinine ratio; WBC=white blood cell; WOCBP=woman of childbearing potential.

16.6.4.2. Urine Sampling and Testing

Urine samples need to be collected in different ways for different tests:

Quantitative proteinuria assessments: A 24-hour urine collection will be used to determine 24 hour total protein excretion, UPCR, [REDACTED]. Total volume of the 24-hour collection will be measured and an aliquot taken for determining protein, [REDACTED] and creatinine concentration to calculate the proteinuria and [REDACTED] assessments. Subjects will be provided with the materials for conducting their 24-hour urine collections and will have to bring the collection to the clinic; for remote study visits, transport of the sample will need to be arranged. At the Screening Visit, the subject will receive the collection materials, and the 24-hour collection should be conducted and brought into the clinic as soon as complete within the Screening Period. At other visits requiring a 24-hour urine collection, the subject is advised to collect the urine starting the day prior to the visit and bring it to the visit.

24-hour urine collection: The 24-hour urine collection should begin 1 day before the study visit and should start with discarding the first morning void, and collecting all urine produced thereafter (through the day and night) up to 24 hours later (including the first morning void of the second morning).

Urine collection: A urine sample from “fresh” urine will be collected during the scheduled clinic visit. Subjects will be provided a urine cup and instructions for a midstream collection to provide a clean catch specimen. The urine collection will be used for routine urinalysis, spot urine, and urine sediment analysis, and at specified visits, for sample storage for future exploratory biomarker analysis (see Section 16.8.1).

16.6.5. Local Tolerability (Injection Site Assessment)

Any clinically significant ISRs will be assessed by the Investigator or his/her designee and recorded as AEs in the eCRF, starting after first study drug administration and continuing through Parts C and D in Phase 3 or Early Treatment Discontinuation (see Table 3).

Any clinically significant injection site symptoms should be reported with the AE verbatim term “injection site reaction”. These events will be captured on the AE page of the eCRF. Clinically significant, multiple symptoms for the same injection should only be entered once on the AE page of the eCRF. For this study, symptoms for ISR assessment include warmth, erythema, edema, pain or tenderness. The grading shown in the table below should be used to grade the severity of ISRs.

Qualitative Toxicity Scale for injection site reactions

Mild	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
Moderate	Pain; lipodystrophy; edema; phlebitis
Severe	Ulceration or necrosis; severe tissue damage; operative intervention indicated

Adapted from CTCAE Version 5.0.

If the subject has any other injection site symptoms not included in the list above (e.g., injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (e.g., injection site abscess, injection site cellulitis) rather than the term “injection site reaction.”

Subjects who complete their last study visit with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required.

16.7. Pharmacokinetics

On Day 1, a blood sample will be collected pre-dose for assessment of baseline anti-drug antibodies (ADA). Another blood sample will be collected between 2-4 hours after first dose for assessment of serum atacicept concentration.

At the Week 36, 52, and 104 visits, PK blood draws will be done for trough PK and ADA. All efforts should be made to ensure that the last dose was given 7 days prior to the blood collection.

At the Week 104 visit, when the subject is expected to have an in-clinic observed injection, blood samples will be collected prior to administration of study drug for trough PK and ADA assessments. All efforts should be made to ensure that the last dose was given 7 days prior to the blood collection. Another blood sample will be collected 2-4 hours post first open-label dose for the assessment of serum atacicept concentration.

On other visits, where PK/ADA samples will be collected (detailed in Schedule of Assessment, [Table 3](#)), blood samples will be collected anytime during the visit for anytime PK and ADA assessments.

Instructions for collection, preparation, and shipping these samples will be provided in a Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Blood samples for assessment of anti-drug antibodies, binding and/or neutralizing, samples will be tested first for binding activity, and those found to be positive will be tested for neutralizing activity when an assay is available.

16.8. Other Assessments

16.8.1. Biomarkers

Storage and analyses of samples will be handled according to the study Laboratory Manual and described in the appropriate Informed Consent Form.

Serum Biomarkers

The following markers may be evaluated: predose serum BAFF and serum APRIL, serum Gd-IgA1, anti-Gd-IgA1, immune complexes, etc.

Exploratory Biomarkers

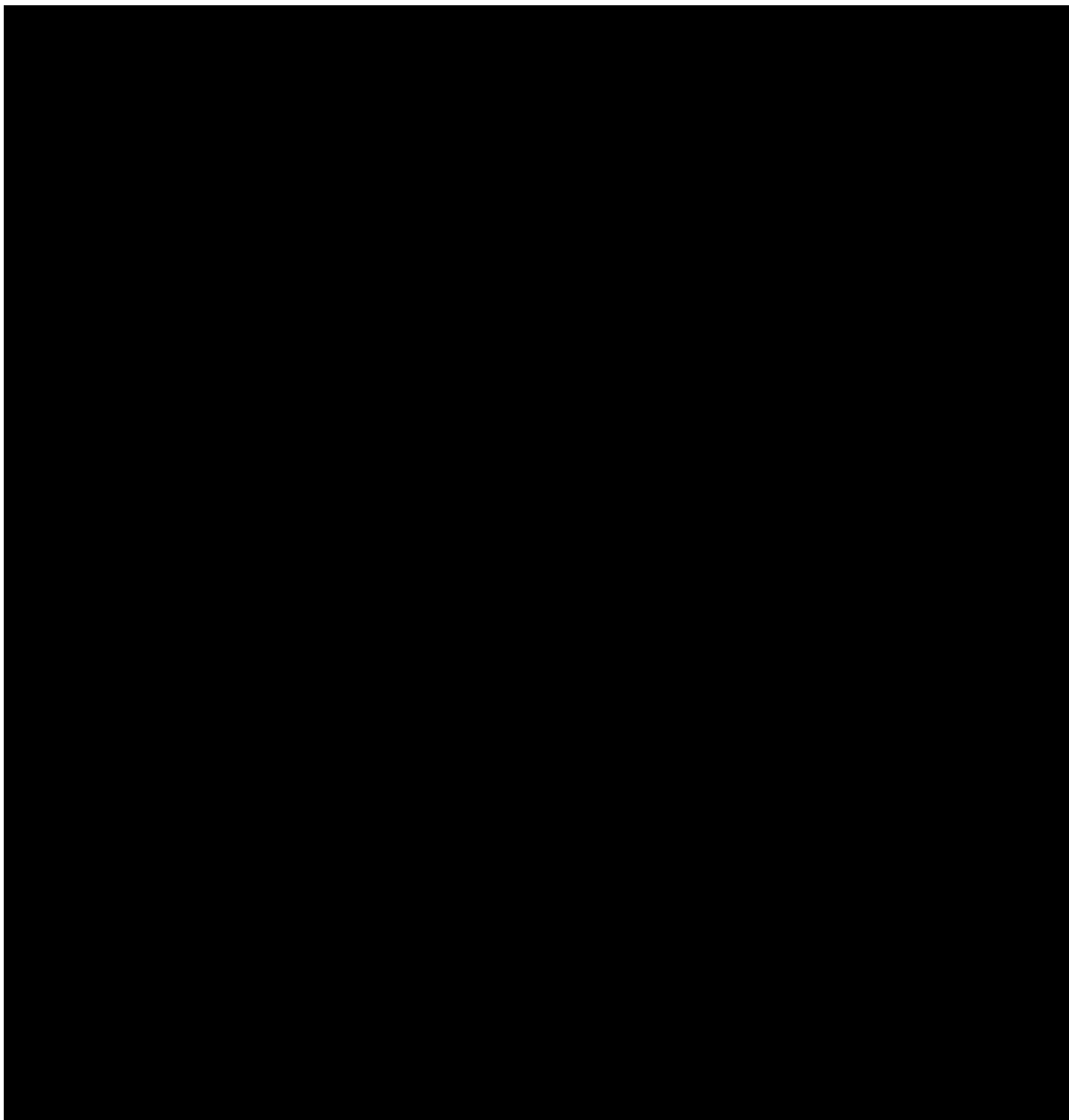
[REDACTED]

Instructions for the preparation and handling/shipment of the samples are provided in a Laboratory Manual.

Pharmacodynamic Assessments

Blood samples will be collected at the timepoints specified in the Schedule of Assessments ([Table 3](#)). Immunoglobulin levels may be integrated into the Population PK, PD and exposure-response modeling and simulation analysis, including assessment of the influence of renal function (e.g., eGFR).

16.8.2. Study Questionnaires



16.9. Considerations for Coronavirus Outbreaks

The global coronavirus pandemic or outbreaks may impose difficulties with study conduct which may inhibit the subject's ability to enter the study site. In cases of coronavirus limitations, it is the Investigator's responsibility to assure the safety of study subjects which should include phone or video contact to assess the subject's well-being including any adverse events, collection of study samples and clinical data as best as possible, and direct shipment of study drug to study subjects, if necessary. These assessments can be performed at a scheduled or unscheduled study visit(s). Where available and appropriate, home health care may be considered to facilitate monitoring of subject safety and study continuity. Documentation of these cases and the site's management of subjects should be recorded in the Investigator study files.

16.10. Discontinuation of Study Drug, Subject Retention and Follow Up Data, and Study Drug Interruption**16.10.1. Discontinuation of Study Drug**

Study drug may be stopped at any time at the Investigator's discretion.

Double-blind treatment period:

If a subject prematurely discontinues study drug or is unblinded (subject should be discontinued from study drug) during the DB treatment period, the subject should remain in the study and continue to perform the required study-related procedures through the end of the DB period (see [Table 3](#)). An ETD visit should be completed within 10 days of the last dose of study drug (Section [16.3.2](#)). If the ETD visit falls near a scheduled visit this will take the place of the scheduled visit. If the subject discontinued study drug more than 26 weeks before the end of the DB period, the subject does not need to complete a further 26 weeks of follow-up. If the subject discontinues less than 26 weeks before the end of the DB period, the subject should complete all DB visits and continue into the 26-week safety follow-up period for the appropriate amount of time to ensure 26 weeks of safety follow-up data are collected after the last dose of study drug.

For subjects who permanently discontinue study drug and wish to no longer remain in the study, the ETD visit must be completed within 10 days of discontinuation, followed by the Safety Follow-up visits as described in Section [16.3.3](#).

Open label extension period:

Subjects who prematurely discontinue study drug during the OLE period should remain in the study, completing an ETD Visit (within 10 days of the last dose of study drug, Section [16.3.2](#)) and continuing in the 26-week safety follow-up period (Section [16.3.3](#)).

Discontinuation of study drug must occur in the event of any of the following:

- Occurrence of an AE/SAE that makes discontinuation of study drug desired or considered necessary by the Investigator and/or the subject.
- Participation in any other interventional study during the duration of this study for which the Investigator or the sponsor considers discontinuation of the IMP necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to Section [17.8](#)).

- If disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes (Section 15.7) is warranted in the view of the Investigator. Discussion with the Medical Monitor should occur prior to discontinuing IMP for this reason.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on Investigator judgment.
- Use of a nonpermitted medicine, as defined in Section 15.7.2. This should first be confirmed with the Medical Monitor before discontinuation of study drug.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance to the required study considerations, as defined in Section 15.6.
- Discontinuation of LTBI therapy before completion if present at the Screening Visit.
- If a subject has 2 consecutive serum IgG < 2 g/L at least 4 weeks apart.
- Surgery considered by the Investigator or Sponsor to be major (see Section 14.2).
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Atacicept is contraindicated in subjects with a history of MS, ON, or any other demyelinating disease. Any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as, but not limited to, MS, ON, or transverse myelitis) should stop dosing of IMP.

The Schedule of Assessments specifies the data to collect at study drug discontinuation and follow-up, and any additional evaluations that need to be completed. The reasons for study drug discontinuation will be documented in eCRF. If a subject is discontinued from study drug due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

16.10.2. Subject Retention and Follow-up Data

In order to minimize missing data from discontinued participants, Investigators should make best efforts to avoid missed visits and/or premature study discontinuation. Approaches to reduce the risk of premature study discontinuation may include:

- Provide regular patient contact and support including visit reminders and follow up calls as needed.
- Discussion of options to ease visit burden.
- Travel support.
- Utilizing unscheduled visits.

16.10.3. Study Drug Interruption

The Medical Monitor must be notified if the subject has missed 2 consecutive doses or 2 doses within a month period. If treatment has been interrupted for ≥ 4 consecutive weeks, the Investigator should discuss with the Medical Monitor whether to restart or discontinue treatment.

If the subject is unable to resume study drug, see Section 16.10.

16.11. Subject Withdrawal from the Study

A subject may withdraw completely from the study at any time, at his/her own request (i.e., withdrawal of consent). Investigator or designee should make reasonable effort to obtain explanation for subject withdrawal and ask about the occurrence of any AEs. The subject will be asked to return for an ETD visit per Schedule of Assessments ([Table 3](#)).

For subjects who withdraw consent or are lost to follow-up or death and no Safety Follow up visit is possible, the appropriate eCRF section must be completed.

Subject withdrawal may occur due to any of the following:

- The subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed
- A subject is considered withdrawn from the study due to death
- A subject will be considered withdrawn from the study if the subject is lost to follow up.
- Discontinuation of the study at the request of the sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

Specific wording in the informed consent allows for collection of follow-up health information when a subject withdraws or is lost to follow-up from the study.

If a subject expresses a wish to withdraw consent from the study, the investigator will review the following options with the subject:

- Follow-up via medical records review and/or other primary care physician, referring specialist, or other healthcare professional
- Follow-up via family member or other third-party contact

For subjects that withdraw consent, information regarding vital status will continue to be collected from available sources including those in the public domain based on accepted local laws and regulations.

When a subject must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor.

If a subject is withdrawn from the study, the samples will be kept, and the subject may be asked to return for Safety Follow-up assessments. If the subject withdraws consent, the Sponsor may retain and continue to use any data collected prior to such withdrawal of consent; however, all samples not tested will be destroyed. If there is a medical reason for withdrawal from the study, the subject will remain under the supervision of the Investigator until satisfactory health has returned or health has stabilized. The Investigator will inform the subject's primary health care provider as applicable and as agreed by the subject if the subject withdraws from the study, to ensure the subject receives the appropriate follow up and care. Subjects who are withdrawn from the study for any reason after receipt of the study drug on or after Day 1 will not be replaced.

16.12. Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). The Investigator reserves the right to discontinue the study should his/her judgment so dictate and should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

16.13. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

In order to make efforts to regain contact with the subject, the following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible
- Counsel the subject on the importance of maintaining the assigned visit schedule
- Ascertain if there are any barriers to participation that can be managed,
- Ascertain if the subject wants to continue in the study.
- Before a subject is deemed “lost to follow-up”, the Investigator or designee must make every effort to regain contact with the subject:
 1. where possible, make 3 telephone calls, AND
 2. send a certified letter (or an equivalent local method) to the subject’s last known mailing address.

These contact attempts should be documented in the subject’s medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study. Specific wording in the informed consent allows for collection of follow up health information when a subject is withdrawn from the study. Information regarding vital status will continue to be collected from available sources including those in the public domain based on accepted local laws and regulations.

16.14. Medical Care of Subjects after End of Study

After a subject has completed the study including the Safety Follow-Up Period, or has withdrawn early, standard treatment should be administered, if required, in accordance with the study site’s SoC and generally accepted medical practice and depending on the subject’s individual medical needs.

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for patients with IgAN.

17. PHASE 3: ADVERSE EVENTS AND TOXICITY MANAGEMENT

17.1. Definitions of Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

- Mild:** The subject is aware of the event or symptom, but the event or symptom is easily tolerated and does not interfere with everyday activities.
- Moderate:** The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe:** Significant impairment of functioning: the subject is unable to carry out his or her usual activities. An AE that is assessed as severe should not be confused with an SAE. An event is defined as “serious” when it meets at least one of the predefined outcomes in the definition of SAE, and not when it is rated as severe.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study drug include, but may not be limited to, temporal relationship between the AE and the study drug, known side effects of study drug, medical history, concomitant medication, course of the underlying disease, and study procedures.

Investigators must also assess the causal relationship of AEs to the study treatment (atacicept or placebo).

- Not related:** Not reasonably related to the study drug. AE could not medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol. A reasonable alternative explanation must be available.
- Related:** Reasonably related to the study drug. AE could medically (pharmacologically/clinically) be attributed to the study drug under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Clinically significant abnormal laboratory or other examination (e.g., electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (e.g., electrocardiogram abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

The severity of abnormal laboratory values or other abnormal clinical findings that are determined to be AEs should be graded using the Qualitative Toxicity Scale as described above for other AEs.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition(s).

Serious Adverse Events

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

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization

Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are baseline conditions (e.g., pre-existing) and are not to be considered AEs. Situations where an untoward medical occurrence has not occurred are not to be considered AEs (e.g., hospitalization for elective surgery, social and/or convenience admissions).

Adverse Events of Special Interest

Adverse events of special interest should be reported as specified in Section 17.5.

Categories of AESIs include:

- Infections
- Hypersensitivity reactions
- Demyelinating disorders
- Cardiac events (cardiac failure, cardiac arrhythmias, and ischemic heart disease)

17.2. Time Period and Frequency for Collecting Adverse Event, Adverse Event of Special Interest and Serious Adverse Event Information

The AE/AESI/SAE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Safety FU Visit. After informed consent, but prior to initiation of study drug, all SAEs and adverse events related to protocol-mandated procedures should be collected.

- Following initiation of study drug, collect all AEs, regardless of cause or relationship.

Any SAE assessed as related to study drug must be recorded and reported, whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE data are detailed in Section 17.5.

17.3. Method of Detecting Adverse Events, Adverse Events of Special Interest and Serious Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, regardless if reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs, including SAEs, experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the eCRF (see Section 17.5).

17.4. Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 17.2, and are assessed for their outcome at the last Safety FU Visit. All SAEs ongoing at the last Safety FU Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

17.5. Investigator Requirement and Instructions for Reporting Adverse Events, Serious Adverse Events, Adverse Events of Special Interest

Recording and Follow-Up of AEs

It is important that each AE include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study drug administration time), its severity, its causal relationship with the study drug, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the eCRF Completion Guidelines provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All reports should be transmitted using the AE page and indicating the AE meets criteria for an SAE in the eCRF. Required information in the eCRF must be completed by the Investigator following specific completion instructions.

In exceptional circumstances (e.g., eDC system is down), an SAE (or follow-up information) may be reported by fax or email; in these cases, a written report using the back-up paper SAE Reporting Form must be sent immediately by fax or email by any study site to the contact information (fax and email) provided on the paper Reporting Form. Once the eDC system becomes accessible, the SAE needs to be entered into the system immediately.

Additional documents will be provided by the Investigator, if requested by the Sponsor or its designee (e.g., laboratory results, hospital report, autopsy report) depending on the availability of the document.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports, by updating the (S)AE form in the eDC system and submitting any supporting documentation (e.g., subject discharge summary or autopsy report) to the Sponsor/designee via e-mail (preferred) or fax. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations. Within 24 hours of receipt of follow up information, the Investigator must update the SAE information in the eDC and submit any supporting documentation as requested (e.g., subject discharge summary or autopsy report) to the Sponsor/designee via e-mail (preferred) or fax. If it is not possible to access the eDC system, refer to the procedures outlined above for initial reporting of SAEs.

Adverse Events of Special Interest

In the event of a serious or nonserious AESI, the Investigator will enter the AE into the eCRF in a timely manner using the process outlined above.

17.6. Regulatory Reporting Requirements for Serious Adverse Events

Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For atacicept, the reference safety information is included in the Investigator’s Brochure currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report where possible.

Regulatory Reporting

The Sponsor or designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the Independent Ethics Committee / Institutional Review Board (IEC/IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the Regulation (EU) No 536/2014, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

17.7. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are hypersensitivity reactions, infections, cardiac disease/disorders (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and demyelination disorders.

17.7.1. Hypersensitivity Reactions

Atacicept is contraindicated in subjects with known hypersensitivity to the drug substance or to any of the excipients. If allergic angioedema or other serious hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions occur, administration of IMP should be discontinued immediately, and appropriate therapy initiated. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for resumption of IMP or permanent discontinuation.

Local ISRs may be treated as per Section [16.6.5](#).

17.7.2. Infections

Treatment of infections must be prompt and done in accordance with local SoC depending on considerations such as the nature and severity of the infection, patient's overall health status, etc.

- Subjects must be carefully examined for signs of infection and questioned about recent infective illnesses and recent vaccination(s)
- If laboratory findings raise concern, in the opinion of the Investigator, that there may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section [14.2](#), and may lead to study drug discontinuation

- Subjects will be instructed by study site personnel to monitor for early signs of infection, such as upper respiratory symptoms, fever, painful urination, productive cough, breathlessness, constitutional symptoms, etc. Subjects should inform the study site if any of these symptoms or signs are present and should be evaluated and treated in a timely manner according to the local SoC. At each study visit, monitoring for subject's symptoms and signs should also be done. Standard medical care will be provided at the study sites for all AEs occurring during the study. Any subject who experiences a chronic or recurrent significant infection, or opportunistic infection, should be re-evaluated (as per Investigator's clinical judgment and discussion with Medical Monitor) as to whether or not continued treatment with atacicept is appropriate.

For infections associated with severe hypogammaglobulinemia (serum IgG < 2 g/L), consideration can be given to administration of Ig and discontinuation of study drug.

17.7.3. Cardiac Disease/Disorders

Treatment with study drug (atacicept/placebo) must be temporarily discontinued in subjects who develop new onset or worsening of clinically significant symptomatic arrhythmias that require medical intervention (such as paroxysmal atrial tachycardia, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia, ventricular fibrillation or ventricular tachycardia), cardiac failure, or cardiac ischemic symptoms. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for discontinuation or resumption of study drug.

17.7.4. Demyelination Disorders

Based on the clinical trial results, MS patients who received atacicept developed significantly more relapses than patients in the placebo group. Therefore, any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as but not limited to MS, optic neuritis or transverse myelitis) should discontinue the study drug.

17.8. Pregnancy

Pregnancy should not be captured as an AE. However, pregnancies with an estimated conception date during the period defined in Section 17.2 must be recorded in the eCRF for both pregnancies in female subjects and pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Section 17.5.

Investigators must actively follow up, document and report on the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, or the child/fetus sustains an event, the SAE should be recorded in the eCRF. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 17.2, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the study, the subject must be discontinued from study drug. The Sponsor/designee must be notified without delay and the subject must be followed as indicated above.

17.9. Special Situation Reports

Special situation reports include site reported instances of overdose, misuse, abuse, medication error, and adverse reactions associated with product complaints.

- **Overdose:** For this study, any instance when IMP is given 3 times or more per week is considered an overdose. Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s), or the Investigator has reason to suspect that the subject has taken additional dose(s).

Note: The Sponsor does not recommend specific treatment for an overdose. The effects of an overdose of atacicept are unknown and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and appropriate supportive treatment should be given as needed per Investigator's clinical judgment.

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors; cases of subjects missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situation will only be recorded if the complaint is associated with an adverse drug reaction.

All special situations should be reported as a protocol deviation and any associated events reported as an AE. Special Situations that are considered to meet SAE criteria will be managed per the same process as SAEs in Section 17.5.

18. PHASE 3: STATISTICAL CONSIDERATIONS

The Statistical Analysis Plans (SAPs) for Phase 3 will be separated from the Phase 2b SAP and will be developed and finalized before the database lock for the corresponding analysis. The SAP will describe the subject populations to be included in the analyses, and procedures for how to handle missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary efficacy and safety endpoints. Analyses of additional measurements collected as part of this protocol will be fully described in the corresponding SAPs. Any deviations from this plan will be noted in the corresponding Clinical Study Report.

Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number. Formal statistical comparisons will be conducted for the data collected in double-blinded period. Strategies for alpha control for multiple comparisons are specified in Section 18.6.1.4.

All statistical analyses will be conducted by the Sponsor or its agent using SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA 27513).

18.1. Planned Analyses

The primary analysis of UPCR was performed after the first 203 subjects completed the Week 36 visit or prematurely discontinued from the study.

[REDACTED]

The details of these analyses will be provided in the SAP.

18.2. Stratification

[REDACTED]

18.3. Statistical Hypotheses

18.3.1. The Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural log-transformed UPCR at Week 36, and was evaluated at the time of the Week 36 interim analysis. The primary comparison of interest was a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.01.

$$H_{10}: \mu_{1,\text{placebo}} = \mu_{1,\text{ATC}} \text{ vs } H_{11}: \mu_{1,\text{placebo}} \neq \mu_{1,\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.005.

$$H_{10}: \mu_{1,\text{placebo}} \leq \mu_{1,\text{ATC}} \text{ vs } H_{11}: \mu_{1,\text{placebo}} > \mu_{1,\text{ATC}}$$

Where:

$\mu_{1,\text{placebo}}$ = the change from baseline at Week 36 in natural log-transformed UPCR for the placebo group;

$\mu_{1,\text{ATC}}$ = the change from baseline at Week 36 in natural log-transformed UPCR for the atacicept 150 mg group.

18.4. Sample Size Determination

The selected sample size provides sufficient power for both the primary endpoint UPCR and the key secondary endpoint eGFR.

The primary efficacy endpoint is the ratio of UPCR at Week 36 compared with baseline, based on 24-hour urine collection. Due to skewed distribution, UPCR was natural log transformed. The primary efficacy endpoint became the change from baseline at Week 36 in natural log-transformed UPCR. A two-sample t-test for ratio was used to determine the sample size for UPCR. It was assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between the atacicept and placebo groups was 0.67 (i.e., the percentage reduction was 33% higher for atacicept than placebo) and the standard deviation (SD) for the mean change of

log(UPCR) from baseline was assumed to be 0.7 in both groups (based on the ORIGIN Phase 2b Primary Endpoint Analysis [data on file]). Based on these assumptions, it was determined that 100 subjects per group would provide 92% power to detect a ratio of 0.67 with a two-sided alpha of 0.01 when the ratio under the null hypothesis is 1 (PASS 2015: two-sided two sample t-test for ratios). Missing data after subject withdrawals were imputed and included in the primary efficacy endpoint analysis and therefore no overage of sample size for withdrawals was necessary.

Table 5 displays statistical power under different scenarios, accounting for uncertainty in estimating UPCR percentage reductions and standard deviations. It was determined that 100 subjects per group would provide at least 78% power at two-sided significant level of 0.01 even if the treatment effect on UPCR reduced from 33% to 30% and/or the standard deviation of the mean change of log(UPCR) from baseline increased from 0.7 to 0.75. A total of 100 subjects per group was determined to provide at least 93% power at two-sided significance level of 0.01 if the treatment effect on UPCR reduction was 35% as observed in ORIGIN Phase 2b Week 36 Analysis.

Table 5: Power Calculation for Primary Endpoint of UPCR Under Different Assumptions.

Sample Size	Treatment Effect on UPCR		Standard Deviation	Alpha	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction			
100	0.67	33%	0.7	0.01	92%
			0.75	0.01	88%
	0.7	30%	0.7	0.01	84%
			0.75	0.01	78%
100	0.65	35%	0.7	0.01	96%
			0.75	0.01	93%

For the key secondary endpoint of eGFR total slope specified in Protocol Amendment 7, a mixed-effects model with random intercept and random slope is planned for comparing 2 slopes, when we estimate the sample size for eGFR slope evaluation (Ahn, 2014). A difference in annualized slope in eGFR is assumed to be 2 mL/min/1.73m²/year, the variance of random slope is 27, and the variance of residuals is 32 based on the atacicept IgAN Phase 2a (JANUS) study. The follow-up period is approximately 2 years (i.e., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between the atacicept and placebo. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) will be enrolled.

Table 6 displays statistical power for annualized eGFR slope comparison under different scenarios; 171 subjects per group will provide at least 87% power at two-sided significant level of 0.05 to detect an annualized slope difference of at least 2.0 mL/min/1.73 m²/year, even if the variances of random slope and residuals increase by approximately 10% to 30 and 36, respectively. The power will be 77% if the expected annualized slope difference decreases to 1.67 mL/min/1.73m²/year.

18.5. Populations for Analyses

The analysis populations are specified below. The final decision to exclude subjects from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Population	Description
Screening	All subjects who sign informed consent.
Intent-to-treat (ITT) Analysis Set	The ITT Analysis Set consists of all randomized subjects. Subjects will be analyzed according to the randomized treatment.
Full Analysis Set (FAS)	The FAS consists of all randomized subjects who have received at least 1 dose of treatment. Subjects will be analyzed according to the randomized treatment and the primary analysis for all efficacy endpoints will be based on the FAS.

Interim Analysis Set (IAS)	The IAS consists of a subset of subjects in the FAS population who completed or prematurely discontinued from study, or otherwise had the potential to complete the Week 36 visit at the time of the data cut date for the Week 36 interim analysis. Subjects will be analyzed according to the randomized treatment and the primary analysis for the primary efficacy endpoint will be based on the IAS at the Week 36 interim analysis.
Week 36 Per-Protocol (PP) Analysis Set	The Week 36 PP Analysis Set consists of all subjects in the IAS who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the Week 36 PP Analysis Set will be provided in the SAP, including exclusion of subjects who take prohibited/rescue medications. The Week 36 PP Analysis Set will be used for supplementary analysis on the primary efficacy endpoint. Subjects will be analyzed according to the actual treatment received.
Safety Analysis Set	The Safety Analysis Set consists of all randomized subjects who receive at least 1 dose of treatment. The Safety Analysis Set is the analysis population for the safety endpoints. Subjects will be analyzed according to the actual treatment received.
Pharmacokinetics Analysis Set	The PK Analysis Set consists of all randomized subjects who were administered at least 1 dose of treatment and have at least 1 evaluable PK concentration. All PK evaluations will be based on this analysis population.
Immunogenicity Analysis Set	The Immunogenicity Analysis set consists of all randomized subjects who receive at least 1 dose of treatment and have at least 1 evaluable ADA measure. Subjects will be analyzed according to the actual treatment received.

Unless otherwise indicated, the IAS or FAS are the primary analysis populations for efficacy endpoints and the Safety Analysis Set is the primary analysis population for safety endpoints.

18.6. Statistical Analysis

18.6.1. Efficacy Analysis

18.6.1.1. The Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in natural log-transformed UPCR at Week 36, and was evaluated at the time of the Week 36 interim analysis. The estimand for the primary analysis of the primary endpoint was as follows:

- The population for the trial was defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The analysis population was based on the IAS at the Week 36 interim analysis.
- The variable of interest was the change from baseline in natural log-transformed UPCR.
- The intercurrent events included: (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplantation, and death. The intercurrent events or missing data were handled as follows:
 - Subjects who discontinued treatment were followed, and all observed data were used according to the intention-to-treat principle or treatment policy strategy.
 - Subjects who initiated rescue/prohibited therapy were followed, and all observed data were used according to the intention-to-treat principle or treatment policy strategy.
 - Values following intercurrent events of dialysis, kidney transplantation, and death were imputed by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy.
 - Missing values due to subjects who withdrew from the study were imputed by jump to reference approach according to the hypothetical strategy.
- The population level summary measure was the reduction in the geometric mean ratio of UPCR relative to baseline in atacicept group compared to placebo group at Week 36, the associated 2 sided 95% confidence intervals (CI), and the p-value.
- The analysis approach uses a mixed-effects model for repeated measures (MMRM) analysis. Change from baseline in natural log-transformed UPCR was the dependent variable. Effects for stratification factor(s), natural log-transformed baseline value, randomized treatment, visit, and treatment-by-visit interaction were included as fixed effects. The primary comparison tested the mean difference between atacicept and placebo groups at Week 36. This statistical comparison was based on linear contrasts of the Least Squares Means (LSMeans) estimated from this model. LSMeans differences were exponentiated to obtain the mean ratio, the associated 2-sided 95% CIs, and the p-value. UPCR values measured after intercurrent events were handled according to the ICE strategies described above. The MMRM described above was fitted on each imputed dataset and the results were combined using Rubin’s rules to obtain the estimate of the % reduction from baseline in UPCR (atacicept 150 mg vs. placebo).

- Sensitivity analyses investigated the effect, if any, of the intercurrent events and missing data on the estimation of treatment effect, such as a two-dimensional tipping point analysis.
- Supplementary analyses included an evaluation of the primary endpoint using the Week 36 PP population.
- Subgroup analyses for the primary endpoint were conducted for the following subgroups as appropriate: age (< median age vs. ≥ median age), sex, region (Asia vs. Other), country (US vs. ex-US), race (White vs. Other), baseline UPCR (< 1.5 g/g vs. ≥ 1.5 g/g), baseline proteinuria (< 2 g/24h vs. ≥ 2 g/24h), baseline eGFR (< 45 mL/min/1.73 m², ≥ 45 and < 90 mL/min/1.73 m², vs. ≥ 90 mL/min/1.73 m²), stable SGLT2i use at baseline (Yes vs. No).

18.6.1.2. The Key Secondary Efficacy Analysis

The key secondary endpoint is the change from baseline [REDACTED] in eGFR evaluated based on the FAS, including data up to [REDACTED]. A similar estimand framework as used for the analysis of the primary endpoint will be applied for analysis of the key secondary endpoint (details will be provided in the SAP). The analysis approach uses an MMRM analysis. Change from baseline in eGFR will be the dependent variable. Effects for stratification factor(s) (except for the eGFR stratification factor), baseline eGFR value, randomized treatment, visit, and treatment-by-visit interaction will be included as fixed effects. The primary comparison will test the mean difference between the atacicept and placebo groups [REDACTED]. This statistical comparison will be based on linear contrasts of the LSMeans estimated from this model, with the associated 2-sided 95% CIs and the p-value also being provided. Rubin's rules will be used to combine results from multiple imputation datasets.

18.6.1.3. Other Efficacy Analyses

All other efficacy endpoints will be evaluated based on the IAS (at the Week 36 interim analysis) or FAS [REDACTED] and final analysis) and including all available data following the treatment-policy strategy, except that data collected after dialysis and kidney transplant are deemed as not interpretable and will be excluded from analysis, unless specified otherwise.

Continuous efficacy endpoints will be analyzed in a similar manner as for the primary efficacy endpoint. In addition, absolute, change from baseline, and percentage change from baseline by treatment for selected continuous efficacy endpoints at all post-baseline visits will be generated.

Binary efficacy endpoints will be presented as the number and percentage of responders by treatment group. The population level summary measure is the odds ratio comparing the odds of being a responder in atacicept vs. placebo group, which will be evaluated by a logistic regression model controlling for stratification factor(s), randomized treatment, and the appropriate baseline value. The odds ratio for the treatment effect, 95% CIs, and p value will be estimated from the model.

Time-to-event efficacy endpoints will be displayed using Kaplan-Meier methodology. The population level summary measure is the ratio of the hazard rates of atacicept vs. placebo group for the corresponding endpoint. The population level study measure will be evaluated using the Cox proportional hazard model with effects for stratification factor(s), randomized treatment,

and the appropriate baseline value. Subjects who do not have an endpoint of interest will be censored at the last assessment of the endpoint. The adjusted hazard ratio of the risk of the event between the atacicept and the placebo group, the corresponding 95% CIs, and p-value will be estimated from this model.

18.6.1.4. Multiple Comparisons

The SAP (Version 2) was developed after Protocol Amendment 7 and finalized before the database lock for the Week 36 interim analysis. Per SAP Version 2, to control the overall type 1 error in the evaluation of the primary and key secondary efficacy endpoints at a two-sided alpha of 0.05, hypothesis testing was to be performed in sequential order by fallback procedure. The primary efficacy endpoint was tested first at a two-sided alpha of 0.01 at the Week 36 interim analysis. Because superiority for the primary endpoint was established, the original key secondary efficacy endpoint was planned to be tested at a two-sided alpha of 0.05 at the planned Week 104 interim analysis. After statistical significance testing for both the primary and key secondary endpoints, the sequential testing approach was planned to be used to test other selected secondary endpoints with a two-sided alpha of 0.05 or 0 at the planned Week 104 interim analysis, based on the results for the primary and key secondary endpoints.

[REDACTED] If superiority for the revised key secondary endpoint is established, selected other secondary endpoints will be tested sequentially at a two-sided alpha of 0.05 using the hierarchical gatekeeping procedure; otherwise, the testing procedure will stop and selected other secondary endpoints will not be tested.

18.6.2. Safety Analyses

Safety analyses will include the examination of vital signs, physical exam, 12-lead ECG, routine clinical laboratory tests (including hematology, blood chemistries, urinalysis), and AEs. All safety evaluations will be conducted based on the Safety Analysis Set and the safety data of each treatment group will be summarized by descriptive statistics.

18.6.2.1. Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent adverse events (TEAEs) will be summarized using descriptive statistics by treatment group. Treatment-emergent adverse events are defined as AEs with onset dates occurring during the study period (i.e., from the first dose until the subject's last study visit) and will be assigned to the most recently received treatment at the start of the AE. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each MedDRA System Organ Class and MedDRA Preferred Term, by treatment group. Treatment-emergent adverse events will also be summarized by relationship to treatment and by severity within each treatment group, and by predefined AESIs.

18.6.2.2. Other Safety Analyses

Laboratory data, vital sign data, and ECG data will be summarized by timepoint and treatment group with descriptive statistics. The prevalence at baseline and incidence rate of subjects developing positive anti-drug antibody will be summarized using descriptive statistics.

18.6.3. Pharmacokinetic and Pharmacodynamic Analyses

Analyses of the PK, serum BAFF, APRIL, and other exploratory biomarkers will be summarized using descriptive statistics. Additional analyses may be detailed in the corresponding SAP.

19. PHASE 3: RESPONSIBILITIES

19.1. Investigator Responsibilities

19.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the protocol, Regulation (EU) No 536/2014, ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

19.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

19.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions on the study.
- Subjects must be informed that their participation is voluntary.
- Subjects or their legal representative under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, subjects must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the subject.

- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

19.1.4. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study subject. The file must identify each subject, contain the following demographic and medical information for the subject, and should be as complete as possible:
 - Subject's full name, date of birth, sex, height, and weight
 - Medical history and concomitant diseases
 - Prior and concomitant therapies (including changes during the study)
 - Study identifier (i.e., the Sponsor's study number) and subject's study number
 - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
 - Any medical examinations and clinical findings predefined in the protocol
 - All AEs
 - Date that the subject left the study, including any reason for early withdrawal from the study or study drug, if applicable
- All source data must be filed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] scan images, ECG recordings, and laboratory results). Each document must clearly identify the subject and the procedure date, ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. Investigators must notify Sponsor in advance if source documents are to be moved to another location, such as for archiving.

19.1.5. Data Protection

- The Sponsor will assign a unique identifier to subjects after obtaining their informed consent. All subject records or datasets transferred to the Sponsor will contain the identifier only; subject names or any identifiable information will not be transferred.
- The Sponsor must inform subjects that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain subject's confidentiality.
- The Investigator will complete the subject registration using the IWRS (Section 15.1). If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject will be registered by IWRS. If the subject is ineligible for the study, a subject number will be allocated and documented.
- The Sponsor will ensure that data will be collected and processed in accordance with the General Data Protection Regulation (GDPR) EU 2016/679.

19.2. Sponsor Responsibilities

This clinical study will be Sponsored by: Vera Therapeutics, Inc.

The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

An iDMC will be formed in this study (see Section 13.3).

19.2.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following: Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH GCP Guidelines
 - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study subjects. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
 - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
 - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

19.2.2. Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to subjects for use during the study. These provide the means for subjects to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the subject. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician (or designee). This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician (or designee) to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

19.2.3. Clinical Study Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

19.2.4. Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator. Selection of the Coordinating Investigator will be performed by the Sponsor, based on the requirements of the study.

19.2.5. Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

19.2.6. Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

19.3. Data Quality Assurance

- All subject study data will be captured:
 - In the eDC system.
 - Through files transmitted to the Sponsor, or designee, electronically (e.g., laboratory data).
- The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by electronically signing the subject casebook.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of subject casebooks will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of subjects are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

19.4. Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
 - Inadequate recruitment of subjects by the Investigator
 - Discontinuation of further development of the Sponsor's compound

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21. APPENDICES

Appendix 1:	Abbreviations
Appendix 2:	Contraception
Appendix 3:	Management of Abnormal and Medically Important Laboratory Abnormality
Appendix 4:	Key Differences Between Phase 2b and Phase 3 Studies
Appendix 5:	Investigator Signature Page
Appendix 6:	Laboratory Vendors

Appendix 1: Abbreviations

Abbreviation	Definition
0035	MS700461-0035
024	EMR700461-024
β-hCG	beta human chorionic gonadotropin
ACEi	angiotensin converting enzyme inhibitor
ADDRESS II	EMR700461-023 Phase II study
AE	adverse event
AESI	adverse event of special interest
anti-HBc	anti-hepatitis B core
APRIL	a proliferation-inducing ligand
APRIL-SLE	EMR700461-27646 Phase II study
ARB	angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker
ATC	Atacicept
BAFF	B-cell activating factor
BILAG	British Isles Lupus Assessment Group (BILAG) Disease Activity Index
BLyS	B lymphocyte stimulator (also called B-cell activating factor)
BP	blood pressure
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	clinical research organization
CS	corticosteroid(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
DBPC	double-blind placebo-controlled
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic Data Capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ePRO	electronic patient reported outcome
ERA	endothelin receptor antagonist
ESRD	end stage renal disease
ET	early termination
ETD	early treatment discontinuation

Abbreviation	Definition
EWB	emotional well-being
FAS	Full Analysis Set
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
FU	follow-up
FWB	functional well-being
GCP	Good Clinical Practice
GCS	Glucocorticosteroids
Gd-IgA1	galactose-deficient IgA1
GN	Glomerulonephritis
HbA1c	hemoglobin-A1c
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDA	high disease activity
HEENT	Head, Ears, Eyes, Nose, Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin (G, A, and M)
IgAN	IgA Nephropathy
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IWRS	interactive web response system
LDA	low disease activity
LSMeans	Least Squares Means
LTBI	latent TB infection
LTE	long-term extension

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MMRM	mixed-effect model with repeated measurement
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTD	maximally tolerated dose
OLE	open label extension
ON	optic neuritis
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
pmp	per million people
PP	per-protocol
PRO	patient-reported outcome
PWB	physical well-being
QoL	quality of life
RAS(i)	renin angiotensin system (inhibitor)
RAAS(i)	renin-angiotensin-aldosterone system (inhibitor)
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SGLT2(i)	sodium-glucose cotransporter-2 (inhibitor)
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index-2000
SoC	standard of care
SRI	SLE Responder Index
SUSAR	suspected unexpected serious adverse reaction
SWB	social/family well-being
TACI	Transmembrane Activator and CAML [calcium-modulator and cyclophilin ligand] Interactor
TB	Tuberculosis
TEAEs	treatment emergent adverse events
Tmax	time to maximum concentration

Abbreviation	Definition
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
████	████████████████████
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US, USA	United States (of America)
VAS	visual analog scale
WBC	white blood cell
WOCBP	woman of childbearing potential

Appendix 2: Contraception

Woman of Childbearing Potential (WOCBP)

A WOCBP (i.e., fertile), following menarche and until either:

1. Becoming postmenopausal; or,
2. Is permanently sterile by means of a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly and are the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - Oral, intravaginal, transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation - Oral, injectable
- Implantable progestogen*-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)*
- Intrauterine hormone-releasing system (IUS)*
- Bilateral tubal occlusion*
- Vasectomized partner*: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject

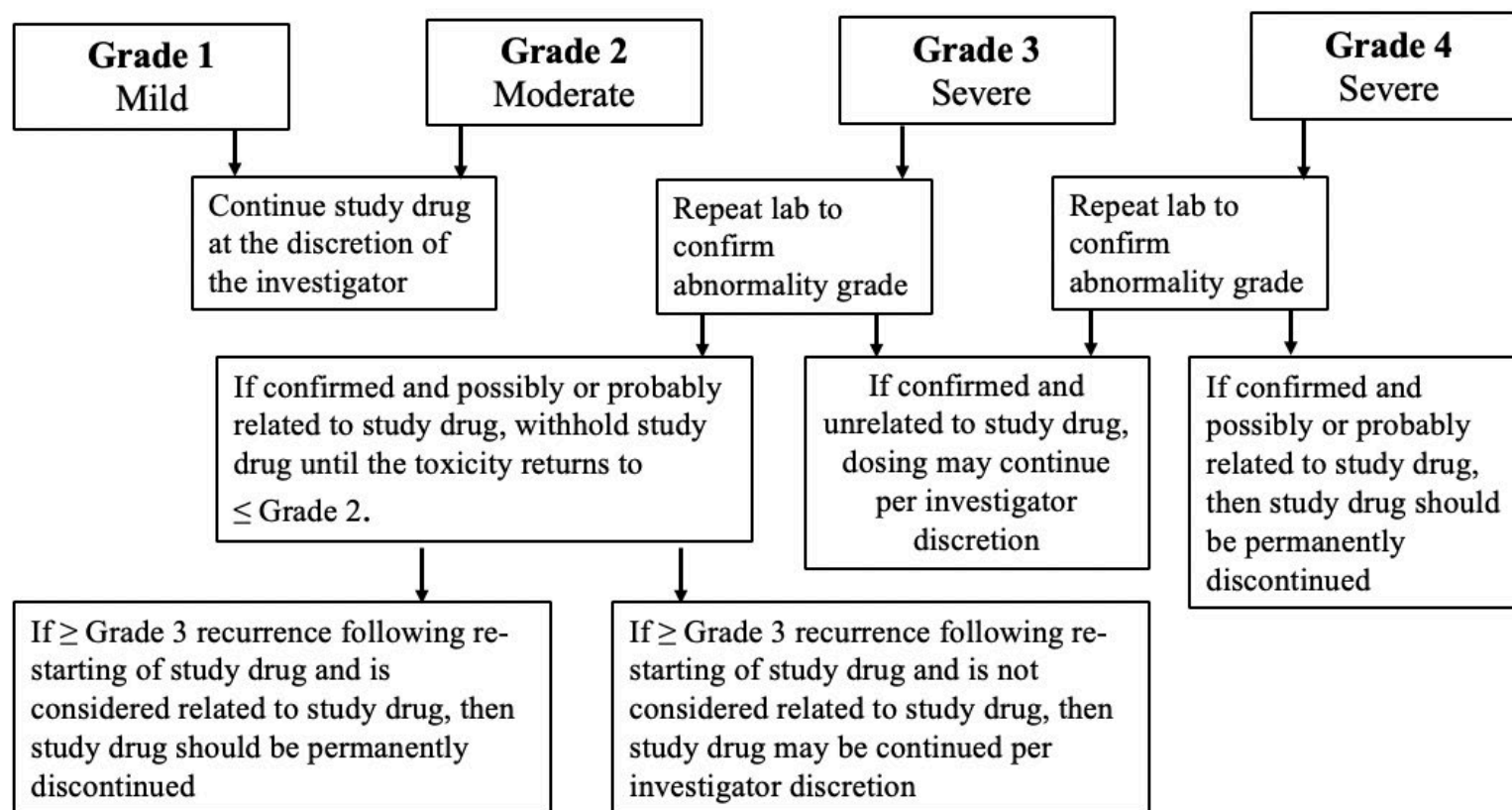
Caution should be taken for hormonal contraception, as the effect of atacicept on hormonal contraception is unknown. Subjects taking hormonal contraception should use a supplementary barrier method (preferably male condom) during screening, during the study drug administration period and for at least 175 days after the last dose of study treatment.

* Invasive Methods: User-independent invasive contraceptive methods herein mentioned in this appendix is provided as a guidance. Women of childbearing potential who are already using one of these highly effective invasive contraceptive methods prior to inclusion OR who will begin using any of these highly effective contraceptive methods by their own decision will be eligible for inclusion.

Contraception for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of child-bearing potential must use condoms during study participation and for 175 days after the last dose of study drug. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during treatment and until at least 175 days after the last dose of study drug.

Appendix 3: Management of Abnormal and Medically Important Laboratory Abnormality



Appendix 5: Investigator Signature Page

Study Acknowledgement

Study Title: A Phase 2b/3, Multi-part Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)

Clinical Study Protocol Version: Amendment 8 Dated 01 June 2026

This protocol has been approved by Vera Therapeutics, Inc. The following signature documents this approval.

[Redacted]

Name (Printed)
Chief Medical Officer

[Redacted Signature]

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I understand and agree that it contains all necessary details for me and my staff to conduct this study as described.

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation, Regulation (EU) No 536/2014, Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vera Therapeutics, Inc.

Principal Investigator Name (Printed)

Signature

Date

Site Number



STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)

Protocol Number: VT-001-0050

Protocol Version / Date: Amendment 7 / 23 December 2024

Investigational Product: Atacicept (VT-001)

Sponsor: Vera Therapeutics, Inc.
2000 Sierra Point Parkway, Suite 1200
Brisbane, CA 94005

SAP Version/Date V 1.0 / 11 Feb 2025
(for Phase 3 Week 36 and Week 104 Interim Analyses)

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SAP SIGNATURE PAGE

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature

Date

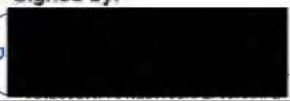
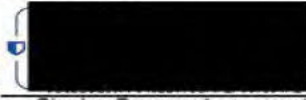
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 <i>Chief Medical Officer, Vera Therapeutics, Inc.</i>	 Signed by: Signing Reason: I approve this document Signing Time: 2/13/2025 5:57:30 AM PST 6BBE8610221E4BC4AE4E6AE0CBB8939D

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
APRIL	a proliferation-inducing ligand
BAFF	B-cell activating factor (also called "BLyS")
C _{max}	maximum concentration
ACEi	Angiotensin Converting Enzyme inhibitor
ADA	Anti-Drug Antibody
AESI	Adverse event of special interest
ARB	Angiotensin II Receptor Blocker
ATC2	Anatomical therapeutic chemical class level 2
BMI	Body mass index
BP	Bodily Pain
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CSR	Clinical Study Report
DB	Double-Blind
DNA	Deoxyribonucleic acid
EC	Exposure as Collected
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EDC	Electronic Data Capture
EOT	End of treatment
[REDACTED]	[REDACTED]
EQ VAS	EQ Visual Analog Scale
ET	Early Termination
EWB	Emotional Well-Being
[REDACTED]	[REDACTED]
FAS	Full analysis set
FS	Fatigue Subscale
FWB	Functional Well-Being
Gd-IgA1	Galactose-deficient IgA1
GH	General Health
GS	Glucocorticosteroids
HbA1c	Hemoglobin-A1c
HbcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HRQOL	Health-Related Quality of Life
IAS	Interim Analysis Set
ICEs	Intercurrent Events
iDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
Ig	Immunoglobulin
IgA, IgG, IgM	Immunoglobulin A, Immunoglobulin G, Immunoglobulin M
IgAN	IgA Nephropathy
IRT	Interactive Response Technology

Abbreviation	Definition
IS	Immunosuppressive
ISR	Injection site reaction
ITT	Intent to treat
IWRS	Interactive web response system
LS Means	Least Squares Means
LSMs	Least Squares Means
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Scores
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MI	Multiple Imputation
MMRM	Mixed-effects model for repeated measures
MNAR	Missing Not At Random
MRA	Mineralocorticoid Receptor Antagonists
OLE	Open-Label Extension
PCS	Physical Component Scores
PF	Physical Functioning
PGx	Pharmacogenetics
PK	Pharmacokinetics
PN	Preferred Name
PP	Per-protocol
PROs	Patient-Reported Outcomes
PT	Preferred Term
PWB	Physical Well-Being
Q1, Q3	First, Third quartile
RASi	Renin-Angiotensin System inhibitor
RE	Role-Emotional
REML	Restricted Maximum Likelihood
RP	Role-Physical
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Social Functioning
SGLT2i	Sodium-glucose cotransporter-2 Inhibitor
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SWB	Social/Family Well-Being
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
TOI	Trial Outcome Index
TSH	Thyroid Stimulating Hormone
UACR	Urine albumin to creatinine ratio
UPCR	Urine protein to creatinine ratio
VAS	Visual Analog Scale
VT	Vitality
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis methods and data presentations to be implemented in tables, figures, and listings (TFLs) to support the primary endpoint analysis at Week 36 and the End of Part C analysis at Week 104 of Phase 3 data for study VT-001-0050 based on protocol (Amendment 7: 23 December 2024). The primary endpoint analysis at Week 36 (referred to as the “Phase 3 Week 36 Interim Analysis” in later sections) will be performed after approximately the first 200 subjects enrolled for the Phase 3 part of this study complete their Week 36 visits or prematurely discontinue from the study. The End of Part C analysis (referred to as the “Phase 3 Week 104 Interim Analysis” in later sections) will be performed when all subjects complete the double-blind portion of the study (Week 104) or prematurely discontinue from the study. The SAP will be finalized prior to database lock for the primary endpoint analysis at Week 36 data cut. Any deviations from the SAP after database lock for the primary endpoint analysis will be documented in the Clinical Study Report (CSR).

Separate SAPs were developed for the interim and final analyses for Phase 2b part of the study. Separate SAPs will be developed to support future interim and/or final analyses for the Phase 3 part of the study.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

- Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN at Week 36.

2.1.2 Key Secondary Objective

- Evaluate the effect of atacicept compared to placebo on annualized rate of change in estimated glomerular filtration rate (eGFR) through Week 104.

2.1.3 Other Secondary Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.1.4 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]

2.1.5 Safety Objective

- Evaluate the safety and tolerability of atacicept during the entire study.

2.2 Study Design

2.2.1 Overview

This is a multi-part study comprising of the original Phase 2b study (i.e., Parts A and B) and the addition of a separate Phase 3 study (i.e., Parts C and D). The results from Phase 2b have been used to determine the dose selection and sample size for the Phase 3 study design.

The Phase 3 study is a multicenter, randomized, double-blinded, placebo-controlled study.

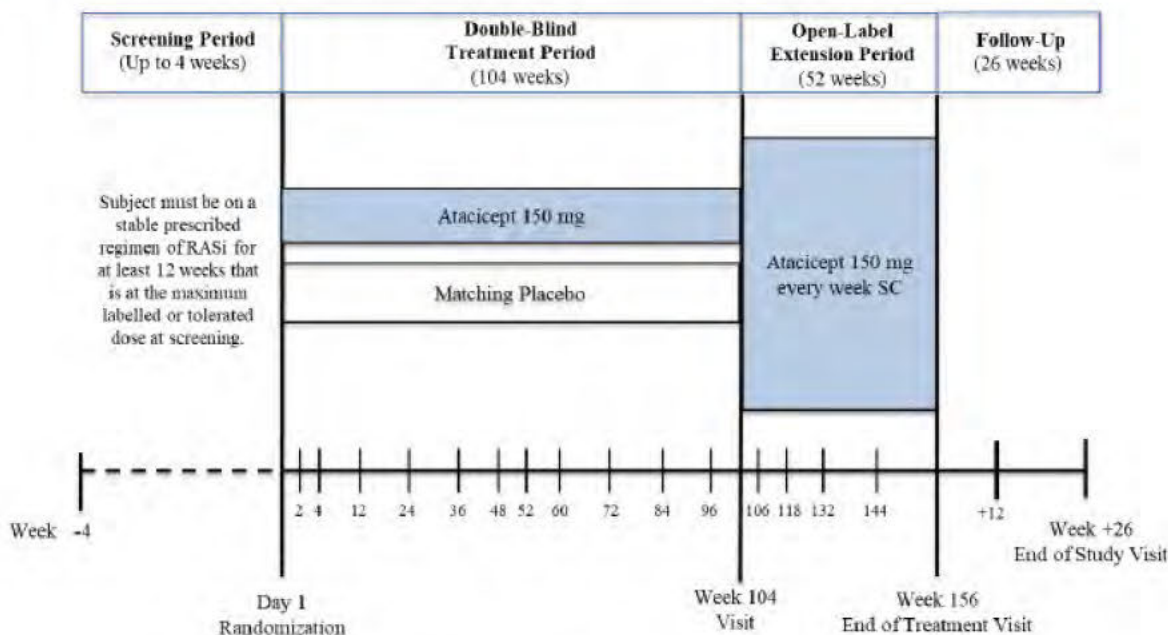
In Part C, approximately 376 subjects will be randomized 1:1 to atacicept 150 mg or placebo for 104 weeks:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly SC injections (N=188)
- Subjects who have participated in Part A or B may not participate in Part C or D.
- Subjects participating in the study will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/1.73 m², or ≥ 45 to <90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m²), total urine protein excretion (<2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (yes or no), and Region (Asia or Other).

The Phase 3 study is composed of a (up to) 4-week Screening Period, a 104-week Double-Blind (DB) Treatment Period (Part C), a 52-week Open-Label Extension (OLE) (Part D) and 26 weeks of follow-up. Subjects who complete the 104-week DB Treatment Period on treatment will be eligible for open-label atacicept at 150 mg for an additional 52 weeks (OLE). Subjects who prematurely discontinue study drug prior to completion of the 104-week DB treatment period should continue with study visits and assessments per protocol through the end of the DB period. After the last subject completes the 104-week DB period or completes an Early Termination Discontinuation (ETD) Visit, the study will be unblinded.

The study will be conducted on an outpatient basis.

Figure 1: Phase 3 Study Schema



RASi= renin-angiotensin system inhibitor; SC=subcutaneous.

2.2.2 Investigational Medicinal Product(s)

In a blinded fashion, 150 mg atacicept or placebo are given as once-weekly SC injections for 104 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept are given as once-weekly SC injections for 52 weeks by prefilled syringe.

2.2.3 Randomization and Blinding

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessment (see [Appendix 2](#)).

This study will be double-blinded for all subjects and Investigators through Part C. IMP packaging and labeling will be prepared to protect the blinded nature of the study. Study drugs will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part D of the study will be conducted in an open-label fashion.

2.2.4 Sample Size Determination

The selected sample size provides sufficient power for both the primary endpoint UPCR and the key secondary endpoint eGFR.

2.2.4.1 Sample Size Determination for the Primary Endpoint of UPCR

The primary efficacy endpoint is the ratio of UPCR at Week 36 compared with baseline, based on 24-hour urine collection. Due to the skewed distribution, UPCR will be natural log transformed. The primary efficacy endpoint becomes the change from baseline at Week 36 in natural log transformed UPCR. A two-sample t-test for ratio was used to determine the sample size for UPCR. It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo groups is 0.67 (i.e., the percentage reduction is 33% higher for atacicept than placebo) and the standard deviation (SD) for the mean change of log (UPCR) from baseline is assumed to be 0.7 in both groups (based on Origin Phase 2b Primary Endpoint Analysis [data on file]). Based on these assumptions, 100 subjects per group will provide 92% power to detect a ratio of 0.67 with a two-sided alpha of 0.01 when the ratio under the null hypothesis is 1 [PASS 2015: two-sided two Sample t-test for ratios]. Missing data after subject withdrawals will be imputed and included in the primary efficacy endpoint analysis and therefore no overage of sample size for withdrawals is necessary.

Table 1 displays statistical power under different scenarios, accounting for uncertainty in estimating UPCR percentage reductions and standard deviations; 100 subjects per group will provide at least 78% power at two-sided significant level of 0.01 even if the treatment effect on UPCR reduces from 33% to 30% and/or the standard deviation of the mean change of log (UPCR) from baseline increased from 0.7 to 0.75. A total of 100 subjects per group will provide at least 93% power at a two-sided significant level of 0.01 if the treatment effect on UPCR reduction is 35% as observed in ORIGIN Phase 2b Week 36 Analysis, which provides reassurance that the proposed sample size is adequate and robust.

Table 1: Power Calculation for Primary Endpoint of UPCR Under Different Assumptions

Sample Size per Group	Treatment Effect on UPCR		Standard Deviation	Alpha	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction			
100	0.67	33%	0.7	0.01	92%
			0.75	0.01	88%
	0.7	30%	0.7	0.01	84%
			0.75	0.01	78%
100	0.65	35%	0.7	0.01	96%
			0.75	0.01	93%

2.2.4.2 Sample Size Determination for the Annualized Rate of Change in eGFR Through Week 104

For the key secondary endpoint, a meta-analysis for the association of treatment effects on early change in UPCR and treatment effect on eGFR annualized slope in IgAN patients by (Inker et al 2021) is referenced to estimate the expected treatment effect on eGFR annualized slope. The mixed-effects model with random intercept and random slope (MMRIRS), which is also known as the random coefficient mix-effect model, is planned for comparing 2 slopes, when we estimate the sample size for eGFR slope evaluation (Ahn, Heo, and Zhang [2014]). It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo is 0.67 based on ORIGIN Phase 2b Primary Endpoint Analysis. According to the established association between UPCR change at 9 month and eGFR annualized slope (Inker et al 2021) and the observation that atacicept did not show an acute eGFR effect in Origin Phase 2b Primary Endpoint Analysis and historical data, the expected difference in annualized slope in eGFR is 2 mL/min/1.73m²/year using linear extrapolation. The variance of random slope is 27 and the variance of residuals is 32 based on the atacicept IgAN Phase 2a (JANUS) study. The follow-up period is approximately 2 years (i.e., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between the atacicept and placebo. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) will be enrolled.

Table 2 displays statistical power for annualized eGFR slope comparison under different scenarios; 171 subjects per group will provide at least 87% power at two-sided significant level of 0.05 to detect an annualized slope difference of at least 2.0 mL/min/1.73m²/year, even if the variances of random slope and residuals increase by approximately 10% to 30 and 36, respectively. The power will be 77% if the expected annualized slope difference decreases to 1.67 mL/min/1.73m²/year, which is associated with a 30% more decrease in UPCR at Week 36 in atacicept compared to placebo. A total of 171 subjects per group will provide at least 93% power at a two-sided significant level of 0.05 if the treatment effect on UPCR reduction is 35% as observed in the ORIGIN Phase 2b Week 36 Analysis, even if the variances of random slope and residuals increase by approximately 10% to 30 and 36, respectively. The deeper UPCR reduction observed in ORIGIN Phase 2b Week 36 analysis provides reassurance that the proposed sample size is adequate and robust.

Table 2: Power for Annualized eGFR Slope Comparison Under Different Assumptions (Alpha = 0.05)

Sample Size per Group	Treatment Effect on UPCR		Annualized Slope Difference in eGFR	Var (Slope)	Var (Residuals)	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction				
171	0.7	30%	1.67	27	32	77%
	0.67	33%	2.0			90%
	0.65	35%	2.22			95%
	0.7	30%	1.67	30	36	73%
	0.67	33%	2.0			87%
	0.65	35%	2.22			93%

2.2.4.3 Potential Adjustment to Sample Size Determination for eGFR

In sample size calculation for the evaluation of difference in 2-year eGFR slope, multiple uncertainties were accounted for, including the treatment effect on UPCR, the modeled relationship between changes in UPCR at 9 months and eGFR slope over 2 years, and the variances of slope and/or residuals in eGFR.

The original sample size calculation was based on the observed 33% placebo-adjusted reduction in UPCR at Week 36 from the Week 24 analysis. At the Week 36 analysis, a deeper placebo-adjusted reduction of 35% at Week 36 was observed and the standard deviation (SD) for the mean change of log (UPCR) from baseline at Week 36 was similar with these at Week 24. No sample size adjustment is necessary based on Phase 2b Week 36 Interim Analysis.

After the completion of Phase 2b final analysis, the sponsor used the actual variances of the random slope and residual of eGFR estimated from Phase 2b long-term eGFR data to recalculate the sample size for the confirmative endpoint of eGFR. The recalculated sample size was not substantially higher than the currently proposed sample size, the sample size will not be adjusted. Since this check is based on data from a separate Phase 2b part of this study to estimate the ‘nuisance parameter’ of variances, no alpha spending is required.

2.3 Study Endpoints for the Phase 3 Week 36 Interim Analysis

Only the primary efficacy endpoint will be formally evaluated with two-sided alpha of 0.01 at the Phase 3 Week 36 Interim Analysis. Key secondary endpoint and other selected secondary endpoints will be formally evaluated at the Phase 3 Week 104 Interim Analysis. Selected other secondary endpoints and exploratory endpoints (detailed below) will be evaluated at the Phase 3 Week 36 Interim Analysis as supportive analyses and no alpha spending is required.

2.3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

2.3.2 Key Secondary Endpoint

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope) with eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults as specified by Levey 2009.

$$\text{eGFR} = 141 \times \min(\text{SCR}/\kappa, 1)^\alpha \times \max(\text{SCR}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018[\text{if Female}] \times 1.159[\text{if Black}]$$

where: SCR = Standardized Serum Creatinine (mg/dL),

κ = 0.7 (females) or 0.9 (males),

α = -0.329 (females) or -0.411 (males),

min indicates the minimum of Scr/ κ or 1,

max indicates the maximum of Scr/ κ or 1,
age in years.

The key secondary endpoint will not be evaluated at the time of Phase 3 Week 36 Interim Analysis. Instead, the following eGFR endpoints will be analyzed:

- Annualized rate of change in eGFR [REDACTED] (i.e., annualized eGFR total slope)
- Change from baseline in eGFR by visit [REDACTED].

2.3.3 Other Secondary Endpoints

Selected other secondary endpoints at the time of the Phase 3 Week 36 Interim Analysis will be analyzed as supportive analyses (i.e., not included in the multiple testing strategy) and include the following endpoints:

- Change from baseline at Week 36 in natural-log transformed Gd-IgA1
- Hematuria resolution (i.e., achieving hematuria of negative or trace) at Week 36 for subjects with hematuria of 1+ or above at baseline.

2.3.4 Exploratory Endpoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.3.5 Safety Endpoints

Safety endpoints include evaluation of routine clinical and laboratory tests, adverse events and anti-drug antibodies (ADA) during the entire study.

2.4 Study Endpoints for the Phase 3 Week 104 Interim Analysis

The key secondary endpoint and other selected secondary endpoints will be formally evaluated at Week 104 Interim Analysis as Specified in Section 3.1.7. All exploratory endpoints (detailed below) will be evaluated at Week 104 Interim Analysis as supportive analyses and no alpha spending is required.

2.4.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

The primary efficacy endpoint will be evaluated at Phase 3 Week 36 Interim Analysis based on Interim Analysis Set (IAS) population and including all UPCR data up to Week 36. The change from baseline in natural-log transformed UPCR at all postbaseline visits up to Week 104 will be evaluated at Phase 3 Week 104 Interim Analysis based on Full Analysis Set (FAS) population.

2.4.2 Key Secondary Endpoint

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope).

2.4.3 Other Secondary Endpoints

Other secondary endpoints include:

- Change from baseline at [REDACTED] and 104 in eGFR.
- Change from baseline at Weeks 36, [REDACTED] and 104 in natural-log transformed Gd-IgA1.
- Hematuria resolution (i.e., achieving hematuria of negative or trace) at Weeks 36, [REDACTED] and 104 for subjects with hematuria of 1+ or above at baseline.
- Time from randomization to the first occurrence of composite kidney failure endpoint event. Where the composite kidney failure endpoint defined as experiencing at least one of the following during the study:
 - At least a 30% reduction relative to baseline in eGFR sustained for at least 30 days
 - eGFR <15 mL/min/1.73m², sustained for at least 30 days
 - Chronic dialysis ≥30 days
 - Kidney transplant
 - Death

2.4.4 Exploratory Endpoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.4.5 Safety Endpoints

Safety endpoints include evaluation of routine clinical and laboratory tests, adverse events and anti-drug antibodies (ADA) during the entire study.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Day

Study day will be calculated from the date of the first dose of study drug. The study day of the first dose of study drug will be Day 1, and the study day immediately before Day 1 will be Day -1. There will be no Day 0.

- For dates before Day 1, study day = date of assessment/event – date of Day 1.
- For dates on or after Day 1, study day = date of assessment/event – date of Day 1 + 1.

3.1.2 Definition of Period

Analysis for the double-blinded (DB) period will include data collected during the screening and DB periods: (1) all available data for subjects who prematurely discontinued the blinded study drug and/or did not receive any dose of open-label atacicept in the OLE period; (2) all available data prior to the first dose data/time of open-label atacicept for subjects who completed the double-blinded drugs and received at least 1 dose of open-label atacicept.

Analysis for the OLE period will include OLE baseline and all data collected on or after the first dose date/time of open-label atacicept through the end of the study.

Analysis for the entire study period will include all the data collected throughout the study, i.e. from screening period to the end of follow-up period.

OLE period and the entire study period may not be defined for the Phase 3 Week 36 Interim Analysis, as we are expecting very few, if not none, subjects will enter the OLE period at the time of Week 36 Interim Analysis data cut.

3.1.3 Definition of Baseline, the First Dose, and the Last Dose

Baseline for DB period (labeled as DB baseline for future reference) will be defined as the last available measurement prior to the first dose of double-blinded study drug (i.e., it is generally the pre-dose assessment on Day 1), except for UPCR, [REDACTED], and other lab tests from 24-hour urine samples or spot urine samples. For UPCR, [REDACTED] and other lab tests from 24-hour urine samples or spot urine samples, the geometric mean of all measurements during the screening period and prior to the first dose of double-blinded study drug will be used as baseline. DB baseline is the default baseline and will be used interchangeably with baseline. For analyses conducted for double-blind treatment period only (such as analyses of primary efficacy endpoint), or for the entire study period (i.e., where DB period and OLE period will be analyzed as a whole), such as summary of demographic and baseline characteristics, the DB baseline will be used as the default baseline.

Baseline for OLE period (labeled as OLE baseline for future reference) will be defined as the last available measurement prior to the first dose of open-label atacicept. OLE baseline may not be defined for the Phase 3 Week 36 Interim Analysis, as we are expecting very few, if not none, subjects will enter the OLE period at the time of Week 36 Interim Analysis data cut. Data collected in the OLE period, if any, will not be summarized but will be included in listings in the Phase 3 Week 36 Interim Analysis.

The first dose date for both the DB period and entire study is the first injection date of any blinded study drug. The first dose date for the OLE period is the first injection date of open-label atacicept.

The last dose date for the DB period is the last injection of any blinded study drug. The last dose date for the OLE period is the last injection date of any open-label atacicept. The last dose date for the entire study is the last injection date of any study drug, including both blinded study drugs and open-label atacicept.

3.1.4 Analysis Visits

All efficacy and safety assessments, regardless collected on schedule or unscheduled visits and regardless collected while on-treatment or off-treatment, will be allocated to analysis visits as defined in [Appendix 3](#). If more than one postbaseline measurements are recorded within a visit window, the following rule will be applied, while baseline is defined in Section [3.1.3](#):

- If there are multiple measurements collected on the same day (even if some measurements are collected as unscheduled measurements or off-treatment measurements), the arithmetic or geometric mean of all measurements will be used for that day. The mean of all measurements collected on that day will be treated as on-treatment measurement if at least one measurement is collected as an on-treatment measurement. Otherwise, it will be treated as an off-treatment measurement. For subjects who don't complete the End of Treatment eCRF (i.e., still receiving study drug), all postbaseline measurements will be considered as on-treatment. For subjects who complete the End of Treatment eCRF, a measurement will be considered as an on-treatment measurement if it is collected on or after the first dose date/time and prior to the last dose date/time + 10.
- If a test is collected in multiple days within a visit window, the measurement taken at the day closest to the target day will be used. If there are multiple days with equidistance from the target day, the latest one will be used.

3.1.5 Stratification

Subjects will be stratified by screening eGFR values calculated by the central lab (< 45 mL/min/1.73 m², or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI), screening total urine protein excretion (< 2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (Yes or No) and Region (Asia or Other). Screening eGFR and total urine protein excretion will be imported from Medpace Central Lab into IRT directly to assign the stratification category, while subject with/without stable SGLT2i use at screening will be manually entered into IRT by site staff. The actual subject with/without stable SGLT2i use at

screening will be derived based on prior/concomitant medication data from EDC. Any discrepancies in SGLT2i screening stratification categories between IRT and EDC will be listed. In addition, eGFR category and total urine protein excretion category at baseline and stable SGLT2i use at baseline will be derived and used for statistical modeling. Any difference between derived stratification categories at screening and these at baseline will be listed.

3.1.6 Statistical Hypotheses

Hypotheses for Primary Study Objective

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR. The primary comparison of interest is a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.01. The statistical hypotheses for the primary efficacy endpoint are:

$$H_{10}: \mu_{\text{placebo}} = \mu_{\text{ATC}} \text{ vs. } H_{11}: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.005.

$$H_{10}: \mu_{\text{placebo}} \leq \mu_{\text{ATC}} \text{ vs } H_{11}: \mu_{\text{placebo}} > \mu_{\text{ATC}}$$

Where:

μ_{placebo} = the change from baseline at Week 36 in natural-log transformed UPCR for placebo group;

μ_{ATC} = the change from baseline at Week 36 in natural-log transformed UPCR for atacicept 150 mg group.

Hypotheses for Key Secondary Study Objective

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope). The primary comparison of interest is a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.05 or 0.04 (depending on the results of the primary efficacy endpoint). The statistical hypotheses for the key secondary efficacy endpoint are:

$$H_{20}: \text{Slope}_{\text{placebo}} = \text{Slope}_{\text{ATC}} \text{ vs. } H_{21}: \text{Slope}_{\text{placebo}} \neq \text{Slope}_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.025 or 0.02 (depending on the results of the primary efficacy endpoint).

$$H_{20}: \text{Slope}_{\text{placebo}} \geq \text{Slope}_{\text{ATC}} \text{ vs. } H_{21}: \text{Slope}_{\text{placebo}} < \text{Slope}_{\text{ATC}}$$

Where:

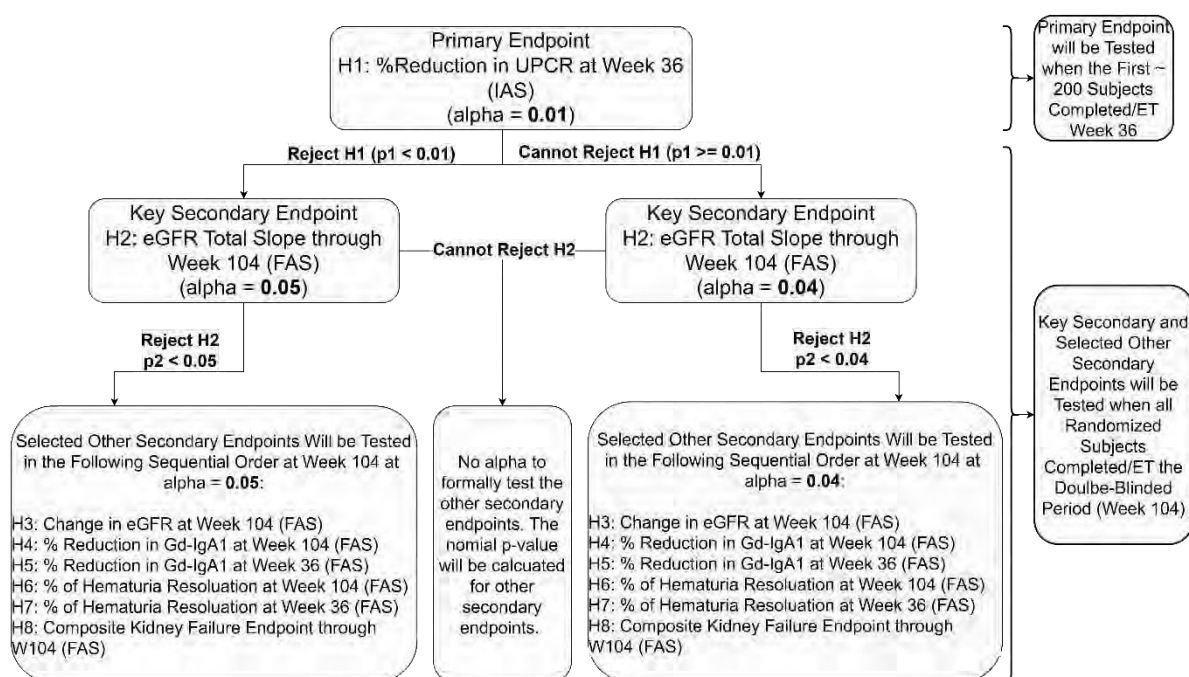
$\text{Slope}_{\text{placebo}}$ = the annualized rate of change in eGFR through Week 104 for placebo group;

$\text{Slope}_{\text{ATC}}$ = the annualized rate of change in eGFR through Week 104 for atacicept 150 mg group.

3.1.7 Multiple Comparisons

To control the overall type 1 error in the evaluation of the primary and key secondary efficacy endpoint at a two-sided alpha of 0.05, the hypothesis testing will be performed in sequential order by fallback procedure. The primary efficacy endpoint will be tested first at a two-sided significance level of 0.01. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at a two-sided significant level of 0.05. If the statistical significance is not met for the primary endpoint, the key secondary efficacy endpoint will be tested at a two-sided significant level of 0.04. After the statistical significances are tested for both the primary and the key secondary endpoints, the sequential testing approach will be used to test other selected secondary endpoints with a two-sided significant level of 0.05, 0.04, or 0 based on the hypotheses testing results from the primary and key secondary efficacy endpoints (see details in Figure 2).

Figure 2: Multiple Testing Flow Chart



3.1.8 Data Summaries and Conventions

All endpoints will be summarized using descriptive statistics. Continuous variables will be summarized descriptively using the number of observations, mean, SD and/or SE, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and population being presented, unless

otherwise specified. All available data will be presented in the data listings by treatment group and subject number.

Mean, median, Q1, Q3, as well as their corresponding confidence intervals (CI) (if applicable) will be reported to one decimal place more than the data reported on the eCRF or by the laboratory/vendor. SD will be reported to two decimal places more than the original data reported. Minimum and maximum will be reported to the same number of decimal places displayed on eCRF or by the laboratory/vendor. P values will be reported to four decimal places. If a p value of “0” or “1” is obtained, display them as “<0.0001” and “>0.9999”, respectively. In general, the number of decimal places should not exceed four.

All tabular summaries will be presented by treatment group (atacicept 150 mg group or placebo group) and/or for overall. They will also be presented by study period (DB period and OLE period) if appropriate.

Formal statistical comparisons will be conducted for the data collected in DB period. Strategies for alpha control for multiple comparisons are specified in Section 3.1.7.

3.1.9 Handling of Dropouts and Missing Data

For prior and concomitant medications/procedures, if a medication/procedure has incomplete start or end dates, dates will be imputed to determine whether a medication/procedure should be considered prior or concomitant. If a medication/procedure start date is incomplete and the start date is in the same year and month as the first dose date, the first dose date will be used to impute the incomplete start date. Otherwise, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a medication/procedure end date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. If the imputed end date is later than the death date, then the end date will be imputed with the death date. Incomplete start and end dates will be listed as collected without imputation.

If it is not possible to determine whether an AE is or is not treatment emergent, or whether an AE starts in the on-treatment period, due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent, i.e., starting in the treatment period. Detailed imputation rule will be documented in ADaM mapping specification.

Descriptive summaries of efficacy and safety measures will be based on observed data. Imputation of missing data for modeling will be detailed in later sections.

3.2 Populations

3.2.1 Screening Population

The Screening Population consists of all subjects who sign informed consent.

3.2.2 Intention-to-Treat (ITT) Population

The ITT Population consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.

3.2.3 Full Analysis Set (FAS) Population

The FAS Population consists of all randomized subjects who have received at least 1 dose of treatment. Unless otherwise indicated, the FAS is the primary analysis population for efficacy endpoints in the Week 104 Interim Analysis, where subjects will be analyzed according to randomized treatment.

3.2.4 Interim Analysis Set (IAS) Population

The IAS Population consists of a subset of subjects in the FAS population who were randomized and dosed on or prior to Sep 12th, 2024 (i.e., 203 subjects were randomized and dosed on or prior to Sep 12th, 2024) or subjects who complete the Week 36 visit at the time of the data cut for the Week 36 Interim Analysis. Unless otherwise indicated, the IAS is the primary analysis population for efficacy endpoints in Week 36 Interim Analysis, where subjects will be analyzed according to randomized treatment. In addition, selected safety endpoints will be analyzed using IAS Population according to actual treatment received during the DB period.

3.2.5 Week 36 Per-Protocol (PP) Population

The Week 36 PP Population consists of all subjects in the IAS Population who do not have any special events that may affect the validity of the primary efficacy endpoint evaluation.

Subjects who experience any CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation will be excluded from the Week 36 PP population. CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation include but are not limited to:

- Eligibility criteria violations that may affect the validity of the primary efficacy endpoint (e.g., screening eGFR < 30 mL/min/1.73m²),
- Study drug compliance outside of 80-120% up to the Week 36 visit, and
- Other substantial CSR reportable protocol violations prior to the Week 36 visit.

Subjects who experience any of the following events that may affect the validity of the primary efficacy endpoint evaluation will be excluded from the Week 36 PP population:

- Use of rescue / prohibited concomitant medication that could have impacted on the efficacy of study treatment prior to the Week 36 visit,
- Change the background medication (i.e., RASi, MRA, or SGLT2i) that could have impacted the efficacy of study treatment within 6 weeks prior to the Week 36 visit,
- Premature discontinuation of study drug prior to the Week 36 visit, and
- Unblinding of the patient prior to the Week 36 visit.

Week 36 PP Population will be determined through blinded review prior to Week 36 database lock. Week 36 PP population will be used as a supportive analysis on the primary efficacy endpoint for Phase 3 Week 36 Interim Analysis. Subjects will be analyzed according to the actual treatment received during the DB period.

3.2.6 Week 104 Per-Protocol (PP) Population

The Week 104 PP Population consists of all subjects in the FAS Population who do not have any clinically important protocol deviations that affect the validity of the key secondary efficacy endpoint evaluation. The Week 104 PP Population will be defined similarly to Week 36 PP Population, except the reference timepoint will change from “Week 36 visit” to “Week 104 visit”. Week 104 PP Population will be determined through blinded review prior to Week 104 database lock. Week 104 PP Population will be used as a supportive analysis on the key secondary efficacy endpoint for Phase 3 Week 104 Interim Analysis. Subjects will be analyzed according to the actual treatment received during the DB period.

3.2.7 Safety Population

The Safety Population consists of all randomized subjects who receive at least 1 dose of treatment. Subjects will be analyzed according to the actual treatment received during the DB period. Unless otherwise indicated, the Safety Population is the primary analysis population for safety endpoints.

3.2.8 Pharmacokinetics Population

The PK Population consists of all randomized subjects who receive at least 1 dose of treatment and have at least 1 evaluable PK concentration. All PK evaluations will be based on this population. PK concentration will be measured for subjects randomized to Atacicept 150 mg only.

3.2.9 Immunogenicity Population

The Immunogenicity Population consists of all randomized subjects who receive at least 1 dose of treatment and have at least 1 evaluable ADA measure. Subjects will be analyzed according to the actual treatment received during the DB period.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented for Screening Population:

- Subjects who failed screening and were not randomized
- Subjects who were randomized

Subjects who failed the screen will be tabulated by primary reason for screen failure/not randomized. The number and percentage of subjects who failed the screen/not randomized due to COVID-19 will also be presented.

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented by treatment group and in total using ITT Population:

- Subjects randomized (ITT Population)
- Subjects treated (FAS/Safety Population)
- Subjects who prematurely discontinued study drug in the DB period by reason
- Subjects who prematurely discontinued the study by reason

The following disposition categories will not be included in Phase 3 Week 36 interim analysis, but will be included in Phase 3 Week 104 interim analysis:

- Subjects who completed study drug in the DB period
- Subjects who completed study drug in the DB period and continued to OLE period
- Subjects who prematurely discontinued study drug in the OLE period by reason
- Subjects who completed study drug in the OLE period
- Subjects who continued to safety follow-up period
- Subjects who completed the study

3.3.2 Protocol Deviations

The number and percentages of subjects with CSR reportable and CSR non-reportable protocol deviations by deviation category will be summarized by treatment group and in total using ITT Population. CSR reportable protocol deviations are deviations related to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment that impact the safety of the subjects or jeopardize the quality of study data. Protocol deviation categories are described in the protocol deviation plan.

All protocol deviations (CSR reportable and CSR non-reportable) will be listed by deviation categories.

3.3.3 Analysis Populations

The number and percentages of subjects in each analysis population will be summarized by treatment group and in total using ITT Population.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to

- Age collected at Screening (years)

- Age collected at Screening categories (years): (1) < 40, ≥ 40 ; and (2) < 45, ≥ 45 to < 65, ≥ 65
- Sex: female, male
- Childbearing potential (female only): yes, no
- Race: (1) American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other pacific islander, White, Other, Unknown or Not Reported, Not Permitted; and (2) White, Non-White, Not Reported or Not Permitted.
- Ethnicity: Hispanic or Latino, not Hispanic or Latino, Unknown or Not Reported, Not Permitted.
- Country: (1) by country; and (2) US, ex-US.
- Region Categories: (1) Asia, Europe, North America, South America; and (2) Asia, Other.
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline body mass index (BMI) (kg/m^2)
- Screening eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)
- Screening eGFR Categories (IRT) ($\text{mL}/\text{min}/1.73 \text{ m}^2$): <45, ≥ 45 to <90, ≥ 90
- Baseline eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)
- Baseline eGFR Categories ($\text{mL}/\text{min}/1.73 \text{ m}^2$): (1) <45, ≥ 45 to <90, ≥ 90 ; and (2) <15, ≥ 15 to <30, ≥ 30 to <45, ≥ 45 to <60, ≥ 60 to <90, ≥ 90
- Baseline Hematuria (%): Negative/Trace, 1+, 2+, 3+
- Baseline UPCR (g/g)
- Baseline UPCR Category (g/g): <1.5, ≥ 1.5
- XXXXXXXXXX
- Screening Proteinuria (g/day)
- Screening Proteinuria Category (IRT) (g/day): <2, ≥ 2
- Baseline Proteinuria (g/day)
- Baseline Proteinuria Categories (g/day): (1) <2, ≥ 2 ; and (2) <2, ≥ 2 to <3.5, ≥ 3.5
- Baseline Gd-IgA1 (ug/L), IgA (mg/dL), IgG (mg/dL), IgM (mg/dL), BAFF (ng/L), APRIL (ug/L)
- Baseline Systolic Blood Pressure (mmHg)
- Baseline Diastolic Blood Pressure (mmHg)
- Duration from IgAN Diagnosis (years)
- Time since Biopsy (years)
- Stable SGLT2i Use at Screening (IRT): yes, no
- Stable SGLT2i Use at Screening (EDC Derived): yes, no
- Stable SGLT2i Use at Baseline (EDC Derived): yes, no

- SGLT2i Use at Baseline (for subjects not on stable SGLT2i use at baseline only): Never Used, Less than 12 Weeks.
- RASi Medication Use at Baseline by Category: No RASi, ACEi only, ARB only, ACEi + ARB.
- Number of Anti-hypertension Medication(s) Used at Baseline: None, At least 1 (further break down by 1, 2, 3, 4+).
- Anti-hypertension Medication Used at Baseline by Class: ACEi, ARB, MRA, Diuretic, Calcium Channel Blocker, Beta Blocker, Direct Renin Inhibitors, Other.
- Prior GS or IS IgA nephropathy treatments: yes, no
- Prior GS or IS IgA nephropathy treatments type: glucocorticosteroids (by subcategory), mycophenolate mofetil, azathioprine, cyclophosphamide, hydroxychloroquine, other
- Kidney Biopsy Results Reported in eCRF: yes, no
- Number of Glomeruli on Biopsy (n)
- Number of Glomeruli on Biopsy Category (n): < 8 , ≥ 8
- Classification Used for Kidney Biopsy Results: Kidney Biopsy Not Reported, Other, OXFORD MEST-C (by Subclassification)

Demographic and baseline characteristics relative to DB baseline will be summarized with descriptive statistics or number and percentages of subjects as appropriate by treatment group and in total for IAS, ITT, and FAS Populations in Phase 3 Week 36 Interim Analyses. If ITT Population and FAS Population are the same, summary will be performed based on ITT Population only.

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The number and percentages of subjects with medical history by SOC and PT will be summarized by treatment group and in total based on the Safety Population.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical class level 2 (ATC2) and preferred name (PN) using the World Health Organization (WHO) Drug Dictionary (B3 Global, September 2024 or later). For summary purposes, medications will be considered prior medications if they ended prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Medications will be considered concomitant medications during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. Medications will be considered concomitant medications during the OLE period if they were taken at any time on or after the first dose date/time of OLE study drug through the end of the study. If medications

cannot be decided as to which period they belong due to completely missing or partial start dates, medications will be considered concomitant during both periods.

In the case where a medication has incomplete start or end dates and cannot be determined as whether the medication should be considered as prior or concomitant medication, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects taking prior and concomitant medications by ATC2 and PN will respectively be summarized and will be summarized by treatment group and in total based on the Safety Population.

3.3.7 Prior and Concomitant Procedures

Prior and Concomitant procedures will be coded to SOC and PT using MedDRA (version 27.1 or later). For summary purposes, procedures will be considered prior procedures if they ended prior to the first dose of study drug and concomitant procedures if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Procedures will be considered concomitant procedures during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. Procedures will be considered concomitant procedures during the OLE period if they were taken at any time on or after the first dose date/time of OLE study drug through the end of the study. If procedures cannot be decided as to which period they belong due to completely missing or partial start dates, procedures will be considered concomitant during both periods.

In the case where a procedure has incomplete start or end dates and cannot be determined as whether the procedure should be considered as prior or concomitant procedure, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects with prior and concomitant procedures by SOC and PT will respectively be summarized and will be summarized by treatment group based on the Safety Population.

3.3.8 Study Drug Exposure and Compliance

Days of exposure to study drug will be defined for DB period, OLE period, and the entire study as follows:

- Days of exposure during the DB period = date of the last dose during the DB period – date of the first dose during the DB period + 7.
- Days of exposure during the OLE period = date of the last dose during the OLE period – date of the first dose during the OLE period + 7.
- Days of exposure during the entire study = date of the last dose during the entire study – date of the first dose during the DB period + 7.

For the calculation of the study drug exposure, the data cut date will be used to impute the corresponding last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment group based on the Safety Population. Descriptive statistics and the number and percentages of subjects with exposure in the following categories will be presented:

- DB Period
 - ≤12 weeks (≤84 days)
 - >12 - ≤24 weeks (>84 to ≤168 days)
 - >24 - ≤36 weeks (>168 to ≤252 days)
 - >36 - ≤48 weeks (>252 to ≤336 days)
 - >48 - ≤52 weeks (>336 to ≤364 days)
 - >52 - ≤60 weeks (>364 to ≤420 days)
 - >60 - ≤72 weeks (>420 to ≤504 days)
 - >72 - ≤84 weeks (>504 to ≤588 days)
 - >84 - ≤96 weeks (>588 to ≤672 days)
 - >96 - ≤104 weeks (>672 to ≤728 days)
 - >104 weeks (>728 days)
- OLE Period
 - ≤14 weeks (≤98 days)
 - >14 - ≤28 weeks (>98 to ≤196 days)
 - >28 - ≤40 weeks (>196 to ≤280 days)
 - >40 - ≤52 weeks (>280 to ≤364 days)
 - >52 - ≤64 weeks (>364 to ≤448 days)
 - >64 - ≤78 weeks (>448 to ≤546 days)
 - >78 weeks (>556 days)
- Entire Study Period
 - ≤12 weeks (≤84 days)
 - >12 - ≤24 weeks (>84 to ≤168 days)
 - >24 - ≤36 weeks (>168 to ≤252 days)
 - >36 - ≤48 weeks (>252 to ≤336 days)
 - >48 - ≤52 weeks (>336 to ≤364 days)
 - >52 - ≤60 weeks (>364 to ≤420 days)
 - >60 - ≤72 weeks (>420 to ≤504 days)
 - >72 - ≤84 weeks (>504 to ≤588 days)
 - >84 - ≤96 weeks (>588 to ≤672 days)
 - >96 - ≤104 weeks (>672 to ≤728 days)
 - >104 - ≤118 weeks (>728 to ≤826 days)

- >118 - ≤132 weeks (>826 to ≤ 924 days)
- >132 - ≤144 weeks (>924 to ≤ 1008 days)
- >144 - ≤156 weeks (>1008 to ≤ 1092 days)
- >156 - ≤168 weeks (>1092 to ≤ 1176 days)
- >168 - ≤182 weeks (>1176 to ≤ 1274 days)
- >182 (>1274 days)

Only study drug exposure for DB period will be derived during Phase 3 Week 36 Interim Analysis.

Percent compliance to study drug regimen will be defined for DB period, OLE period, and the entire study period. Percent compliance will be calculated as $100 \times \text{actual number of drug syringe injected} / \text{number of expected drug syringe injected}$. The actual and expected number of drug syringes injected will be calculated as follows:

- For the DB period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken and with date of injection on or prior to the last DB EC record date. The number of syringes expected will be the ceiling of $\{(\text{the last DB EC record date} - \text{the first DB dose date} + 1) / 7\}$.
- For the OLE period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken and with date of injection on or after the first OL dose date. The number of syringes expected will be the ceiling of $\{(\text{the last OL EC record date} - \text{the first OL dose date} + 1) / 7\}$.
- For the entire study period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken. The number of syringes expected will be the ceiling of $\{(\text{the last EC record date} - \text{the first dose date} + 1) / 7\}$.
- Answers in “Weekly Injection Diary” eCRF indicate dose (i.e., injection) was taken including:
 - “Yes, Dose in Clinic” or “Yes, Dose off site” is selected for question “Did you dose this week?”, or
 - “Yes” is selected for question “Was the entire dose administered?”, or
 - Date or time is entered for “Please enter the date of this dose” or “Please enter the time of this dose”, or
 - Location is entered for “Please record the injection location by tapping the number associated with your injection site”.

Percent compliance to study drug regimen will be defined for DB period only during Phase 3 Week 36 Interim Analysis.

Descriptive statistics of percent compliance for DB period, OLE period, and the entire study, once defined will be presented using Safety Population. In addition, the number and percentages

of subjects with compliance in the following categories $\leq 80\%$, 80% to $\leq 90\%$, 90% to $\leq 100\%$, 100% to $\leq 120\%$, and $> 120\%$ will be presented.

3.4 Efficacy Assessment for the Phase 3 Week 36 Interim Analysis

The Phase 3 Week 36 Interim Analysis will take place when approximately the first 200 subjects complete their Week 36 visits or prematurely discontinue from the study. For Phase 3 Week 36 Interim Analysis, efficacy data will be summarized by randomized treatment based on the IAS. Unless otherwise indicated, the IAS is the primary analysis population for efficacy endpoints in Phase 3 Week 36 Interim Analysis.

3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR (i.e., $\log(\text{UPCR})$) at Week 36.

3.4.1.1 Primary Analysis

The primary efficacy endpoint will be analyzed by mixed-effects model for repeated measures (MMRM) including UPCR data up to Week 36 for IAS population. Formal statistical comparisons will be performed to compare the percentage change in UPCR between atacicept and placebo at each visit up to Week 36.

The estimand for the primary analysis of the primary efficacy endpoint is as follows:

- The population for the trial is defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The analysis population is based on the IAS population.
- The variable of interest is the change from baseline in $\log(\text{UPCR})$.
- The intercurrent events (ICEs) include (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplant, or death; (5) study withdrawal, including lost to follow-up. The intercurrent events and missing data will be handled in the order as described below:
 - Step 1: Intercurrent Events Strategy
 - For subjects who discontinue treatment, all observed data will be used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who initiate rescue/prohibited therapy, all observed data will be used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the data collected after the first occurrence of above ICEs will be deemed not interpretable and will be excluded from the analysis.
 - Step 2: Intermittent Missing Data
 - Intermittent missing data will be imputed by multiple imputation based on MCMC Monotone option in SAS PROC MI by treatment group under the missing at random assumption with 50 imputations.

- Step 3: Missing Data due to Intercurrent Events
 - After intermittent missing data were imputed in Step 2, the rest of the missing data mainly due to subjects who withdraw from the study, subjects who missed the last visit(s) while still ongoing in the study, or subjects experience dialysis, kidney transplant, or death. All these data will be imputed by “jump to reference” approach first according to the hypothetical strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the values after the first occurrence of such ICEs will be imputed again (i.e., replaced) by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy. Some subjects may experience dialysis or kidney transplant first, then experience other ICEs (such as study withdrawn). The ICEs of dialysis, kidney transplant, or death will take the priority. The values after the ICE of dialysis, kidney transplant, or death will be replaced by the “worst case” approach regardless of whether other ICEs occurred or not. The sufficiently unfavorable value is defined as the 99 percentiles of the change from baseline in log (UPCR) from all postbaseline visits and both treatments using the observed data from Step 1, since for UPCR endpoint, the higher the value is, the worse the IgAN disease status is. The random error is estimated by the residual error calculated from the same analysis model using the observed data from Step 1.
- Step 4: Statistical Analysis
 - Perform MMRM Analysis for each imputation data set.
 - Combine MMRM analysis results using Rubin’s rule (Rubin 1987).
- The population level summary measure is the reduction in the geometric mean ratio of UPCR relative to baseline in atacicept group compared to placebo group at Week 36, the associated 2-sided 95% confidence intervals (CI), and the p-value.

Baseline value for UPCR will be derived as the geometric mean of all measurements prior to the first dose of study drug. All UPCR data (including baseline and post-baseline) will be natural-log transformed prior to multiple imputation and analysis.

Following the above specified ICEs and missing data handling strategies, the statistical analysis method for the primary estimand is as follows. The primary efficacy endpoint will be analyzed using a MMRM model. Change from baseline in log (UPCR) will be the dependent variable. Effects for stable SGLT2i use at baseline (Yes, No), Region (Asia, Other), baseline eGFR category (< 45 , ≥ 45 and < 90 , or ≥ 90 mL/min/1.73m²), baseline natural-log transformed (UPCR), randomized treatment (atacicept, placebo), visit (Week 12, 24 and 36), and treatment-by-visit interaction will be included as independent fixed effects, and subjects will be included as a random effect. An unstructured covariance matrix will be used to model the within-subject correlation of data. In case some of the MMRM models fail to converge, the results based on these imputed datasets will be excluded from calculating the combined results using Robin’s rule.

The primary comparison will test the mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week 36. The statistical comparison will be based on linear contrasts of the Least Square Means (LSMs) estimated by the MMRM model.

Let T_{0i} and T_{1i} be the baseline UPCR and UPCR at Week v for the i subject in atacicept group, P_{0i} and P_{1i} be the baseline UPCR and UPCR at Week v for the i subject in placebo group, $i = 1, 2, 3, \dots, n$ and $v = 12, 24, 36$.

Mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week v can be expressed as:

$$\frac{\sum(\log T_{1i} - \log T_{0i})}{n} - \frac{\sum(\log P_{1i} - \log P_{0i})}{n} = \log\left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}}\right] \quad (1)$$

The exponentiation of (1) is the ratio of geometric mean ratio of UPCR at Week v to baseline between atacicept and placebo groups:

$$\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}} = \left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}} \quad (2)$$

The percentage reduction of the geometric mean ratio of UPCR at Week v relative to baseline for atacicept group vs. placebo group can be obtained as follow:

$$1 - \left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}}\right] \quad (3)$$

The LSM differences in natural-log scale, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values obtained from the MMRM model, while the relative reduction of geometric mean ratio or the estimated percentage reduction from baseline (i.e., $1 - \exp(\text{LSM difference})$), associated standard errors, associated 2-sided 95% CIs, will all be presented in the summary table.

The sample SAS code for primary efficacy endpoint analysis is provided in Appendix 8.4.1.

3.4.1.2 Sensitivity Analyses

Sensitivity Analysis 1: While-On-Treatment Analysis

The first sensitivity analysis will investigate the effect of different intercurrent events handling approaches on the estimation of treatment effect.

The estimand for the first sensitivity analysis is the same as that of the primary analysis with the following exceptions:

- While-on-treatment policy will be used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE will be used, and data collected after the first ICE will be treated as missing in the next step.
- After including all data collected on or prior to the first ICE, missing data will be imputed according to the hypothetical strategy.

- Intermittent missing: multiple imputation will be used to impute the intermittent missing based on MCMC monotone option in SAS PROC MI by treatment group under the missing at random assumption.
- Missing after the last observed data on or prior to the first ICE: multiple imputation will be used to impute missing data by treatment group using the regression option from the monotone statement of SAS PROC MI.
- Perform MMRM Analysis for each imputation data set.
- Combine MMRM analysis results using Rubin's rule.

Sensitivity Analysis 2: Tipping Point Analysis

The second sensitivity analysis will be a two-dimensional tipping point analysis to assess the robustness of the “worst case” and “jump to reference” imputation strategies used in the primary analysis. The two-dimensional tipping point analysis is a delta-adjust method under the Missing Not At Random (MNAR) assumption. It explores the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis become non-significant.

Two different fixed and definite sets of shift parameters will be imposed on the multiply imputed missing data respectively for atacicept group and placebo group to encapsulate the change in efficacy results. The shift parameters for both atacicept group and placebo group are ranged from -2.7 to 2.7 by 0.2 (i.e., -2.7, -2.5, -2.3, ..., 2.5, 2.7). The range and increments of shift parameters may be adjusted if tipping points are not identified in the range. For each given pair of shift parameters, adjust the imputed values by the shift parameters for atacicept group and placebo group respectively. The tipping points are the minimum shifts needed to make the results become non-significant. After the tipping point is identified, clinical judgement will be needed to assess the plausibility of the assumptions under the tipping point. The reverse of study conclusion under a plausible tipping point indicates that the primary analysis assumption may not be reasonable.

The pairs of shift parameters where the test results changed from significant to non-significant will be the tipping points. The shift parameters, the corresponding LS mean for each treatment, treatment difference, and associated p-value will be present in the table. A heat map will be plotted for shift parameters and p-values.

The SAS sample code for the tipping point sensitivity analysis is provided in Appendix [8.4.2](#).

3.4.1.3 Supplementary Analyses

A supplementary analysis for the primary endpoint will be conducted by using the Week 36 PP population using the observed data following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis, whereas other elements of the estimand will be the same as that of primary analysis, and the same MMRM model will be used (see Section [3.4.1.1](#)).

3.4.1.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the primary endpoint may be conducted for the following subgroups as appropriate based on IAS population:

- Age (< 40 , ≥ 40)
- Sex (Male, Female)
- Region (Asia, Other)
- Country (US, ex-US)
- Race (White, Non-White)
- Baseline UPCR (< 1.5 g/g, ≥ 1.5 g/g)
- Baseline Proteinuria (< 2 g/day, ≥ 2 g/day)
- Baseline eGFR (< 60 mL/min/1.73 m², ≥ 60 mL/min/1.73 m²)
- Stable SGLT2 use at baseline (Yes, No)

The subgroup analyses will be conducted using the same imputed data sets and the same MMRM model as that of the primary analysis for each subgroup category, separately. If the subgroup is one of the covariates in the model, the covariate will be removed from the model statement when the model is performed for the particular subgroup. If the sample size for a subgroup at a particular category is too small, the analysis might not be conducted.

A forest plot with geometric mean ratios, standard errors, associated 2-sided 95% CIs for the above subgroups and overall, when appropriate, will be presented.

3.4.2 Key Secondary Endpoint

The key secondary endpoint is the annualized rate change in eGFR through Week 104.

3.4.2.1 Primary Analyses

The analysis of the key secondary endpoint will take place when all study subjects complete the double-blind portion of the study (i.e., Week 104 visits) or prematurely discontinue from the study, which is specified in Section 3.5.2.1.

3.4.2.2 Interim Analyses for eGFR

At the time of Phase 3 Week 36 Interim Analysis, the following two endpoints will be analyzed for eGFR including data [REDACTED] based on IAS population:

- Annualized rate of change in eGFR [REDACTED].
- Change from baseline in eGFR by visit [REDACTED].

The estimand for analyzing the annualized rate of change in eGFR [REDACTED] is as follows:

- The population is defined in a similar manner as for the primary endpoint.
- The intercurrent events are defined in the same manner as for the primary endpoint. This endpoint will be analyzed based on IAS and including all available data [REDACTED] following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, no multiple imputation is planned for this endpoint.
- The variable of interest is the annualized rate of change in eGFR [REDACTED].
- The population level summary measure is the difference between atacicept and placebo group in the annualized rate of change in eGFR [REDACTED], the associated 2-sided 95% CI, and the p-value.

The analysis approach uses a mixed-effects model with random intercept and random slope (MMRIRS) to analyze the annualized rate of change in eGFR. In the MMRIRS model, eGFR will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category (< 2 g/24h or ≥ 2 g/24h), randomized treatment, time, and the treatment-by-time interaction. The actual time measurements, in years after the first injection (i.e., total slope), will be included in the model as a continuous variable. The baseline eGFR value recorded per subject will be assigned a time value of 0. The analysis testing the differences between the treatment groups will be constructed using linear contrasts of the appropriate LS Means from the MMRIRS model, where the difference in eGFR slope corresponds to the parameter for the treatment-by-time interaction term. BTUPE, and BGFR.

- The SAS sample code for the MMRIRS model is provided as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* TIME = Time in years calculated as (study visit date – the first DB dose date + 1)/365.25
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [ $< 45$ ,  $\geq 45$  to  $< 90$ , and  $\geq 90$  mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [ $< 2$ ,  $\geq 2$  g/24h]
* AVAL = eGFR value at each visit including baseline visit
*****
proc mixed data=efficacy method=reml;
  class TRTN USUBJID SGLT2 REGION BGFR BTUPE;
  model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TRTN*TIME /solution cl ddfm=kr;
  random INT TIME/ sub = USUBJID type = un;
  estimate 'Total Slope in Placebo' TIME 1 TRTN*TIME 1 0 / cl alpha=0.05;
  estimate 'Total Slope in Atacicept' TIME 1 TRTN*TIME 0 1 / cl alpha=0.05;
  estimate 'Total Slope Difference' TRTN*TIME -1 1 / cl alpha=0.05;
  ods output estimates=estimates;
run;
```

- Sensitivity analysis for the annualized rate of change in eGFR will not be conducted in the Week 36 Interim Analysis but will be conducted in the Week 104 Interim Analysis.

The estimand for analyzing the change from baseline in eGFR is as follows:

- The population is defined in a similar manner as for the primary endpoint.
- The intercurrent events are defined in the same manner as for the primary endpoint. This endpoint will be analyzed based on IAS and including all available data [REDACTED] following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, no multiple imputation is planned for this endpoint.
- The variable of interest is the change from baseline in eGFR.
- The population level summary measure is the difference between atacicept and placebo group in the change from baseline in eGFR, the associated 2-sided 95% CI, and the p-value.
- The analysis method is similar to that of the primary endpoint. Change from baseline in eGFR will be the dependent variable. Effects for stable SGLT2i use at baseline, region, baseline total urine protein excretion category, baseline eGFR, randomized treatment, visit, and treatment-by-visit interaction will be included as independent fixed effects, and subjects will be included as a random effect.
- Sensitivity analysis for the change from baseline in eGFR will not be conducted in the Week 36 Interim Analysis but will be conducted in the Week 104 Interim Analysis.

3.4.3 Analyses of Other Secondary Endpoints

For Phase 3 Week 36 Interim Analysis, selected other secondary endpoints will be evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment-policy strategy, except that data (i.e., Gd-IgA1 and Hematuria) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, no multiple imputation is planned for other secondary endpoints.

3.4.3.1 Change from Baseline at Week 36 in Natural-log Transformed Gd-IgA1

Differences in percentage change from baseline in Gd-IgA1 in atacicept group compared to placebo group at Week 36 will be analyzed using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, will all be presented in summary table.

3.4.3.2 Hematuria Resolution at Week 36

Hematuria categories are defined based on urine dipstick (labelled as “occult blood” in laboratory database) results into 4 categories: Negative/Trace = Negative or 0.03; 1+ = 0.06 or 0.1; 2+ = 0.2 or 0.5; and 3+ = 1.0 or >1.0.

- Hematuria resolution is defined as hematuria improvement to Negative/Trace from those with hematuria 1+ to 3+ at baseline.

The following analyses will be conducted:

- The number and percentage of subjects with hematuria resolution by visit and treatment group for subjects with 1+ to 3+ hematuria at baseline.

A logistic regression model for repeated measures will be used to estimate the odds ratio of achieving hematuria resolution for subjects treated with atacicept 150 mg versus subjects treated with the placebo for each postbaseline visit up to Week 36. The logistic regression model will include the indicator variable of whether a subject achieves hematuria resolution as the dependent variable, stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category, randomized treatment, visit, and treatment-by-visit interaction as fixed effects. The odds ratios for the treatment effect at each postbaseline visit up to Week 36, associated 2-sided 95% CIs, and 2-sided p-values will be presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment at each postbaseline visit, their associated 2-sided 95% CIs, will also be presented.

If the model does not converge, the covariates will be removed one by one until the model converges in the following sequential order: region, stable SGLT2i use at baseline, baseline total urine protein excretion category, and baseline eGFR category.

The sample SAS code for logistic regression analysis is provided in Appendix [8.4.3](#).

In addition, the number and percentage of subjects in each hematuria category will be summarized by visit and treatment group for the IAS population.

3.4.4 Exploratory Endpoints

For the Week 36 Interim Analysis, selected exploratory endpoints will be evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment policy strategy, except that data (i.e., [REDACTED], total urine protein, IgA, IgG, IgM, spot UPCR, and spot [REDACTED]) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, no multiple imputation is planned for exploratory endpoints.

3.4.4.1 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.4.4.2 Proportion of Subjects Achieving Desirable Total Urine Protein Reduction from Baseline at Week 36

- Proportion of subjects reaching total urine protein < 1 g/day and $\geq 25\%$ reduction from baseline at Week 36 will be evaluated based on IAS.

A logistic regression model for repeated measures will be used to analyze the proportion of subjects reaching the desirable total urine protein reduction from baseline at each postbaseline visit up to Week 36 similar to the model used for hematuria resolution (see Section 3.4.3.2 for details).

3.4.4.3 Change from Baseline at Week 36 in IgA, IgG, IgM, Spot UPCR, [REDACTED]

For each immunoglobulin biomarkers (i.e., IgA, IgG, and IgM), lab parameters from spot urine samples (i.e., spot UPCR [REDACTED]), the differences in percentage change from baseline in atacicept group compared to placebo group up to Week 36 will be analyzed, separately, using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values will all be presented in summary tables.

3.5 Efficacy Assessment for Phase 3 Week 104 Interim Analysis

Phase 3 Week 104 Interim Analysis will take place when all subjects complete the double-blind portion of the study at Week 104 or prematurely discontinue from the study. For Phase 3 Week 104 Interim Analysis, efficacy data will be summarized by randomized treatment based on the FAS population. Unless otherwise indicated, the FAS is the primary analysis population for efficacy endpoints in Phase 3 Week 104 Interim Analysis.

3.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR (i.e., $\log(\text{UPCR})$) at Week 36.

The primary efficacy endpoint would have been evaluated at Week 36 Interim Analysis based on IAS population and including all UPCR data up to Week 36. The change from baseline in natural-log transferred UPCR up to Week 104 will be evaluated at Week 104 Interim Analysis as a supportive analysis (i.e., not included in the multiple testing strategy) based on FAS population. The same estimand framework as specified for the primary analysis of the primary

efficacy endpoint will be followed (see details in Section 3.4.1.1) to estimate the treatment effect on UPCR by visit.

3.5.2 Key Secondary Endpoint

The key secondary endpoint is the annualized rate of change in eGFR through Week 104.

3.5.2.1 Primary Analyses

The estimand for the primary analysis of the key secondary endpoint is as follows:

- The population is defined in a similar manner as for the primary efficacy endpoint. The analysis population is based on the FAS population.
- The variable of interest is the annualized rate of change in eGFR through Week 104.
- The intercurrent events (ICEs) include (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplant, or death; (5) study withdrawal, including lost to follow-up. The intercurrent events and missing data will be handled in the order as described below:
 - Step 1: Intercurrent Events Strategy
 - For subjects who discontinue treatment, all observed data will be used according to treatment policy strategy.
 - For subjects who initiate rescue/prohibited therapy, all observed data will be used according to treatment policy strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the data collected after the first occurrence of above ICEs will be deemed not-interpretable and will be excluded from the analysis.
 - Step 2: Intermittent Missing Data
 - Intermittent missing data will be imputed by multiple imputation based on MCMC Monotone option in SAS PROC MI by treatment group under the missing at random assumption with 50 imputations.
 - Step 3: Missing Data due to Intercurrent Events
 - After intermittent missing data were imputed in Step 2, the rest of the missing data mainly due to subjects who withdraw from the study, subjects who missed the last visit(s) while still ongoing in the study, or subjects experience dialysis, kidney transplant, or death. All these missing data will be imputed by “jump to reference” approach first according to the hypothetical strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the values after the first occurrence of such ICEs will be imputed again (i.e., replaced) by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy. Some subjects may experience dialysis or kidney transplant first, then experience other ICEs (such as study withdrawn). The ICEs of dialysis, kidney transplant, or death will take the priority. The values after the ICE of dialysis, kidney transplant, or death will be replaced by the “worst case” approach regardless of whether other ICEs occurred or not. The sufficiently unfavorable value is defined as the 1 percentile of the

eGFR values from all visits and both treatments using the observed data from Step 1, since for eGFR endpoint, the lower the value is, the worse the renal function is. The random error is estimated by the residual error calculated from the same analysis model using the observed data from Step 1.

- For subjects who withdraw from the study and do not experience dialysis, kidney transplant, and death, the values after study withdrawn will be imputed by “jump to reference” approach according to the hypothetical strategy.
- Step 4: Statistical Analysis
 - Perform MMRIRS model for each imputation data set.
 - Combine MMRIRS model results using Rubin’s rule.
- The population level summary measure is the difference between atacicept and placebo group in the annualized rate of change in eGFR through Week 104, the associated 2-sided 95% CI, and the p-value.

The analysis approach uses a MMRIRS to analyze the annualized rate of change in eGFR. In the model, eGFR will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category, randomized treatment, time, and the treatment-by-time interaction. The actual time measurements, in years after the first injection (i.e., total slope), will be included in the model as a continuous variable. The baseline eGFR value recorded per subject will be assigned a time value of 0. The analysis testing the differences between the treatment groups will be constructed using linear contrasts of the appropriate LS Means from the MMRIRS model, where the difference in eGFR slope corresponds to the parameter for the treatment-by-time interaction term.

- The sample SAS code for primary analysis of the key secondary efficacy endpoint is provided in Appendix [8.4.3](#).

3.5.2.2 Sensitivity Analyses

Sensitivity Analysis 1: While-On-Treatment Analysis

The first sensitivity analysis will investigate the effect of different intercurrent events handling approach on the estimation of treatment effect.

The estimand for the first sensitivity analysis is the same as that of the primary analysis with the following exceptions:

- While-on-treatment policy will be used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE will be used, and data collected after the first ICE will be treated as missing in the next step.
- After including all data collected on or prior to the first ICE, missing data will be imputed according to the hypothetical strategy.

- Intermittent missing: multiple imputation will be used to impute the intermittent missing based on MCMC monotone option in SAS PROC MI by treatment group under the missing at random assumption with 50 imputations.
- Missing after the last observed data on or prior to the first ICE: multiple imputation will be used to impute missing data by treatment group using the regression option from the monotone statement of SAS PROC MI.
- Perform MMRIRS Analysis for each imputation data set.
- Combine MMRIRS analysis results using Rubin's rule.

Sensitivity Analysis 2: Tipping Point Analysis

The second sensitivity analysis will be a two-dimensional tipping point analysis to assess the robustness of the “worst case” and “jump to reference” imputation strategies used in the primary analysis. The two-dimensional tipping point analysis is a delta-adjust method under the Missing Not At Random (MNAR) assumption. It explores the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis become non-significant.

Two different fixed and definite sets of shift parameters will be imposed on the multiply imputed missing data respectively for atacicept group and placebo group to encapsulate the annualized total slope in efficacy results. The shift parameters for total slope for both atacicept group and placebo group are ranged from -8 to 8 by 2 (i.e., -8, -6, ..., 6, 8). The range and increments of shift parameters may be adjusted if tipping points are not identified in the range. For each given pair of shift parameters, it adjusts the imputed eGFR values over time by the shift parameters for atacicept group and placebo group respectively. The tipping points are the shift needed to make the results become statistically non-significant, or in other words, they are the minimum deviation of the distribution of missing data needed to make the results become statistically non-significant. After the tipping points are identified, clinical judgement will be needed to assess the plausibility of the assumptions under the tipping points. The reverse of study conclusion under plausible tipping points indicates that the primary analysis assumption may not be reasonable.

The SAS sample code for the tipping point sensitivity analysis is provided in [Appendix 0](#).

Sensitivity Analysis 3: Two-slopes MMRIRS

Sensitivity analysis may be conducted to estimate the annualized eGFR chronic slope if data suggests there is an acute eGFR effect, i.e., a noticeable acute increase/decrease in eGFR observed in atacicept group at an early post-baseline visit, such as Week 12.

Statistical analysis will be carried out using a MMRIRS model allowing for two slope parameters, corresponding to acute (or short-term) and chronic (or long-term) eGFR slope effects, in order to characterize longitudinal trends in the rate of eGFR decline. The model is formulated via the definition of a changepoint in time at which the chronic effect starts. The changepoint will be selected based on visualization of Phase 3 eGFR data and confirmed by fitting the model considering changepoints at Weeks 4 to 24 and selecting the changepoint

corresponding to the best fitting model as determined by the Akaike's Information Criterion (AIC) using the observed data set.

This sensitivity analysis will use the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1). The two-slope MMRIRS model described below will be fitted on each imputed dataset and the results will be combined using Rubin's rules to obtain the estimates of the difference and its associated 95% CI in acute slope and total slope, respectively.

Let t^* denote the selected changepoint and let $time_cp = \max \{ time - t^*, 0 \}$ be the truncated time after the changepoint. In the two-slope MMRIRS model, eGFR will be the dependent variable, with random subject effects for intercepts and two slopes; Fixed effects include baseline eGFR category, baseline total urine protein excretion category, stable SGLT2i use at baseline, region, randomized treatment, time, time_cp, treatment-by-time interaction, and treatment-by-time_cp interaction. The actual *time* measurements, in years after the first injection, and the truncated *time_cp* measurement, in years after the changepoint, will be included in the model as continuous variables. The baseline eGFR value recorded per subject will be assigned a time value of 0. An unstructured covariance matrix will be used to model the within subject correlation of data. In case the model fails to converge using an unstructured covariance matrix at any stage, compound symmetric covariance matrix will be used. If convergence still fails, statistically insignificant (i.e., $p > 0.05$) stratification factors may be removed from the model to satisfy the convergence criteria. If issues persist, a modified single-slope MMRIRS excluding eGFR values prior to the changepoint will be instead fit.

The SAS sample code for the two-slope MMRIRS is provided in Appendix 8.4.6.

3.5.2.3 Supplementary Analyses

A supplementary analysis for the key secondary endpoint will be conducted using the Week 104 PP population using the observed data following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis, whereas other elements of the estimand will be the same as that of primary analysis and the same MMRIRS will be repeated (see Section 3.5.2.1).

3.5.2.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the key secondary endpoint may be conducted for the following subgroups as appropriate based on FAS population:

- Age (< 40 , ≥ 40)
- Sex (Male, Female)
- Region (Asia, Other)
- Country (US, ex-US)
- Race (White, Non-White)
- Baseline UPCR (< 1.5 g/g, ≥ 1.5 g/g)
- Baseline Proteinuria (< 2 g/day, ≥ 2 g/day)

- Baseline eGFR ($< 60 \text{ mL/min/1.73 m}^2$, $\geq 60 \text{ mL/min/1.73 m}^2$)
- Stable SGLT2i use at baseline (Yes, No)

The subgroup analyses will be conducted using the same MMRIRS as that of primary analysis and the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1) for each subgroup category, separately. If the subgroup is one of the covariates in the model, the covariate will be removed from the model statement when the model is performed for the particular subgroup. If the sample size for a subgroup at a particular category is too small, the analysis might not be conducted.

A forest plot with total slope difference, standard errors, associated 2-sided 95% CIs obtained from the MMRIRS for the above subgroups, when appropriate, will be presented.

3.5.3 Analyses of Other Secondary Endpoints

For Phase 3 Week 104 Interim Analysis, selected other secondary endpoints will be formally evaluated according to the hierarchical multiple testing approach prespecified in Section 3.1.7 based on FAS and including all available data up to Week 104.

For the change from baseline in eGFR at [REDACTED] 104 endpoints, the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1) will be used to support this secondary endpoint.

All other secondary endpoints, excluding the change from baseline in eGFR [REDACTED] and 104, will be analyzed following the treatment-policy strategy, except that data (e.g., Gd-IgA1, eGFR, and Hematuria) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, no multiple imputation is planned for other secondary endpoints.

3.5.3.1 Change from Baseline at [REDACTED] and 104 in eGFR

For each imputed dataset, the differences in change from baseline in eGFR in atacicept group compared to placebo group at each post baseline visit will be analyzed using the MMRM model. Change from baseline in eGFR will be the dependent variable. Effects for stable SGLT2i use at baseline, Region, baseline total urine protein category, baseline eGFR, randomized treatment, visit, and treatment-by-visit interaction will be included as fixed effects, and subjects will be included as a random effect. The results will be combined using Rubin's rule to obtain the final result. The LSM differences, standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-values will be presented in the summary table.

3.5.3.2 Change from Baseline at Weeks 36, 52, and 104 in Gd-IgA1

Differences in percentage change from baseline in Gd-IgA1 in atacicept group compared to placebo group at each postbaseline visit up to Week 104 will be analyzed using MMRM similar to the one as described in Phase 3 Interim Analysis (see Section 3.4.3.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction

from baseline, associated standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-value will all be presented in summary table.

3.5.3.3 Hematuria Resolution at Weeks 36, 52, and 104

Hematuria resolution will be analyzed using logistic regression model with repeated measurements similarly as described in Phase 3 Week 36 Interim Analysis (see Section 3.4.3.2 for details) using FAS population and including data up to Week 104. The odds ratios for the treatment effect at each postbaseline visit up to Week 104, associated 2-sided 95% CIs, and 2-sided p-values will be presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment and by visit, their associated 2-sided 95% CIs, will also be presented.

3.5.3.4 Time from Randomization to the First Occurrence of Composite Kidney Failure Endpoint Event

Time to the first occurrence of composite kidney failure endpoint event will be analyzed using a Cox proportional hazards model including stable SGLT2i use at baseline, Region, baseline eGFR category, baseline total urine protein category, and randomized treatment as fixed effects. The estimated hazard ratio, the corresponding 2-sided 95% CIs, and 2-sided p-values will be presented. Participants who have not had an event up to Week 104 will be censored in the analysis. Cumulative incidence curves will be presented by treatment group.

3.5.4 Exploratory Endpoints

For Week 104 Interim Analysis, all exploratory endpoints will be evaluated as supportive analyses similarly as they are analyzed in Phase 3 Week 36 Interim Analysis (see Section 3.4.4 for details) based on FAS and including all available data up to Week 104.

3.6 Safety Assessment

Safety data will be summarized by actual treatment received based on the Safety Population.

For Phase 3 Week 36 Interim Analysis, as we expect a minimal number of subjects will complete the DB period and enter into the OLE period, safety assessments will be summarized for the DB period only.

For Phase 3 Week 104 Interim Analysis, safety assessments will be summarized for DB period, OLE period, and the entire study period, separately.

For both interim analyses, all safety data, regardless of being collected in DB period, OLE period, or follow-up period will be listed for Safety population.

3.6.1 Adverse Events (AEs)

All AEs occurring from the date of the first informed consent to the last safety follow-up visit will be collected and captured by eCRF. All AEs will be coded and categorized using SOC and

PT using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The severity of AEs will be assessed by the Investigator as mild, moderate, or severe.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates occurring during the study period (i.e., on or after the first dose date/time until the subject's last study visit). TEAEs will be assigned to the most recently received treatment at the start of the AE.

AEs will be considered treatment-emergent during the DB period if they start on or after the first dose date/time of double-blinded study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. AEs will be considered treatment-emergent during the OLE period if they start on or after the first dose date/time of OLE study drug through the end of the study. If AEs cannot be decided as to which period they belong due to completely missing or partial AE onset dates, AEs will be considered treatment-emergent during both periods.

An overview summary of the number and percentage of subjects with the following TEAEs will be provided:

- TEAEs (overall and by severity)
- Study drug related TEAEs (overall and by severity)
- Treatment-emergent serious AEs (TESAEs)
- Study drug related TESAEs
- TEAEs of special interest (TEAESI) defined by relevant SMQ narrow scope search (overall and by severity)
- TEAEs of injection site reaction (ISR) defined by injection site reaction PT or by combined PTs (overall and by severity)
- TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death

In addition, the following TEAEs will be summarized by SOC and/or PT separately:

- TEAEs by SOC and PT
- Study drug related TEAEs by SOC and PT
- TESAEs by SOC and PT
- Study drug related TESAEs by SOC and PT
- TEAESIs by Category and PT
- TEAEs leading to study drug interruption by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

- Common TEAEs by PT ($\geq 5\%$ incident rate in either treatment arm)

A subject experienced multiple TEAEs within a SOC or PT will be counted only once for the SOC or PT. For tabulations that include classification by relationship to study treatment, TEAEs with missing relationship will be considered related to study drug. When summarized by severity, a subject with TEAEs with multiple severity categories will be summarized under the maximum severity category (severe > moderate > mild). If missing severity category exists, TEAEs with missing severity will be summarized under a missing category and displayed as the last category in severity summary table.

Adverse events of special interest (AESIs) include infections, hypersensitivity reactions, demyelination disorders, and cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease).

AESI of infections will be identified by SOC of “infections and infestations”, all serious infections or severe infections will be summarized by treatment.

For hypersensitivity reactions, demyelination disorders, and cardiac events, a list of preferred terms from the relevant Standardized MedDRA Query (SMQ) narrow scope will be used to flag these AESI in a systematic and objective way. AESIs identified by SMQ narrow search will be included for tabulation summary and listing.

Listings will be presented specifically for AEs, SAEs, AESIs, AEs leading to study drug discontinuation, AEs leading to study discontinuation, and AEs leading to death.

3.6.2 Clinical Laboratory Tests

Clinical laboratory tests in this study include hematology, clinical chemistry, urine sediment, routine urinalysis and other tests.

Summary statistics for selected hematology, clinical chemistry, urine sediment, and routine urinalysis at DB baseline, at all scheduled post-baseline visits, as well as for change from baseline for all scheduled post baseline visits will be provided by treatment group. Results of clinical laboratory tests will be flagged as abnormal if they are out of normal ranges.

Listings of hematology, clinical chemistry, urine sediment, routine urinalysis and other tests will be provided respectively.

3.6.3 Vital Signs

Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, and at the scheduled visits.

Summary statistics for systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature at DB baseline, at all scheduled post baseline visits, as well as for change from baseline for all scheduled post-baseline visits will be provided by treatment group.

A listing of vital signs will be provided.

3.6.4 Electrocardiograms (ECG)

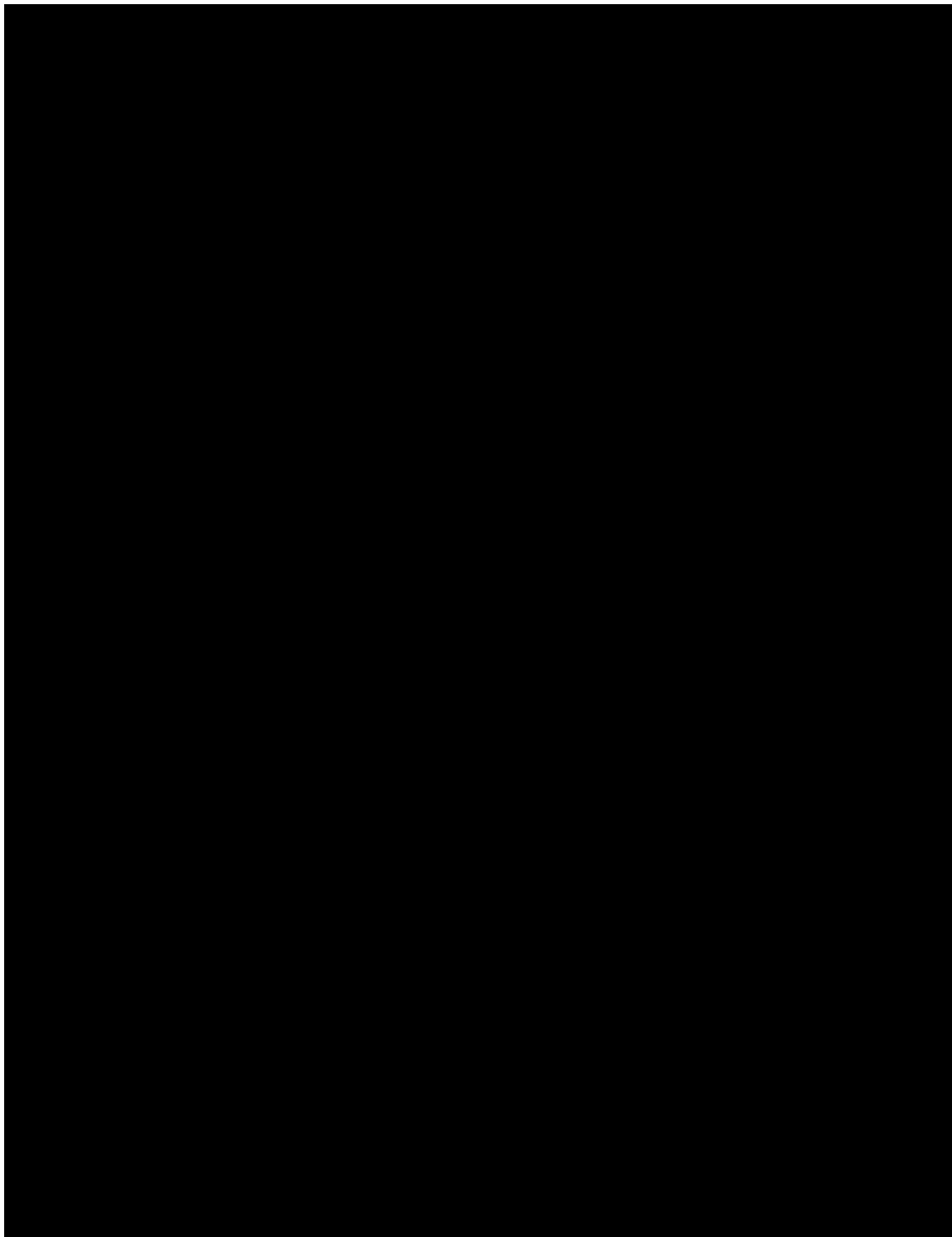
The overall interpretation of ECG results will be categorized as abnormal (further categorized as clinically significant abnormal or not clinically significant abnormal), indeterminate, normal, not evaluable, and unknown. The number and percentage of subjects with different categories of overall interpretation of ECG results will be summarized by visits (including baseline and scheduled post-baseline visits).

A listing of ECG will be provided.

3.6.5 Physical Examinations

A complete physical examination will include, at a minimum, assessment of the general appearance, skin, lymph nodes (cervical), head, ears, eyes, nose, throat (HEENT), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems. Complete physical examination will be performed at screening and Week 104 visits. On other visits, a symptom-driven physical examination will be performed and will include assessment of any new subject complaints or changes from baseline.

Findings from physical examinations will be categorized as clinically significant and not clinically significant. As physical examination findings are qualitative and there is significant inter-observer variation, no analyses will be performed on the physical examination data. All physical examination findings will be presented in a listing.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.7 Anti-Drug Antibody Assessment

ADA results from each sample are reported as either positive or negative based on the confirmatory assay. If the sample is positive, the ADA titer is reported as well. In addition, the presence of neutralizing antibody (nAb) may be tested for all ADA-positive samples. The nAb results are reported as positive or negative. A patient is defined as being ADA-positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements. A patient is defined as being ADA-negative if the patient has no positive ADA assessments at all available assessments.

Number and percentage of immunogenicity-evaluable subjects (i.e., subjects in the Immunogenicity Population) in the following categories are provided. The number of immunogenicity-evaluable subjects in each treatment group will be used as the denominator for percentage calculation. Descriptive statistics (N, minimum, Q1, median, Q3, and maximum) for maximum post-baseline ADA titers for each ADA category will be provided.

- ADA positive at baseline or post-baseline: subjects with any positive ADA assessment at baseline or post-baseline. The percentage of these subjects in a population is known as ADA prevalence.

- Treatment-induced ADA positive: subjects who were ADA negative or missing at baseline and became ADA positive post-baseline.
- Treatment-boosted ADA positive: subjects who were ADA positive at both baseline and post-baseline but had a meaningful increase in ADA titer by at least 2-fold of dilution factors from baseline to post-baseline. For example, if the dilution factor is 2, a meaningful increase means at least 4-fold increase in ADA titer from baseline to post-baseline.
- Treatment-emergent ADA positive (TE-ADA+): subjects who were either treatment-boosted ADA positive or treatment-induced ADA positive. The percentage of these subjects in a population is known as ADA incidence.
- Non-TE-ADA+: subjects who were ADA positive but not fulfilling the criteria for being TE-ADA+.

ADA results at each visit and the corresponding efficacy endpoints (i.e., percentage change from baseline in UPCR and change from baseline in eGFR) and PK concentration will be presented in a subject listing. In addition, a treatment-emergent adverse event listing will be reported for ADA positive subjects.

4 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (iDMC) will monitor the safety and wellbeing of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority in all aspects. Details regarding the role, responsibilities, and data review requirements of the iDMC will be outlined in a separate iDMC charter.

5 MID-STUDY ANALYSIS AND FINAL ANALYSIS TIMING

5.1 Primary Endpoint Analysis at Week 36 Data Cut

The primary analysis of UPCR will be performed after approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study. This data cut will include all data from all subjects when approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study, including data from subjects who have completed visits beyond Week 36.

5.2 End of Part C Analysis at Week 104 Data Cut

An end of Part C analysis will be performed when all subjects complete the double-blind portion of the study at Week 104 or prematurely discontinue from the study. This data cut will include all data from all subjects when all subjects complete the Week 104 visit or prematurely discontinue from the study, including data from subjects who have completed visits beyond Week 104.

5.3 Final Analysis

A final analysis will be conducted once all subjects complete the OLE and safety follow-up visits or discontinue from the trial.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Protocol Amendment 7 specified the annualized rate of change in eGFR through Week 104 as the key secondary endpoint. Since we expect a very few subjects will complete Week 104 visits by the time of Week 36 data cut, we will not evaluate the annualized rate of change in eGFR through Week 104, instead the annualized rate change in eGFR [REDACTED] and the change from baseline in eGFR by visit [REDACTED] will be evaluated at the time of Phase 3 Week 36 Interim Analysis. The corresponding estimand elements are detailed in Section [3.4.2](#).

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by treatment group, subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

8 APPENDICES

8.1 Appendix 1: References

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4. Inker LA, Heerspink HJL, Tighiouart H. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Subject Meta-analysis. *Am J Kidney Dis*. 2021;78:340-349.e1.
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7. Rubin, D. B.. Multiple Imputation for Nonresponse in Surveys. Wiley 1987.

[REDACTED]

[REDACTED]

8.2 Appendix 2: Schedule of Assessment

Study Period	Screening	PART C ¹ Blinded Treatment Period													PART D ¹ Open-Label Extension Period (OLE)					Follow-Up	
Week	-4	0	2	4	12	24	36	48	52	60	72	84	96	104 ¹	106	118	132	144	156/ET	+12	+26
Study Day	-28 to -1	1	15	29	85	169	253	337	365	421	505	589	673	729	743	827	925	1009	1093	From W156/ET Visit	
Visit Window (±day)			±5	±5	±7	±7	±14	±7	±7	±14	±14	±14	±14	±14	±5	±14	±14	±14	±14	±14	±14
Informed consent	X																				
Inclusion/exclusion criteria Review ²	X	X																			
Randomization		X																			
Demographic data	X																				
Medical history	X																				
Optional remote visit ³				X				X				X			X		X				
Assessments																					
Vital signs, weight, height ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X												X					X		
Complete physical examination	X													X							
Symptom-driven physical examination		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Tuberculosis assessment	X																				
Study questionnaires (EQ-5D-5L, SF-36, FACIT-F)		X				X	X		X		X			X			X		X		
Laboratory Assessments																					
Routine hematology, chemistry, urinalysis ⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X																				
Serum Virology ⁶	X																				
Serum pregnancy test ⁷	X																				

Study Period	Screen- ing	PART C ³ Blinded Treatment Period													PART D ⁵ Open-Label Extension Period (OLE)					Follow-Up	
Week	-4	0	2	4	12	24	36	48	52	60	72	84	96	104 ⁷	106	118	132	144	156/ET	+12	+26
Study Day	-28 to -1	1	15	29	85	169	253	337	365	421	505	589	673	729	743	827	925	1009	1093	From W156/ET Visit	
Visit Window (±day)			±5	±5	±7	±7	±14	±7	±7	±14	±14	±14	±14	±14	±5	±14	±14	±14	±14	±14	±14
HbA1c	X																				
Urine pregnancy test ^h		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine collection for quantitative analysis ⁱ	X	X			X	X	X		X		X			X		X	X	X	X		
Spot urine ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Archival kidney biopsy/ Pre-treatment kidney biopsy ^k	X																				
Pharmacokinetic Assessments																					
Serum atacicept ^l		X	X	X	X	X	X	X	X		X		X	X		X		X		X	X
Anti-drug antibodies ^l		X	X	X	X	X	X	X	X		X		X	X		X		X		X	X
Pharmacodynamic Assessment																					
Immunoglobulins (IgG,IgA,IgM)	X ^m	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gd-IgA1		X		X	X	X	X		X		X			X	X		X		X	X	X
Serum BlyS & APRIL level ⁿ		X				X	X		X					X					X		
Exploratory Biomarkers ^o		X		X	X	X	X	X	X			X	X	X	X	X		X	X	X	X
Safety and Study Drug																					
Prior/Concomitant medications and procedures		Continuous																			
Adverse events		Continuous																			
Injection site assessment		Continuous																			
IMP accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	Screen- ing	PART C ⁵ Blinded Treatment Period													PART D ⁵ Open-Label Extension Period (OLE)					Follow-Up	
Week	-4	0	2	4	12	24	36	48	52	60	72	84	96	104 [†]	106	118	132	144	156/ET	+12	+26
Study Day	-28 to -1	1	15	29	85	169	253	337	365	421	505	589	673	729	743	827	925	1009	1093	From W156/ET Visit	
Visit Window (±day)			±5	±5	±7	±7	±14	±7	±7	±14	±14	±14	±14	±14	±5	±14	±14	±14	±14	±14	±14
IMP administration [‡]			X [‡]	X	X	X	X	X	X	X	X	X	X	X [‡]	X	X	X	X	X		
IMP dispensing to subject		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pregnancy test dispensing to subject [§]				X	X	X	X	X	X	X	X	X			X	X	X	X			

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; [REDACTED]; [REDACTED] ET=early termination; [REDACTED]; Gd-IgA1=galactose deficient IgA1; HbA1c=hemoglobin-A1c; Ig=immunoglobulin; IgAN=IgA Nephropathy; IMP=investigational medicinal product; ISR=injection site reaction; PGx=pharmacogenetics; PK=pharmacokinetics; [REDACTED] TSH=Thyroid stimulating hormone; WOCBP=woman of childbearing potential.

- Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization. Predose assessments on Day 1 are considered baseline measurements prior to first dose of study drug.
- IgAN clinical diagnosis, medical history, medications, previous vaccinations, surgery/procedures. Documentation of IgAN on biopsy within 10 years. See Protocol Section 14.
- For Weeks 4, 48, 84, 106, and 132, at the Investigator's discretion, the study visit(s) can be conducted in-clinic or remotely. If conducted remotely, the visit will include alternative methods for safety, efficacy and distribution/collection of Investigational Medicinal Product (IMP), including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery of IMP and home health care (if available). For the Phase 3 study, facilitation of optional remote visit(s) is the responsibility of the Investigator and site staff.
- Vital signs measured per Protocol Section 16.6.2. Order of procedures done per Protocol Section 16. Height to be measured at screening only.
- eGFR will be calculated using the CKD-EPI formula. Routine urinalysis: A sample from "fresh" urine will be collected during the scheduled clinic visit. Subjects will be provided with a urine cup and instructions for a mid-stream collection to provide a clean-catch specimen. For Optional Remote Visits, urine should be collected via clean catch.
- Includes testing for Hepatitis B, Hepatitis C and HIV. Subjects who are HbsAg negative, HbcAb positive, HbsAb positive with no detectable HBV DNA are not excluded but require monthly HBV DNA monitoring ±10 days.
- Women of childbearing potential (WOCBP) only. Screening test is serum.
- Women of childbearing potential (WOCBP) only Post screening, positive urine pregnancy test results will be confirmed by serum pregnancy testing.
- 24-hour urine collection should begin 1 day before the study visit and should start with discarding the first morning void, and collecting all urine produced thereafter (through the day and night) up to 24 hours later (including the first morning void of the second morning). Subjects will be provided with adequate urine collection cups in advance of 24-hour urine collection timepoints.
- Spot urine sample will be obtained from the routine urinalysis sample.
- A confirmed biopsy report (within 10 years of Screening Visit) is required to confirm IgAN diagnosis. If unavailable, a pre-treatment kidney biopsy is required to confirm eligibility.

- l. On Day 1, a blood sample will be collected pre-dose for ADA. PK will be collected between 2-4 hours after the first study dose. At Week 104 a blood sample for PK and ADA will be collected prior to drug administration on site. At Week 12 and Week 118, a blood sample for PK and ADA will be collected and all efforts should be made to ensure that last dose of study drug was given 7 days prior to the blood sample collection for Weeks 12, 104 and 118. Time and date of last dose of study drug will be collected for each collection.
- m. At Screening, IgG only.
- n. Test performed if assay is available.
- o. Blood and urine samples will be collected and stored for future clinical laboratory testing, in order to provide additional clinical data. No genetic testing will be performed on samples.
- p. See Protocol Section 15.4. IMP to be administered once weekly. Injections at Day 1 and Week 104 are given in clinic. At the Week 104 Visit after completion of all study visit assessments, subjects will switch from double-blinded treatment to open-label treatment.
- q. Sites will provide WOCBP with enough tests to conduct pregnancy testing once per month until the next scheduled study visit during Parts C and D and will contact these subjects monthly to confirm that the pregnancy test has been performed, and the results are negative.
- r. At the Week 104 Visit after completion of all study visit assessments, subjects will switch from double-blinded treatment to open-label treatment.
- s. If in the opinion of the Investigator, additional subject monitoring is needed, additional visits can be conducted at Weeks 1, 3, and 105. Assessments may include AEs, concomitant medications, vitals, symptom-driven physical exam, and IMP administration.

8.3 Appendix 3: Analysis Window Relative to DB Baseline

Analysis Visit	Target Analysis Day	Earliest Analysis Day	Latest Analysis Day
Screening	-1		-1
DB Baseline (Day 1)	1		prior to the first DB dose date/time
Week 2	15	On or after the first DB dose date/time	21
Week 4	29	22	56
Week 12	85	57	126
Week 24	169	127	210
Week 36	253	211	294
Week 48	337	295	350
Week 52	365	351	392
Week 60	421	393	462
Week 72	505	463	546
Week 84	589	547	630
Week 96	673	631	700
Week 104	729	701	735 for subjects not participating in OLE; prior to the OLE first dose date/time for subjects continuing in OLE
Week 106	743	On or after the OLE first dose date/time	784
Week 118	827	785	875
Week 132	925	876	966
Week 144	1009	967	1050
Week 156	1093	1051	1134
Week 168	1177	1135	1225
Week 182	1275	1226	NA

Note: Analysis Day = Event Date – First Date of Dosing in DB period +1 for events on first date of dosing in DB period and after. Analysis Day = Event Date – First Date of Dosing for events prior to first date of dosing in DB period.

8.4 Appendix 4: Program Specifications

8.4.1 Primary Analysis for the Primary Efficacy Endpoint at Week 36 Interim Analysis

The sample SAS code for primary efficacy endpoint analysis is provided as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* VISIT = Post-baseline study visits (Week 12, Week 24, and Week 36)
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, and >=90 mL/min/1.73m2]
* BHEMA = Baseline hematuria category [Negative/Trace, 1+, 2+, and 3+]
* BASE = log (baseline UPCR)
* CHG = Change of natural logarithmic UPCR at each post-baseline visit calculated as AVAL-BASE.
      where AVAL= log transformed UPCR value at each visit
* WEEK12, WEEK24, WEEK36 = Natural-log transformed UPCR values at Week 12, Week 24 and Week 36
*****;
/*Take log-transformation for UPCR at each visit. BASE, AVAL, and CHG are the baseline, absolute value, and the
change from baseline in log(UPCR), respectively*/
/*Transpose the change from baseline in log-transformed UPCR (i.e., CHG) to wide format, one record per subject*/

/*Step 1: Intercurrent Event Strategy*/
/*Exclude values collected on and after ICEs of dialysis, kidney transplant */

/*Step 2: Intermittent Missing Data Imputation Using MCMC*/
proc mi data=in seed=123 nimpute=50 out=mono;
  by TRTN;
  var BASE WEEK12 WEEK24 WEEK36;
  mcmc impute=monotone nbiter=5000 niter=5000;
run;

/*Step 3.1: Missing Data due to ICEs*/
/* All missing values should theoretically result from study withdrawal, dialysis, kidney transplant, or
death. However, there may occasionally be a few subjects with missing values at their last visits while still
remaining on-study. For simplicity, all missing values will be imputed using the 'Jump to reference' strategy. */
proc mi data=mono seed=123 nimpute=1 out=outmi;
  class TRTN SGLT2 REGION BGFR BHEMA;
  by _imputation_ ;
  monotone reg(/details);
  mnar model (WEEK12 / modelobs= (TRTN= '1'));
  mnar model (WEEK24 / modelobs= (TRTN= '1'));
  mnar model (WEEK36 / modelobs= (TRTN= '1'));
  var SGLT2 REGION BGFR BHEMA BASE WEEK12 WEEK24 WEEK36;
run;

/* Step 3.2: Missing Data due to Dialysis, Kidney transplant, or Death */
/* Impute values in visits on and after ICEs of dialysis, kidney transplant, and death*/
/* In each imputation, replace the values on and after the above ICEs with rand('normal',U,E); */
/* Where U and E are the mean and random error for the unfavorable values for change in ln(UPCR).*/

/*Step 4: Statistical Analysis*/
```

/*Analyze the imputation data sets after transposing to long format, one record per visit per subject per imputation*/
proc mixed data=efficacy (where=(CHG ne . and BASE ne.)) method=reml;

```
by _imputation_;  
class TRTN USUBJID VISIT SGLT2 REGION BGFR;  
model CHG = SGLT2 REGION BGFR BASE TRTN VISIT TRTN*VISIT /ddfm=kr;  
repeated VISIT/ sub = USUBJID type = un;  
lsmean TRTN*VISIT / cl alpha=0.05 OM;  
estimate 'Week 36 Effect' TRTN -1 1 TRTN*VISIT 0 0 -1 0 0 1 / cl alpha=0.05;  
estimate 'Week 24 Effect' TRTN -1 1 TRTN*VISIT 0 -1 0 0 1 0 / cl alpha=0.05;  
estimate 'Week 12 Effect' TRTN -1 1 TRTN*VISIT -1 0 0 1 0 0 / cl alpha=0.05;  
ods output Estimates=Estimates;  
run;
```

/*Combine the analysis results using Rubin's rule*/

```
proc mianalyze data=estimates;  
where Label = 'Week 36 Effect';  
modeleffects estimate;  
stderr stderr;  
ods output parameterestimates=diffs1;  
run;
```

8.4.2 Sensitive Analysis for the Primary Efficacy Endpoint at Week 36 Interim Analysis: Tipping Point Analysis

The SAS sample code for the tipping point sensitivity analysis is provided as follows:

Step 1. Set Week 36 values to missing for all subjects with ICEs of dialysis, kidney transplant, death, and study withdrawal from the primary imputed analysis dataset.

```
*****
* TRTN = treatment group (1=Placebo 2 =atacicept 150mg)
* BASE = Natural-log transformed UPCR value at baseline
* SGLT2 REGION BGFR= baseline stratification variables
* WEEK12, WEEK24, WEEK36 = Natural-log transformed UPCR values at Week 12, Week 24 and Week 36
* k1= -2.7, -2.5, ..., 2.5, 2.7
* k2= -2.7, -2.5, ..., 2.5, 2.7
*****;
```

Step 2. Apply MNAR assumption under each pair of shift parameters (k1, k2) for each imputed data set generated from Step 1.

```
proc mi data= adeff mono nimpute=1 SEED=439384 OUT=imputed;
  class SGLT2 REGION BGFR;
  by __imputation__;
  var SGLT2 REGION BGFR BASE WEEK12 WEEK24 WEEK36;
  monotone reg;
  mnar adjust (WEEK36 / shift = &k1. adjustobs=(TRTN='1' ));
  mnar adjust (WEEK36 / shift = &k2. adjustobs=(TRTN='2' ));
run;
```

Step 3. Apply MMRM model used for the primary analysis for each adjusted data set generated from Step 2.

Step 4. Obtain pooled results per Rubin's Rule for each pair of shift parameters (k1, k2).

```
proc mianalyze;
  by Label;
  modeleffects estimate;
  stderr stderr;
run;
```

8.4.3 Analysis for Hematuria Resolution

The sample SAS code for logistic regression analysis is provided as follows:

```
*****
* TRTN = Treatment group [1 = Placebo, 2 = Atacicept 150 mg]
* RESL = indicator variable of whether a participant achieves hematuria resolution [1 = Yes, 2 = No]
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, or >=90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, >=2 g/24h]
* VISIT = Visit Number [2, 4, 12, 24, 36]
*****
PROC GENMOD data = efficacy;
  class USUBJID SGLT2 REGION BGFR BTUPE TRTN VISIT;
  model resl(event="1") = SGLT2 REGION BGFR BTUPE TRTN VISIT TRTN*VISIT / dist=binomial link=logit;
  repeated subject = USUBJID;
  lsmeans TRTN*VISIT / om cl exp ilink pdiff oddsratio;
  ods output Lsmeans = lsmeans Diffs = diff;
run;
```

where *om* specifies the weighting scheme for LS-means computation as determined by the input data set; *cl* and *exp* compute and display estimate and confidence intervals for odds of subjects achieving hematuria resolution; *ilink* computes and displays estimate, standard error, and confidence intervals for probability of subjects achieving hematuria resolution; *pdiff* and *oddsratio* compute and display estimate and confidence intervals for odds ratio between atacicept and placebo.

8.4.4 Primary Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis

The sample SAS code for primary analysis of the key secondary efficacy endpoint is as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* VISIT = Post-baseline study visits (Week 2, Week 4, ..., and Week 104)
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, and >=90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, >=2 g/24h]
* BHEMA = Baseline hematuria category [n=Negative/Trace, 1+, 2+, and 3+]
* BASE = Baseline eGFR
* CHG = Change of eGFR at each post-baseline visit calculated as AVAL-BASE
* AVAL = eGFR value at each visit
* WEEK2, WEEK4, ..., WEEK104 = eGFR values at Week 2, Week 4, ..., and Week 104
* TIME = Time in years calculated as (study visit date - the first DB dose date + 1)/365.25
* For the imputed eGFR values without actual visit, TIME = (7X+1)/365.25 for Week X
*****
/*BASE, AVAL, and CHG are the baseline, absolute value, and the change from baseline in eGFR, respectively,
with ANL01FL = "Y"*/
/*Transpose the eGFR (i.e., AVAL) to wide format, one record per subject*/

/*Step 1: Intercurrent event strategy */
/*Exclude values collected after ICEs of dialysis, kidney transplant, and death*/

/*Step 2: Intermittent Missing Data Imputation Using MCMC. */
proc mi data=in seed=123 nimpute=50 out=mono;
  by TRTN;
  var BASE WEEK2 - WEEK104;
  mcmc impute=monotone nbiter=5000 niter=5000;
run;

/*Step 3.1: Missing Data due to ICEs*/
/* All missing values should theoretically result from study withdrawal, dialysis, kidney transplant, or
death. However, there may occasionally be a few subjects with missing values at their last visits while still
remaining on-study. For simplicity, all missing values will be imputed using the 'Jump to reference' strategy. */
proc mi data=mono seed=123 nimpute=1 out=outmi;
  class SGLT2 REGION BGFR BTUPE BHEMA;
  by _imputation_ TRTN;
  monotone reg(/details);
  Mnar model (WEEK2 / modelobs= (TRTN= '1'));
  ...
  Mnar model (WEEK104 / modelobs= (TRTN= '1'));
  var SGLT2 REGION BGFR BTUPE BHEMA BASE WEEK2-WEEK104;
run;

/* Step 3.2: Missing Data due to Dialysis, Kidney Transplant, or Death */
```



```
/*      Impute values in visits on and after ICEs of dialysis, kidney transplant, and death */
/*      In each imputation, replace the values on and after above ICEs with rand('normal',U,E); */
/*      Where U and E are the mean and random error for the unfavorable values for eGFR.*/
```

```
/*Step 4: Statistical Analysis*/
```

```
/*Transpose the imputed datasets into long format, one record per visit per subject per imputation*/
```

```
/*Pool transposed and imputed dataset with the rest eGFR data with ANL01FL = ""*/
```

```
/*Analyze the pooled data by random coefficient mixed-effect model*/
```

```
proc mixed data=efficacy method=reml;
  class TRTN USUBJID SGLT2 REGION BGFR BTUPE;
  model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TRTN*TIME /solution ddfm=kr covb cl;
  random INT TIME/ sub = USUBJID type = un;
  estimate 'slope for placebo'      TIME 1 TRTN*TIME 1 0 / cl alpha=0.05;
  estimate 'slope for atacicept'    TIME 1 TRTN*TIME 0 1 / cl alpha=0.05;
  estimate 'slope difference'       TRTN*TIME -1 1 / cl alpha=0.05;
  ods output covparms=covparms;
  ods output estimates=estimates;
run;
```

```
/*Combine the analysis results using Rubin's rule*/
```

```
proc mianalyze data=estimates;
  by label;
  modeleffects estimate;
  stderr stderr;
  ods output parameterestimates=diffs1;
run;
```

8.4.5 Sensitivity Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis: Tipping Point Analysis

The SAS sample code for the tipping point sensitivity analysis is provided as follows:

Step 1. Set all post-baseline eGFR to missing for all subjects with ICEs of dialysis, kidney transplant, death, and study withdrawal from the primary imputed analysis dataset.

```
*****
* BASE = eGFR value at baseline
* WEEK 2, WEEK4, WEEK12, WEEK24, ... , WEEK104 = eGFR values at Week 2, Week 4, Week 12, Week 24,
... , and Week 104
* k1= -8, -6 , ..., 6, 8
* k2= -8, -6 , ..., 6, 8
*****;
```

Step 2. Apply MNAR assumption under each pair of shift parameters (k1, k2) to generate post-baseline eGFR values for subjects with ICE only in each imputed data set generated from Step 1, where `est_slope_trt` and `stderr` are the slope estimates from the primary analysis and associated standard error for specific treatment group. `Stddev` is from the sqrt of the model residual. For each treatment group, generate eGFR with below code using the corresponding treatment & shift parameter.

```
slope = &est_slope_trt + rand('normal', &shift, &stderr);
WEEK2 = base + 2/52*slope + rand('normal',0, &stddev);
WEEK4 = base + 4/52*slope + rand('normal',0, &stddev);
WEEK12 = base + 12/52*slope + rand('normal',0, &stddev);
WEEK24 = base + 24/52*slope + rand('normal',0, &stddev);
....
WEEK104 = base + 104/52*slope + rand('normal',0, &stddev);
```

Step 3. Apply MMRIRS model used for the primary analysis for each adjusted data set generated from Step 2.

Step 4. Obtain pooled results per Rubin's Rule for each shift parameter pair.

```
proc mianalyze;
  by label;
  modeleffects estimate;
  stderr stderr;
run;
```

8.4.6 Sensitivity Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis: Two-Slope MMRIRS

The SAS sample code for the two-slope MMRIRS is provided as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, ≥ 45 to < 90, and ≥ 90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, ≥2 g/24h]
* TIME = Time in years calculated as (study visit date – baseline date + 1)/365.25
* TIME_cp = Truncated time in years after changepoint calculated as max(TIME – Change Point, 0)
* AVAL = eGFR value at each visit including baseline visit
*****;
proc mixed data=efficacy;
  class TRTN USUBJID SGLT2 REGION BGFR BTUPE;
  model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TIME_CP TRTN*TIME TRTN*TIME_CP/s
  ddfm=kr;
  random INT TIME TIME_CP/ sub = USUBJID type = un;
  estimate "Acute Slope: Atacicept"    TIME 1 TIME_CP 0 TRTN*TIME 0 1 TRTN*TIME_CP 0 0;
  estimate "Acute Slope: Placebo"      TIME 1 TIME_CP 0 TRTN*TIME 1 0 TRTN*TIME_CP 0 0;
  estimate "Acute Slope: Diff"         TIME 0 TIME_CP 0 TRTN*TIME -1 1 TRTN*TIME_CP 0 0;
  estimate "Chronic Slope: Atacicept"  TIME 1 TIME_CP 1 TRTN*TIME 0 1 TRTN*TIME_CP 0 1;
  estimate "Chronic Slope: Placebo"    TIME 1 TIME_CP 1 TRTN*TIME 1 0 TRTN*TIME_CP 1 0;
  estimate "Chronic Slope: Diff"       TIME 0 TIME_CP 0 TRTN*TIME -1 1 TRTN*TIME_CP -1 1;
  estimate "Slope Change: Atacicept"  TIME 0 TIME_CP 1 TRTN*TIME 0 0 TRTN*TIME_CP 0 1;
  estimate "Slope Change: Placebo"    TIME 0 TIME_CP 1 TRTN*TIME 0 0 TRTN*TIME_CP 1 0;
  estimate "Slope Change: Diff"       TIME 0 TIME_CP 0 TRTN*TIME 0 0 TRTN*TIME_CP -1 1;
  ods output estimates=estimates;
run;
```



STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)

Protocol Number: VT-001-0050

Protocol Version / Date: Amendment 7 / 23 December 2024

Investigational Product: Atacicept (VT-001)

Sponsor: Vera Therapeutics, Inc.
2000 Sierra Point Parkway, Suite 1200
Brisbane, CA 94005

SAP Version/Date V 2.0 / 23 May 2025
(for Phase 3 Week 36 and Week 104 Interim Analyses)
(for Regulatory Submission Outside the United States)

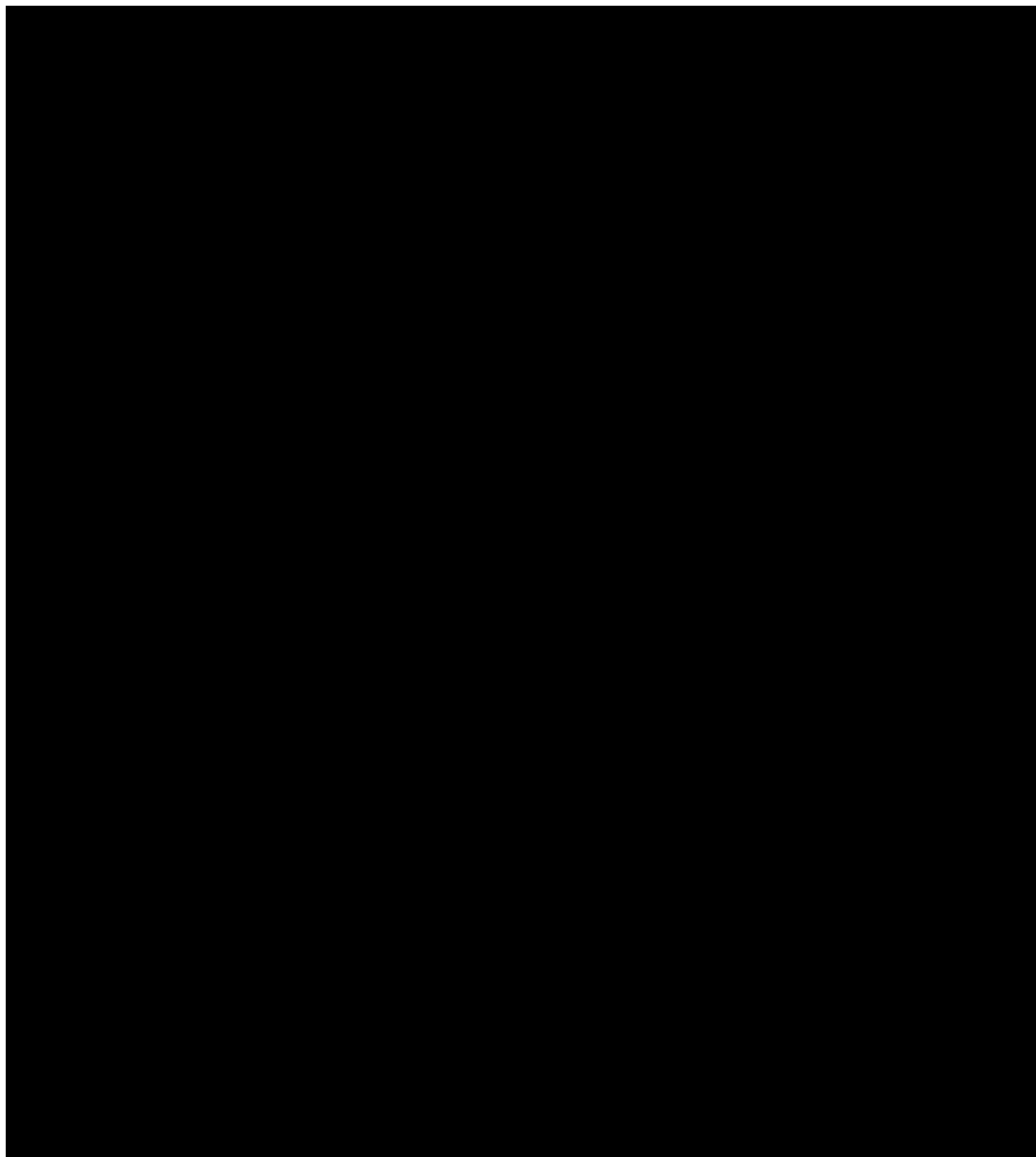
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SAP SIGNATURE PAGE

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature / Date



VERSION HISTORY

Version	Version Date	Description
1.0 (Final Draft for FDA Review)	13 August 2024	Signed final draft version 1.0 for FDA review
1.0 (Final)	11 Feb 2025	Updated based on FDA feedback
2.0 (Final)	23 May 2025	<ol style="list-style-type: none"> 1. Based on the US FDA comments received on April 29th and May 9th, 2025, the following updates were incorporated in SAP version 2.0: <ol style="list-style-type: none"> a. Added predictive power calculation for eGFR total slope endpoint. b. Changed “time to composite kidney failure endpoint through Week 104” to “time to a sustained $\geq 30\%$ decline in eGFR”. c. Added a table to include detailed description of how intercurrent events and missing data will be handled for all endpoints included in multiple testing hierarchy. d. Increased the number of imputations for missing data from 50 imputations to 100 imputations. e. Removed “study withdrawal, including lost to follow-up” from the list of intercurrent events. 2. Added % reduction in UPCR at Weeks 36/104 and change from baseline in eGFR [REDACTED] in the multiple testing hierarchy. 3. Added the definition of AEs associated with Injection Site Reaction. 4. Updated ADA analysis.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
APRIL	a proliferation-inducing ligand
BAFF	B-cell activating factor (also called "BLyS")
C _{max}	maximum concentration
ACEi	Angiotensin Converting Enzyme inhibitor
ADA	Anti-Drug Antibody
AESI	Adverse event of special interest
ARB	Angiotensin II Receptor Blocker
ATC	Anatomical therapeutic chemical class
BMI	Body mass index
BP	Bodily Pain
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CSR	Clinical Study Report
DB	Double-Blind
DNA	Deoxyribonucleic acid
EC	Exposure as Collected
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EDC	Electronic Data Capture
EOT	End of treatment
[REDACTED]	[REDACTED]
EQ VAS	EQ Visual Analog Scale
ET	Early Termination
EWB	Emotional Well-Being
[REDACTED]	[REDACTED]
FAS	Full analysis set
FS	Fatigue Subscale
FWB	Functional Well-Being
Gd-IgA1	Galactose-deficient IgA1
GH	General Health
GS	Glucocorticosteroids
HbA1c	Hemoglobin-A1c
HbcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HRQOL	Health-Related Quality of Life
IAS	Interim Analysis Set
ICEs	Intercurrent Events
iDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
Ig	Immunoglobulin
IgA, IgG, IgM	Immunoglobulin A, Immunoglobulin G, Immunoglobulin M
IgAN	IgA Nephropathy
IRT	Interactive Response Technology

Abbreviation	Definition
IS	Immunosuppressive
ISR	Injection site reaction
ITT	Intent to treat
IWRS	Interactive web response system
LS Means	Least Squares Means
LSMs	Least Squares Means
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Scores
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MI	Multiple Imputation
MMRM	Mixed-effects model for repeated measures
MNAR	Missing Not At Random
MRA	Mineralocorticoid Receptor Antagonists
OLE	Open-Label Extension
PCS	Physical Component Scores
PF	Physical Functioning
PGx	Pharmacogenetics
PK	Pharmacokinetics
PN	Preferred Name
PP	Per-protocol
PROs	Patient-Reported Outcomes
PT	Preferred Term
PWB	Physical Well-Being
Q1, Q3	First, Third quartile
RASi	Renin-Angiotensin System inhibitor
RE	Role-Emotional
REML	Restricted Maximum Likelihood
RP	Role-Physical
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Social Functioning
██████	██
SGLT2i	Sodium-glucose cotransporter-2 Inhibitor
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SWB	Social/Family Well-Being
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
TOI	Trial Outcome Index
TSH	Thyroid Stimulating Hormone
██████	██
UPCR	Urine protein to creatinine ratio
VAS	Visual Analog Scale
VT	Vitality
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis methods and data presentations to be implemented in tables, figures, and listings (TFLs) to support the primary endpoint analysis at Week 36 and the End of Part C analysis at Week 104 of Phase 3 data for study VT-001-0050 based on protocol (Amendment 7: 23 December 2024). The primary endpoint analysis at Week 36 (referred to as the “Phase 3 Week 36 Interim Analysis” in later sections) will be performed after approximately the first 200 subjects enrolled in the Phase 3 part of this study complete their Week 36 visits or prematurely discontinue from the study. The End of Part C analysis (referred to as the “Phase 3 Week 104 Interim Analysis” in later sections) will be performed when all subjects complete the double-blind portion of the study (Week 104) or prematurely discontinue from the study. The SAP will be finalized prior to database lock for the primary endpoint analysis at Week 36 data cut. Any deviations from the SAP after database lock for the primary endpoint analysis will be documented in the Clinical Study Report (CSR).

Separate SAPs were developed for the interim and final analyses for Phase 2b part of the study. Separate SAPs will be developed to support future interim and/or final analyses for the Phase 3 part of the study.

Based on the US FDA’s feedback received on April 29th, 2025, and May 9th, 2025 (see details in Section 6), the following updates were made in this version of the SAP (Version 2), which are not incorporated into the Protocol Amendment 7.0 yet:

- The endpoint of “time from randomization to the first occurrence of the composite kidney failure event” was changed to “time from randomization to the first occurrence of a sustained $\geq 30\%$ decline in eGFR”.
- The list of intercurrent events was modified to remove “study withdrawal, including lost to follow-up”.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

- Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN at Week 36.

2.1.2 Key Secondary Objective

- Evaluate the effect of atacicept compared to placebo on the annualized rate of change in estimated glomerular filtration rate (eGFR) through Week 104.

2.1.3 Other Secondary Objectives

- Evaluate the effect of atacicept compared to placebo on change in Gd-IgA1 at Weeks 36, 52, and 104.
- Evaluate the effect of atacicept compared to placebo on change from baseline in eGFR at Weeks 52 and 104.
- Evaluate the effect of atacicept compared to placebo on achieving hematuria resolution at Weeks 36, 52, and 104.
- Evaluate the effect of atacicept compared to placebo on time from randomization to the first occurrence of a sustained $\geq 30\%$ decline in eGFR through Week 104.

2.1.4 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]

2.1.5 Safety Objective

- Evaluate the safety and tolerability of atacicept during the entire study.

2.2 Study Design

2.2.1 Overview

This is a multi-part study comprising of the original Phase 2b study (i.e., Parts A and B) and the addition of a separate Phase 3 study (i.e., Parts C and D). The results from Phase 2b have been used to determine the dose selection and sample size for the Phase 3 study design.

The Phase 3 study is a multicenter, randomized, double-blinded, placebo-controlled study.

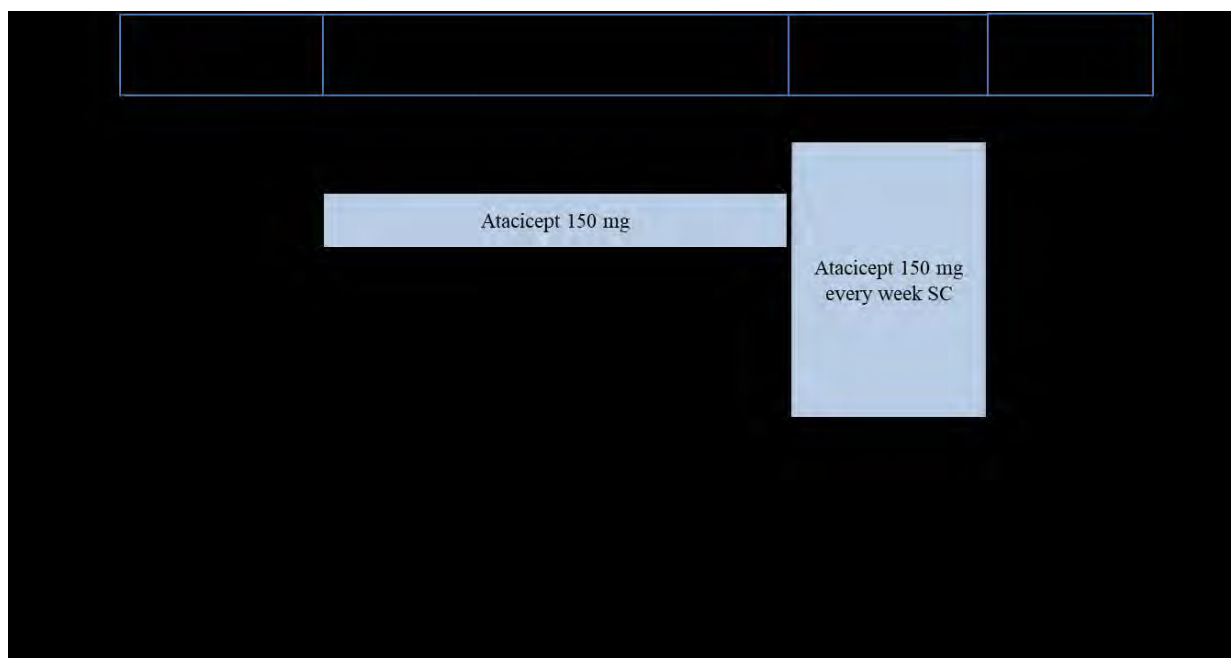
In Part C, approximately 376 subjects will be randomized 1:1 to atacicept 150 mg or placebo for 104 weeks:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly SC injections (N=188)
- Subjects who have participated in Part A or B may not participate in Part C or D.
- Subjects participating in the study will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/1.73 m², or ≥ 45 to <90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m²), total urine protein excretion (<2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (yes or no), and Region (Asia or Other).

The Phase 3 study is composed of a (up to) 4-week Screening Period, a 104-week Double-Blind (DB) Treatment Period (Part C), a 52-week Open-Label Extension (OLE) (Part D) and 26 weeks of follow-up. Subjects who complete the 104-week DB Treatment Period on treatment will be eligible for open-label atacicept at 150 mg for an additional 52 weeks (OLE). Subjects who prematurely discontinue study drug prior to completion of the 104-week DB treatment period should continue with study visits and assessments per protocol through the end of the DB period. After the last subject completes the 104-week DB period or completes an Early Termination Discontinuation (ETD) Visit, the study will be unblinded.

The study will be conducted on an outpatient basis.

Figure 1: Phase 3 Study Schema



RASi= renin-angiotensin system inhibitor; SC=subcutaneous.

2.2.2 Investigational Medicinal Product(s)

In a blinded fashion, 150 mg atacicept or placebo are given as self-administered and once-weekly SC injections for 104 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept are given as self-administered and once-weekly SC injections for 52 weeks by prefilled syringe.

2.2.3 Randomization and Blinding

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessment (see Protocol Amendment 7.0 Table 3).

This study will be double-blinded for all subjects and Investigators through Part C. IMP packaging and labeling will be prepared to protect the blinded nature of the study. Study drug will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part D of the study will be conducted in an open-label fashion.

2.2.4 Sample Size Determination

The selected sample size provides sufficient power for both the primary endpoint UPCR and the key secondary endpoint eGFR.

2.2.4.1 Sample Size Determination for the Primary Endpoint of UPCR

The primary efficacy endpoint is the ratio of UPCR at Week 36 compared with baseline, based on 24-hour urine collection. Due to the skewed distribution, UPCR will be natural log transformed. The primary efficacy endpoint is the change from baseline at Week 36 in natural log transformed UPCR. A two-sample t-test for ratio was used to determine the sample size for UPCR. It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo groups is 0.67 (i.e., the percentage reduction is 33% higher for atacicept than placebo) and the standard deviation (SD) for the mean change of log (UPCR) from baseline is assumed to be 0.7 in both groups (based on the Origin Phase 2b Primary Endpoint Analysis [data on file]). Based on these assumptions, 100 subjects per group will provide 92% power to detect a ratio of 0.67 with a two-sided alpha of 0.01 when the ratio under the null hypothesis is 1 [PASS 2015: two-sided two sample t-test for ratios]. Missing data after subject withdrawals will be imputed and included in the primary efficacy endpoint analysis and therefore no overage of sample size for withdrawals is necessary.

Table 1 displays statistical power under different scenarios, accounting for uncertainty in estimating UPCR percentage reductions and standard deviations; 100 subjects per group will provide at least 78% power at two-sided significant level of 0.01 if the treatment effect on UPCR reduces from 33% to 30% and/or the standard deviation of the mean change of log (UPCR) from baseline increased from 0.7 to 0.75. A total of 100 subjects per group will provide at least 93% power at a two-sided significant level of 0.01 if the treatment effect on UPCR reduction is 35% (as observed in ORIGIN Phase 2b Week 36 Analysis).

Table 1: Power Calculation for Primary Endpoint of UPCR Under Different Assumptions

Sample Size per Group	Treatment Effect on UPCR		Standard Deviation	Alpha	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction			
100	0.67	33%	0.7	0.01	92%
			0.75	0.01	88%
	0.7	30%	0.7	0.01	84%
			0.75	0.01	78%
100	0.65	35%	0.7	0.01	96%
			0.75	0.01	93%

2.2.4.2 Sample Size Determination for the Annualized Rate of Change in eGFR Through Week 104

For the key secondary endpoint, a meta-analysis for the association of treatment effects on early change in UPCR and treatment effect on eGFR annualized slope in IgAN patients by (Inker et al 2021) is referenced to estimate the expected treatment effect on eGFR annualized slope. The mixed-effects model with random intercept and random slope (MMRIRS), which is also known as the random coefficient mixed-effect model, is planned for comparing 2 slopes, when we estimate the sample size for eGFR slope evaluation (Ahn, Heo, and Zhang [2014]). It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo is 0.67 based on ORIGIN Phase 2b Primary Endpoint Analysis. According to the association between UPCR change at 9 month and eGFR annualized slope (Inker et al 2021) and the observation that atacicept did not show an acute eGFR effect in Origin Phase 2b Primary Endpoint Analysis and historical data, the expected difference in annualized slope in eGFR is 2 mL/min/1.73m²/year using linear extrapolation. The variance of random slope is 27 and the variance of residuals is 32 based on the atacicept IgAN Phase 2a (JANUS) study. The follow-up period is approximately 2 years (i.e., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between the atacicept and placebo. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) are planned to be enrolled.

Table 2 displays statistical power for annualized eGFR slope comparison under different scenarios; 171 subjects per group will provide at least 87% power at two-sided significant level of 0.05 to detect an annualized slope difference of at least 2.0 mL/min/1.73m²/year, if the variances of random slope and residuals increase by approximately 10% to 30% and 36%, respectively. The power will be 77% if the expected annualized slope difference decreases to 1.67 mL/min/1.73m²/year, which is associated with a 30% greater decrease in UPCR at Week 36 in atacicept compared to placebo. A total of 171 subjects per group will provide at least 93% power at a two-sided significant level of 0.05 if the treatment effect on UPCR reduction is 35% (as observed in the ORIGIN Phase 2b Week 36 Analysis), if the variances of random slope and residuals increase by approximately 10% to 30% and 36%, respectively.

Table 2: Power for Annualized eGFR Slope Comparison Under Different Assumptions (Alpha = 0.05)

Sample Size per Group	Treatment Effect on UPCR		Annualized Slope Difference in eGFR	Var (Slope)	Var (Residuals)	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction				
171	0.7	30%	1.67	27	32	77%
	0.67	33%	2.0			90%
	0.65	35%	2.22			95%
	0.7	30%	1.67	30	36	73%
	0.67	33%	2.0			87%
	0.65	35%	2.22			93%

2.2.4.3 Potential Adjustment to Sample Size Determination for eGFR

In sample size calculation for the evaluation of difference in 2-year eGFR slope, multiple uncertainties were accounted for, including the treatment effect on UPCR, the modeled relationship between changes in UPCR at 9 months and eGFR slope over 2 years, and the variances of slope and/or residuals in eGFR.

The original sample size calculation was based on the observed 33% placebo-adjusted reduction in UPCR at Week 36 from Week 24 analysis. At the Week 36 analysis, a deeper placebo-adjusted reduction of 35% at Week 36 was observed and the standard deviation (SD) for the mean change of log (UPCR) from baseline at Week 36 was similar with these at Week 24. No sample size adjustment is necessary based on Phase 2b Week 36 Interim Analysis.

After the completion of Phase 2b final analysis, the sponsor used the actual variances of the random slope and residual of eGFR estimated from Phase 2b long-term eGFR data to re-calculate the sample size for the confirmative endpoint of eGFR. The recalculated sample size was not substantially higher than the currently proposed sample size, the sample size will not be adjusted. Since this check is based on data from a separate Phase 2b part of this study to estimate the ‘nuisance parameter’ of variances, no alpha spending is required.

2.3 Study Endpoints for the Phase 3 Week 36 Interim Analysis

Only the primary efficacy endpoint will be formally evaluated with two-sided alpha of 0.01 at the Phase 3 Week 36 Interim Analysis. Key secondary endpoint and other selected secondary endpoints will be formally evaluated at the Phase 3 Week 104 Interim Analysis. Other selected secondary endpoints and exploratory endpoints (detailed below) will be evaluated at the Phase 3 Week 36 Interim Analysis as supportive analyses and no alpha spending is required.

2.3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

2.3.2 Key Secondary Endpoint

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope) with eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults as specified by Levey 2009.

$$\text{eGFR} = 141 \times \min(\text{SCR}/\kappa, 1)^\alpha \times \max(\text{SCR}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018[\text{if Female}] \times 1.159[\text{if Black}]$$

where: SCR = Standardized Serum Creatinine (mg/dL),

κ = 0.7 (females) or 0.9 (males),

α = -0.329 (females) or -0.411 (males),

min indicates the minimum of Scr/ κ or 1,

max indicates the maximum of Scr/ κ or 1,
age in years.

The key secondary endpoint will not be evaluated at the time of Phase 3 Week 36 Interim Analysis. Instead, the following eGFR endpoints will be analyzed:

- Annualized rate of change in eGFR through Week 52 (i.e., annualized eGFR total slope)
- Change from baseline in eGFR by visit up to Week 52.

2.3.3 Other Secondary Endpoints

Selected “other secondary endpoints” at the time of the Phase 3 Week 36 Interim Analysis will be analyzed as supportive analyses (i.e., not included in the multiple testing strategy) and include the following endpoints:

- Change from baseline at Week 36 in natural-log transformed Gd-IgA1
- Hematuria resolution (i.e., achieving hematuria of negative or trace) at Week 36 for subjects with hematuria of 1+ or above at baseline.

2.3.4

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

2.3.5 Safety Endpoints

Safety endpoints include evaluation of routine clinical and laboratory tests, adverse events and anti-drug antibodies (ADA) during the entire study.

2.4 Study Endpoints for the Phase 3 Week 104 Interim Analysis

The key secondary endpoint and other selected secondary endpoints will be formally evaluated at Week 104 Interim Analysis as Specified in Section 3.1.7. All exploratory endpoints (detailed below) will be evaluated at Week 104 Interim Analysis as supportive analyses, and no alpha spending is required.

2.4.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

The primary efficacy endpoint will be evaluated based on the Interim Analysis Set (IAS) population and include all UPCR data up to Week 36. The change from baseline in natural-log transformed UPCR at all post-baseline visits up to Week 104 will be evaluated in the Week 104 Interim Analysis using the Full Analysis Set (FAS) population.

2.4.2 Key Secondary Endpoint

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope).

2.4.3 Other Secondary Endpoints

Other secondary endpoints include:

- Change from baseline at Weeks 52 and 104 in eGFR.
- Change from baseline at Weeks 36, 52, and 104 in natural-log transformed Gd-IgA1.
- Hematuria resolution (i.e., achieving hematuria of negative or trace) at Weeks 36, 52, and 104 for subjects with hematuria of 1+ or above at baseline.
- Time from randomization to the first occurrence of a sustained $\geq 30\%$ decline in eGFR. Where a sustained $\geq 30\%$ decline in eGFR is defined as a decrease of 30% or more from baseline that is maintained for a minimum of 30 days.

2.4.4

- [REDACTED]
- [REDACTED]
 - [REDACTED]
 - [REDACTED]

2.4.5 Safety Endpoints

Safety endpoints include evaluation of routine clinical and laboratory tests, adverse events and anti-drug antibodies (ADA) during the entire study.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Day

Study day will be calculated from the date of the first dose of study drug. The study day of the first dose of study drug will be Day 1, and the study day immediately before Day 1 will be Day -1. There will be no Day 0.

- For dates before Day 1, study day = date of assessment/event – date of Day 1.
- For dates on or after Day 1, study day = date of assessment/event – date of Day 1 + 1.

3.1.2 Definition of Period

Analysis for the double-blinded (DB) period will include data collected during the screening and DB periods: (1) all available data for subjects who prematurely discontinued the blinded study drug and/or did not receive any dose of open-label atacicept in the OLE period; (2) all available data prior to the first dose data/time of open-label atacicept for subjects who completed the double-blinded drugs and received at least 1 dose of open-label atacicept.

Analysis for the OLE period will include OLE baseline and all data collected on or after the first dose date/time of open-label atacicept through the end of the study.

Analysis for the entire study period will include all the data collected throughout the study, i.e. from screening period to the end of follow-up period.

OLE period and the entire study period may not be defined for the Phase 3 Week 36 Interim Analysis, as we are expecting very few, if not none, subjects will enter the OLE period at the time of Week 36 Interim Analysis data cut.

3.1.3 Definition of Baseline, the First Dose, and the Last Dose

Baseline for DB period (labeled as DB baseline for future reference) will be defined as the last available measurement prior to the first dose of double-blinded study drug (i.e., it is generally the pre-dose assessment on Day 1), except for UPCR, [REDACTED], and other lab tests from 24-hour urine samples or spot urine samples. For UPCR, [REDACTED], and other lab tests from 24-hour urine samples or spot urine samples, the geometric mean of all measurements during the screening period and prior to the first dose of double-blinded study drug will be used as baseline. DB baseline is the default baseline and will be used interchangeably with baseline. For analyses conducted for double-blind treatment period only (such as analyses of primary efficacy endpoint), or for the entire study period (i.e., where DB period and OLE period will be analyzed as a whole), such as summary of demographic and baseline characteristics, the DB baseline will be used as the default baseline.

Baseline for OLE period (labeled as OLE baseline for future reference) will be defined as the last available measurement prior to the first dose of open-label atacicept. OLE baseline may not be defined for the Phase 3 Week 36 Interim Analysis, as we are expecting very few, if not none, subjects will enter the OLE period at the time of Week 36 Interim Analysis data cut. Data collected in the OLE period, if any, will not be summarized but will be included in listings in the Phase 3 Week 36 Interim Analysis.

The first dose date for both the DB period and entire study is the first injection date of any blinded study drug. The first dose date for the OLE period is the first injection date of open-label atacicept.

The last dose date for the DB period is the last injection of any blinded study drug. The last dose date for the OLE period is the last injection date of any open-label atacicept. The last dose date for the entire study is the last injection date of any study drug, including both blinded study drugs and open-label atacicept.

3.1.4 Analysis Visits

All efficacy and safety assessments, regardless collected on schedule or unscheduled visits and regardless collected while on-treatment or off-treatment, will be allocated to analysis visits as defined in Appendix 8.2. If more than one postbaseline measurements are recorded within a visit window, the following rule will be applied, while baseline is defined in Section 3.1.3:

- If there are multiple measurements collected on the same day (even if some measurements are collected as unscheduled measurements or off-treatment measurements), the arithmetic or geometric mean of all measurements will be used for that day. The mean of all measurements collected on that day will be treated as on-treatment measurement if at least one measurement is collected as an on-treatment measurement. Otherwise, it will be treated as an off-treatment measurement. For subjects who don't complete the End of Treatment eCRF (i.e., still receiving study drug), all postbaseline measurements will be considered as on-treatment. For subjects who complete the End of Treatment eCRF, a measurement will be considered as an on-treatment measurement if it is collected on or after the first dose date/time and prior to the last dose date/time + 10.
- If a test is collected in multiple days within a visit window, the measurement taken at the day closest to the target day will be used. If there are multiple days with equidistance from the target day, the latest one will be used.

3.1.5 Stratification

Subjects will be stratified by screening eGFR values calculated by the central laboratory (< 45 mL/min/1.73 m², or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI), screening total urine protein excretion (< 2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (Yes or No) and Region (Asia or Other). Screening eGFR and total urine protein excretion will be imported from central laboratory into IRT directly to assign the stratification category, while subject with/without stable SGLT2i use at screening will be manually entered into IRT. Subjects with/without stable SGLT2i use at screening will be derived based on

prior/concomitant medication data from EDC. Any discrepancies in SGLT2i screening stratification categories between IRT and EDC will be listed. In addition, eGFR category and total urine protein excretion category at baseline and stable SGLT2i use at baseline will be derived and used for statistical modeling. Any difference between derived stratification categories at screening and these at baseline will be listed.

3.1.6 Statistical Hypotheses

Hypotheses for Primary Study Objective

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR. The primary comparison of interest is a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.01. The statistical hypotheses for the primary efficacy endpoint are:

$$H_{10}: \mu_{\text{placebo}} = \mu_{\text{ATC}} \text{ vs. } H_{11}: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.005.

$$H_{10}: \mu_{\text{placebo}} \leq \mu_{\text{ATC}} \text{ vs. } H_{11}: \mu_{\text{placebo}} > \mu_{\text{ATC}}$$

Where:

μ_{placebo} = the change from baseline at Week 36 in natural-log transformed UPCR for placebo;

μ_{ATC} = the change from baseline at Week 36 in natural-log transformed UPCR for atacicept 150 mg.

Hypotheses for Key Secondary Study Objective

The key secondary efficacy endpoint is the annualized rate of change in eGFR through Week 104 (i.e., annualized eGFR total slope). The primary comparison of interest is a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.05 or 0.04 (depending on the results of the primary efficacy endpoint). The statistical hypotheses for the key secondary efficacy endpoint are:

$$H_{20}: \text{Slope}_{\text{placebo}} = \text{Slope}_{\text{ATC}} \text{ vs. } H_{21}: \text{Slope}_{\text{placebo}} \neq \text{Slope}_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.025 or 0.02 (depending on the results of the primary efficacy endpoint).

$$H_{20}: \text{Slope}_{\text{placebo}} \geq \text{Slope}_{\text{ATC}} \text{ vs. } H_{21}: \text{Slope}_{\text{placebo}} < \text{Slope}_{\text{ATC}}$$

Where:

$\text{Slope}_{\text{placebo}}$ = the annualized rate of change in eGFR through Week 104 for placebo group;

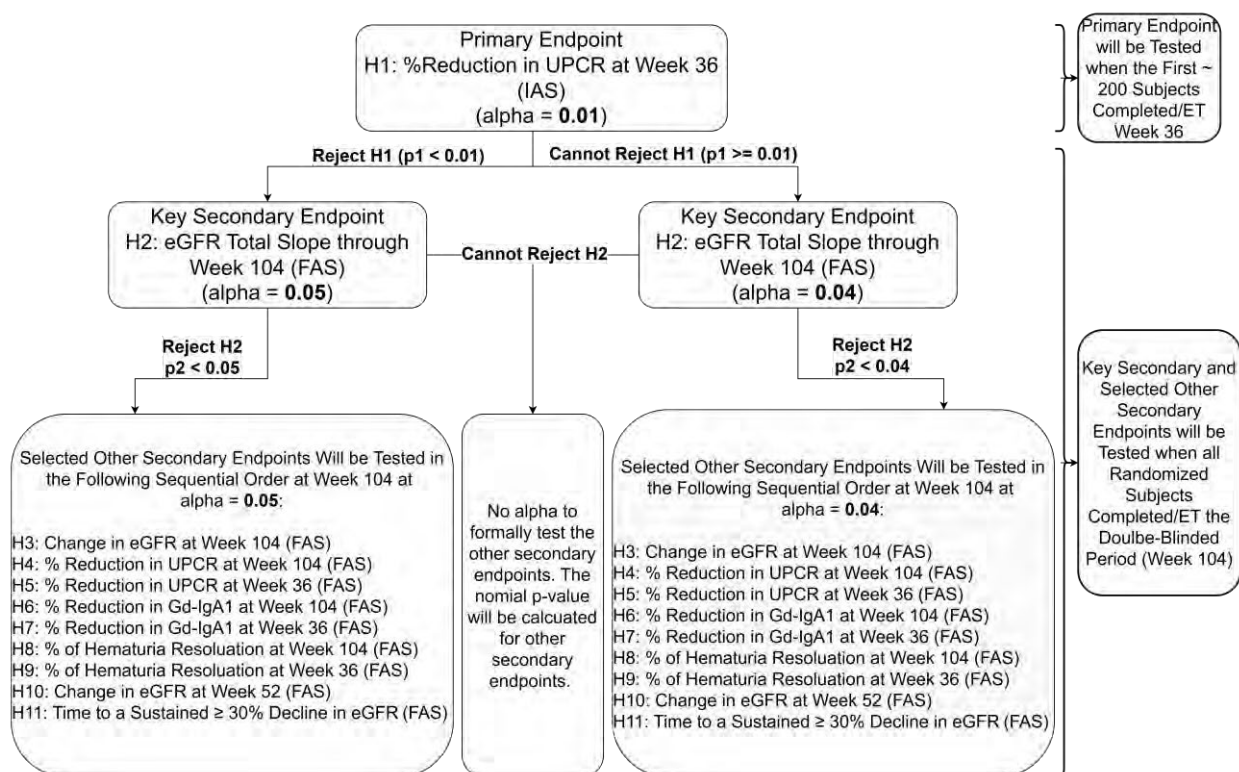
$\text{Slope}_{\text{ATC}}$ = the annualized rate of change in eGFR through Week 104 for atacicept 150 mg group.

3.1.7 Multiple Comparisons

To control the overall type 1 error in the evaluation of the primary and key secondary efficacy endpoint at a two-sided alpha of 0.05, the hypothesis testing will be performed in sequential order by fallback procedure. The primary efficacy endpoint will be tested first at a two-sided significance level of 0.01. If superiority for the primary endpoint is established, the key secondary efficacy endpoint will then be tested at a two-sided significant level of 0.05. If the statistical significance is not met for the primary endpoint, the key secondary efficacy endpoint will be tested at a two-sided significant level of 0.04. After the statistical significances are tested for both the primary and the key secondary endpoints, the sequential testing approach will be used to test other selected secondary endpoints with a two-sided significant level of 0.05, 0.04, or 0 based on the hypotheses testing results from the primary and key secondary efficacy endpoints (see details in [Figure 2](#)).

A detailed description of how intercurrent events and missing data will be handled in the primary analysis of all the endpoints included in Figure 2 are summarized in Appendix 8.3.

Figure 2: Multiple Testing Hierarchy



3.1.8 Data Summaries and Conventions

All endpoints will be summarized using descriptive statistics. Continuous variables will be summarized descriptively using the number of observations, mean, SD and/or SE, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and population being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number.

Mean, median, Q1, Q3, as well as their corresponding confidence intervals (CI) (if applicable) will be reported to one decimal place more than the data reported on the eCRF or by the laboratory/vendor. SD will be reported to two decimal places more than the original data reported. Minimum and maximum will be reported to the same number of decimal places displayed on eCRF or by the laboratory/vendor. P values will be reported to four decimal places. If a p value of “0” or “1” is obtained, display them as “<0.0001” and “>0.9999”, respectively. In general, the number of decimal places should not exceed four.

All tabular summaries will be presented by treatment group (atacicept 150 mg group or placebo group) and/or for overall. They will also be presented by study period (DB period and OLE period) if appropriate.

Formal statistical comparisons will be conducted for the data collected in DB period. Strategies for alpha control for multiple comparisons are specified in Section 3.1.7.

For the immunogenicity summary, titer result will be displayed as “< 50” in the listings and will be treated as missing for calculating summary statistics if an ADA sample result is “Negative”; the titer result will be displayed as “≤ 50” in the listings and will be imputed as 50 for calculating summary statistics if an ADA sample result is “Positive” and the titer value was below the assay cut point.

3.1.9 Handling of Dropouts and Missing Data

For prior and concomitant medications/procedures, if a medication/procedure has incomplete start or end dates, dates will be imputed to determine whether a medication/procedure should be considered prior or concomitant. If a medication/procedure start date is incomplete and the start date is in the same year and month as the first dose date, the first dose date will be used to impute the incomplete start date. Otherwise, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a medication/procedure end date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. If the imputed end date is later than the death date, then the end date will be imputed with the death date. Incomplete start and end dates will be listed as collected without imputation.

If it is not possible to determine whether an AE is or is not treatment emergent, or whether an AE starts in the on-treatment period, due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent,

i.e., starting in the treatment period. Detailed imputation rule will be documented in ADaM mapping specification.

Descriptive summaries of efficacy and safety measures will be based on observed data. Imputation of missing data for modeling will be detailed in later sections.

3.2 Populations

3.2.1 Screening Population

The Screening Population consists of all subjects who sign informed consent.

3.2.2 Intention-to-Treat (ITT) Population

The ITT Population consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.

3.2.3 Full Analysis Set (FAS) Population

The FAS Population consists of all randomized subjects who have received at least 1 dose of treatment. Unless otherwise indicated, the FAS is the primary analysis population for efficacy endpoints in the Week 104 Interim Analysis, where subjects will be analyzed according to randomized treatment.

3.2.4 Interim Analysis Set (IAS) Population

The IAS Population consists of a subset of subjects in the FAS population who were randomized and dosed on or prior to Sep 12th, 2024 (i.e., 203 subjects were randomized and dosed on or prior to Sep 12th, 2024) or subjects who complete the Week 36 visit at the time of the data cut for the Week 36 Interim Analysis. Unless otherwise indicated, the IAS is the primary analysis population for efficacy endpoints in Week 36 Interim Analysis, where subjects will be analyzed according to randomized treatment. In addition, selected safety endpoints will be analyzed using IAS Population according to actual treatment received during the DB period.

3.2.5 Week 36 Per-Protocol (PP) Population

The Week 36 PP Population consists of all subjects in the IAS Population who do not have any special events that may affect the validity of the primary efficacy endpoint evaluation.

Subjects who experience any CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation will be excluded from the Week 36 PP population. CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation include but are not limited to:

- Eligibility criteria violations that may affect the validity of the primary efficacy endpoint (e.g., screening eGFR < 30 mL/min/1.73m²),
- Study drug compliance outside of 80-120% up to the Week 36 visit, and
- Other substantial CSR reportable protocol violations prior to the Week 36 visit.

Subjects who experience any of the following events that may affect the validity of the primary efficacy endpoint evaluation will be excluded from the Week 36 PP population:

- Use of rescue / prohibited concomitant medication that could have impacted on the efficacy of study treatment prior to the Week 36 visit,
- Change the background medication (i.e., RASi, MRA, or SGLT2i) that could have impacted the efficacy of study treatment within 6 weeks prior to the Week 36 visit,
- Premature discontinuation of study drug prior to the Week 36 visit and with missing Week 36 on-treatment UPCR, and
- Unblinding of the patient prior to the Week 36 visit.

Week 36 PP Population will be determined through blinded review prior to Week 36 database lock. Week 36 PP population will be used as a supportive analysis on the primary efficacy endpoint for Phase 3 Week 36 Interim Analysis. Subjects will be analyzed according to the actual treatment received during the DB period.

3.2.6 Week 104 Per-Protocol (PP) Population

The Week 104 PP Population consists of all subjects in the FAS Population who do not have any clinically important protocol deviations that affect the validity of the key secondary efficacy endpoint evaluation. The Week 104 PP Population will be defined similarly to Week 36 PP Population, except the reference timepoint will change from “Week 36 visit” to “Week 104 visit”. Week 104 PP Population will be determined through blinded review prior to Week 104 database lock. Week 104 PP Population will be used as a supportive analysis on the key secondary efficacy endpoint for Phase 3 Week 104 Interim Analysis. Subjects will be analyzed according to the actual treatment received during the DB period.

3.2.7 Safety Population

The Safety Population consists of all randomized subjects who receive at least 1 dose of treatment. Subjects will be analyzed according to the actual treatment received during the DB period. Unless otherwise indicated, the Safety Population is the primary analysis population for safety endpoints.

3.2.8 Pharmacokinetics Population

The PK Population consists of all randomized subjects who receive at least 1 dose of treatment and have at least 1 evaluable PK concentration. All PK evaluations will be based on this population. PK concentration will be measured for subjects randomized to Atacicept 150 mg only.

3.2.9 Immunogenicity Population

The Immunogenicity Population consists of all subjects in the IAS population who receive at least 1 dose of treatment and have at least 1 evaluable ADA measure. Subjects will be analyzed according to the actual treatment received during the DB period.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented for Screening Population:

- Subjects who failed screening and were not randomized
- Subjects who were randomized

Subjects who failed the screen will be tabulated by primary reason for screen failure/not randomized. The number and percentage of subjects who failed the screen/not randomized due to COVID-19 will also be presented.

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented by treatment group and in total using ITT Population:

- Subjects randomized (ITT Population)
- Subjects treated (FAS/Safety Population)
- Subjects who prematurely discontinued study drug in the DB period by reason
- Subjects who prematurely discontinued the study by reason

The following disposition categories will not be included in Phase 3 Week 36 interim analysis, but will be included in Phase 3 Week 104 interim analysis:

- Subjects who completed study drug in the DB period
- Subjects who completed study drug in the DB period and continued to OLE period
- Subjects who prematurely discontinued study drug in the OLE period by reason
- Subjects who completed study drug in the OLE period
- Subjects who continued to safety follow-up period
- Subjects who completed the study

3.3.2 Protocol Deviations

The number and percentages of subjects with CSR reportable and CSR non-reportable protocol deviations by deviation category will be summarized by treatment group and in total using ITT Population. CSR reportable protocol deviations are deviations related to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment that impact the safety of the subjects or jeopardize the quality of study data. Protocol deviation categories are described in the protocol deviation plan.

All protocol deviations (CSR reportable and CSR non-reportable) will be listed by deviation categories.

3.3.3 Analysis Populations

The number and percentages of subjects in each analysis population will be summarized by treatment group and in total using ITT Population.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to

- Age collected at Screening (years)
- Age collected at Screening categories (years): (1) < 40, ≥40; and (2) < 45, ≥ 45 to < 65, ≥ 65
- Sex: female, male
- Childbearing potential (female only): yes, no
- Race: (1) American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other pacific islander, White, Other, Unknown or Not Reported, Not Permitted; and (2) White, Non-White, Not Reported or Not Permitted.
- Ethnicity: Hispanic or Latino, not Hispanic or Latino, Unknown or Not Reported, Not Permitted.
- Country: (1) by country; and (2) US, ex-US.
- Region Categories: (1) Asia, Europe, North America, South America; and (2) Asia, Other.
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline body mass index (BMI) (kg/m²)
- Screening eGFR (mL/min/1.73 m²)
- Screening eGFR Categories (IRT) (mL/min/1.73 m²): <45, ≥45 to <90, ≥90
- Baseline eGFR (mL/min/1.73 m²)
- Baseline eGFR Categories (mL/min/1.73 m²): (1) <45, ≥45 to <90, ≥90; and (2) <15, ≥15 to <30, ≥30 to <45, ≥45 to <60, ≥60 to <90, ≥90
- Baseline Hematuria (%): Negative/Trace, 1+, 2+, 3+
- Baseline UPCR (g/g)
- Baseline UPCR Category (g/g): <1.5, ≥1.5
- [REDACTED]
- Screening Proteinuria (g/day)
- Screening Proteinuria Category (IRT) (g/day): <2, ≥2
- Baseline Proteinuria (g/day)
- Baseline Proteinuria Categories (g/day): (1) <2, ≥2; and (2) <2, ≥2 to <3.5, ≥3.5
- Baseline Gd-IgA1 (ug/L), IgA (mg/dL), IgG (mg/dL), IgM (mg/dL), BAFF (ng/L), APRIL (ug/L)
- Baseline Systolic Blood Pressure (mmHg)
- Baseline Diastolic Blood Pressure (mmHg)

- Duration from IgAN Diagnosis (years)
- Time since Biopsy (years)
- Stable SGLT2i Use at Screening (IRT): yes, no
- Stable SGLT2i Use at Screening (EDC Derived): yes, no
- Stable SGLT2i Use at Baseline (EDC Derived): yes, no
- SGLT2i Use at Baseline (for subjects not on stable SGLT2i use at baseline only): Never Used, Less than 12 Weeks.
- RASi Medication Use at Baseline by Category: No RASi, ACEi only, ARB only, ACEi + ARB.
- Number of Anti-hypertension Medication(s) Used at Baseline: None, At least 1 (further break down by 1, 2, 3, 4+).
- Anti-hypertension Medication Used at Baseline by Class: ACEi, ARB, MRA, Diuretic, Calcium Channel Blocker, Beta Blocker, Direct Renin Inhibitors, Other.
- Prior GS or IS IgA nephropathy treatments: yes, no
- Prior GS or IS IgA nephropathy treatments type: corticosteroids (by subcategory), mycophenolate mofetil, azathioprine, cyclophosphamide, hydroxychloroquine, other
- Kidney Biopsy Results Reported in eCRF: yes, no
- Number of Glomeruli on Biopsy (n)
- Number of Glomeruli on Biopsy Category (n): < 8 , ≥ 8
- Classification Used for Kidney Biopsy Results: Kidney Biopsy Not Reported, Other, OXFORD MEST-C (by Subclassification)

Demographic and baseline characteristics relative to DB baseline will be summarized with descriptive statistics or number and percentages of subjects as appropriate by treatment group and in total for IAS, ITT, and FAS Populations in Phase 3 Week 36 Interim Analyses. If ITT Population and FAS Population are the same, summary will be performed based on ITT Population only.

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The number and percentages of subjects with medical history by SOC and PT will be summarized by treatment group and in total based on the Safety Population.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical class (ATC) and preferred name (PN) using the World Health Organization (WHO) Drug Dictionary (B3 Global, September 2024 or later). For summary purposes, medications will be considered prior medications if they ended prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Medications will be considered concomitant medications during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. Medications will be considered concomitant medications during the OLE period if they were taken at any time on or after the first dose date/time of OLE study drug through the end of the study. If medications cannot be decided as to which period they belong due to completely missing or partial start dates, medications will be considered concomitant during both periods.

In the case where a medication has incomplete start or end dates and cannot be determined as whether the medication should be considered as prior or concomitant medication, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects taking prior and concomitant medications by ATC2 and PN will respectively be summarized and will be summarized by treatment group and in total based on the Safety Population.

3.3.7 Prior and Concomitant Procedures

Prior and Concomitant procedures will be coded to SOC and PT using MedDRA (version 27.1 or later). For summary purposes, procedures will be considered prior procedures if they ended prior to the first dose of study drug and concomitant procedures if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Procedures will be considered concomitant procedures during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. Procedures will be considered concomitant procedures during the OLE period if they were taken at any time on or after the first dose date/time of OLE study drug through the end of the study. If procedures cannot be decided as to which period they belong due to completely missing or partial start dates, procedures will be considered concomitant during both periods.

In the case where a procedure has incomplete start or end dates and cannot be determined as whether the procedure should be considered as prior or concomitant procedure, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects with prior and concomitant procedures by SOC and PT will respectively be summarized and will be summarized by treatment group based on the Safety Population.

3.3.8 Study Drug Exposure and Compliance

Days of exposure to study drug will be defined for DB period, OLE period, and the entire study as follows:

- Days of exposure during the DB period = date of the last dose during the DB period – date of the first dose during the DB period + 7.
- Days of exposure during the OLE period = date of the last dose during the OLE period – date of the first dose during the OLE period + 7.
- Days of exposure during the entire study = date of the last dose during the entire study – date of the first dose during the DB period + 7.

For the calculation of the study drug exposure, the data cut date will be used to impute the corresponding last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment group based on the Safety Population. Descriptive statistics and the number and percentages of subjects with exposure in the following categories will be presented:

- DB Period
 - ≤12 weeks (≤84 days)
 - >12 - ≤24 weeks (>84 to ≤168 days)
 - >24 - ≤36 weeks (>168 to ≤252 days)
 - >36 - ≤48 weeks (>252 to ≤336 days)
 - >48 - ≤52 weeks (>336 to ≤364 days)
 - >52 - ≤60 weeks (>364 to ≤420 days)
 - >60 - ≤72 weeks (>420 to ≤504 days)
 - >72 - ≤84 weeks (>504 to ≤588 days)
 - >84 - ≤96 weeks (>588 to ≤672 days)
 - >96 - ≤104 weeks (>672 to ≤728 days)
 - >104 weeks (>728 days)
- OLE Period
 - ≤14 weeks (≤98 days)
 - >14 - ≤28 weeks (>98 to ≤196 days)
 - >28 - ≤40 weeks (>196 to ≤280 days)
 - >40 - ≤52 weeks (>280 to ≤364 days)
 - >52 - ≤64 weeks (>364 to ≤448 days)
 - >64 - ≤78 weeks (>448 to ≤546 days)
 - >78 weeks (>556 days)

- Entire Study Period
 - ≤ 12 weeks (≤ 84 days)
 - $>12 - \leq 24$ weeks (>84 to ≤ 168 days)
 - $>24 - \leq 36$ weeks (>168 to ≤ 252 days)
 - $>36 - \leq 48$ weeks (>252 to ≤ 336 days)
 - $>48 - \leq 52$ weeks (>336 to ≤ 364 days)
 - $>52 - \leq 60$ weeks (>364 to ≤ 420 days)
 - $>60 - \leq 72$ weeks (>420 to ≤ 504 days)
 - $>72 - \leq 84$ weeks (>504 to ≤ 588 days)
 - $>84 - \leq 96$ weeks (>588 to ≤ 672 days)
 - $>96 - \leq 104$ weeks (>672 to ≤ 728 days)
 - $>104 - \leq 118$ weeks (>728 to ≤ 826 days)
 - $>118 - \leq 132$ weeks (>826 to ≤ 924 days)
 - $>132 - \leq 144$ weeks (>924 to ≤ 1008 days)
 - $>144 - \leq 156$ weeks (>1008 to ≤ 1092 days)
 - $>156 - \leq 168$ weeks (>1092 to ≤ 1176 days)
 - $>168 - \leq 182$ weeks (>1176 to ≤ 1274 days)
 - >182 (>1274 days)

Only study drug exposure for DB period will be derived during Phase 3 Week 36 Interim Analysis.

Percent compliance to study drug regimen will be defined for DB period, OLE period, and the entire study period. Percent compliance will be calculated as $100 \times \text{actual number of drug syringe injected} / \text{number of expected drug syringe injected}$. The actual and expected number of drug syringes injected will be calculated as follows:

- For the DB period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken and with date of injection on or prior to the last DB EC record date. The number of syringes expected will be the ceiling of $\{(\text{the last DB EC record date} - \text{the first DB dose date} + 1) / 7 \}$.
- For the OLE period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken and with date of injection on or after the first OL dose date. The number of syringes expected will be the ceiling of $\{(\text{the last OL EC record date} - \text{the first OL dose date} + 1) / 7 \}$.
- For the entire study period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken. The number of syringes expected will be the ceiling of $\{(\text{the last EC record date} - \text{the first dose date} + 1) / 7 \}$.

- Answers in “Weekly Injection Diary” eCRF indicate dose (i.e., injection) was taken including:
 - “Yes, Dose in Clinic” or “Yes, Dose off site” is selected for question “Did you dose this week?”, or
 - “Yes” is selected for question “Was the entire dose administered?”, or
 - Date or time is entered for “Please enter the date of this dose” or “Please enter the time of this dose”, or
 - Location is entered for “Please record the injection location by tapping the number associated with your injection site”.

Percent compliance to study drug regimen will be defined for DB period only during Phase 3 Week 36 Interim Analysis.

Descriptive statistics of percent compliance for DB period, OLE period, and the entire study, once defined will be presented using Safety Population. In addition, the number and percentages of subjects with compliance in the following categories $\leq 80\%$, 80% to $\leq 90\%$, 90% to $\leq 100\%$, 100% to $\leq 120\%$, and $> 120\%$ will be presented.

3.4 Efficacy Assessment for the Phase 3 Week 36 Interim Analysis

The Phase 3 Week 36 Interim Analysis will take place when approximately the first 200 subjects complete their Week 36 visits or prematurely discontinue from the study. For Phase 3 Week 36 Interim Analysis, efficacy data will be summarized by randomized treatment based on the IAS. Unless otherwise indicated, the IAS is the primary analysis population for efficacy endpoints in Phase 3 Week 36 Interim Analysis.

3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR (i.e., $\log(\text{UPCR})$) at Week 36.

3.4.1.1 Primary Analysis

The primary efficacy endpoint will be analyzed by mixed-effects model for repeated measures (MMRM) including UPCR data up to Week 36 for IAS population. Formal statistical comparisons will be performed to compare the percentage change in UPCR between atacicept and placebo at each visit up to Week 36.

The estimand for the primary analysis of the primary efficacy endpoint is as follows:

- The population for the trial is defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The analysis population is based on the IAS population.
- The variable of interest is the change from baseline in $\log(\text{UPCR})$.

- The intercurrent events (ICEs) include (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplant, or death. The intercurrent events and missing data will be handled in the order as described below:
 - Step 1: Intercurrent Events Strategy
 - For subjects who discontinue treatment, all observed data will be used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who initiate rescue/prohibited therapy, all observed data will be used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the data collected after the first occurrence of the above ICEs will be deemed not interpretable and will be excluded from the analysis.
 - Step 2: Intermittent Missing Data
 - Intermittent missing data will be imputed by multiple imputation based on MCMC Monotone option in SAS PROC MI by treatment group under the missing at random assumption with 100 imputations.
 - Step 3: Monotone Missing Data
 - After intermittent missing data were imputed in Step 2, the rest of the missing data mainly due to subjects who withdraw from the study, subjects who missed the last visit(s) while still ongoing in the study, or subjects experience dialysis, kidney transplant, or death. All these data will be imputed by “jump to reference” approach first according to the hypothetical strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the values after the first occurrence of such ICEs will be imputed again (i.e., replaced) by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy. Some subjects may experience dialysis or kidney transplant first, then experience other ICEs (such as initiation of rescue therapy). The ICEs of dialysis, kidney transplant, or death will take the priority. The values after the ICE of dialysis, kidney transplant, or death will be replaced by the “worst case” approach regardless of whether other ICEs occurred or not. The sufficiently unfavorable value is defined as the 99 percentiles of the change from baseline in log (UPCR) from all postbaseline visits and both treatments using the observed data from Step 1, since for UPCR endpoint, the higher the value is, the worse the IgAN disease status is. The random error is estimated by the residual error calculated from the same analysis model using the observed data from Step 1.
 - Step 4: Statistical Analysis
 - Perform MMRM Analysis for each imputation data set.
 - Combine MMRM analysis results using Rubin’s rule (Rubin 1987).
- The population level summary measure is the reduction in the geometric mean ratio of UPCR relative to baseline in atacicept group compared to placebo group at Week 36, the associated 2-sided 95% confidence intervals (CI), and the p-value.

Baseline value for UPCR will be derived as the geometric mean of all measurements prior to the first dose of study drug. All UPCR data (including baseline and post-baseline) will be natural-log transformed prior to multiple imputation and analysis.

Following the above specified ICEs and missing data handling strategies, the statistical analysis method for the primary estimand is as follows. The primary efficacy endpoint will be analyzed using a MMRM model. Change from baseline in log (UPCR) will be the dependent variable. Effects for stable SGLT2i use at baseline (Yes, No), Region (Asia, Other), baseline eGFR category (< 45, ≥ 45 and < 90, or ≥ 90 mL/min/1.73m²), baseline natural-log transformed (UPCR), randomized treatment (atacicept, placebo), visit (Week 12, 24 and 36), and treatment-by-visit interaction will be included as independent fixed effects, and subjects will be included as a random effect. An unstructured covariance matrix will be used to model the within -subject correlation of data. In case some of the MMRM models fail to converge, the results based on these imputed datasets will be excluded from calculating the combined results using Robin's rule.

The primary comparison will test the mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week 36. The statistical comparison will be based on linear contrasts of the Least Square Means (LSMs) estimated by the MMRM model.

Let T_{0i} and T_{1i} be the baseline UPCR and UPCR at Week v for the i subject in atacicept group, P_{0i} and P_{1i} be the baseline UPCR and UPCR at Week v for the i subject in placebo group, $i = 1, 2, 3, \dots, n$ and $v = 12, 24, 36$.

Mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week v can be expressed as:

$$\frac{\sum(\log T_{1i} - \log T_{0i})}{n} - \frac{\sum(\log P_{1i} - \log P_{0i})}{n} = \log\left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}}\right] \quad (1)$$

The exponentiation of (1) is the ratio of geometric mean ratio of UPCR at Week v to baseline between atacicept and placebo groups:

$$\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}} = \left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}} \quad (2)$$

The percentage reduction of the geometric mean ratio of UPCR at Week v relative to baseline for atacicept group vs. placebo group can be obtained as follow:

$$1 - \left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}}\right] \quad (3)$$

The LSM differences in natural-log scale, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values obtained from the MMRM model, while the relative reduction of geometric mean ratio or the estimated percentage reduction from baseline (i.e., 1-exp(LSM difference)), associated standard errors, associated 2-sided 95% CIs, will all be presented in the summary table.

The sample SAS code for primary efficacy endpoint analysis is provided in Appendix 8.6.1.

3.4.1.2 Sensitivity Analyses

Sensitivity Analysis 1: While-On-Treatment Analysis

The first sensitivity analysis will investigate the effect of different intercurrent events handling approaches on the estimation of treatment effect.

The estimand for the first sensitivity analysis is the same as that of the primary analysis with the following exceptions:

- While-on-treatment policy will be used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE will be used, and data collected after the first ICE will be treated as missing in the next step.
- After including all data collected on or prior to the first ICE, missing data will be imputed according to the hypothetical strategy.
 - Intermittent missing: multiple imputation will be used to impute the intermittent missing based on MCMC monotone option in SAS PROC MI by treatment group under the missing at random assumption.
 - Missing after the last observed data on or prior to the first ICE: multiple imputation will be used to impute missing data by treatment group using the regression option from the monotone statement of SAS PROC MI.
 - Perform MMRM Analysis for each imputation data set.
 - Combine MMRM analysis results using Rubin's rule.

Sensitivity Analysis 2: Tipping Point Analysis

The second sensitivity analysis will be a two-dimensional tipping point analysis to assess the robustness of the “worst case” and “jump to reference” imputation strategies used in the primary analysis. The two-dimensional tipping point analysis is a delta-adjust method under the Missing Not At Random (MNAR) assumption. It explores the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis become non-significant.

Two different fixed and definite sets of shift parameters will be imposed on the multiply imputed missing data respectively for the atacicept and placebo groups to encapsulate the change in efficacy results. For each given pair of shift parameters, adjust the imputed values by the shift parameters for atacicept group and placebo group respectively. The pairs of shift parameters where the test results changed from significant to non-significant will be the tipping points. After the tipping points are identified, clinical judgement will be needed to assess the plausibility of the assumptions under the tipping points.

The shift parameters, the corresponding LS mean for each treatment, treatment difference, and associated p-value will be presented in a table. A heat map will be plotted for shift parameters and p-values.

The SAS sample code for the tipping point sensitivity analysis is provided in Appendix [8.6.2](#).

3.4.1.3 Supplementary Analyses

A supplementary analysis for the primary endpoint will be conducted by using the Week 36 PP population using the observed data following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis, whereas other elements of the estimand will be the same as that of primary analysis, and the same MMRM model will be used (see Section 3.4.1.1).

3.4.1.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the primary endpoint may be conducted for the following subgroups as appropriate based on IAS population:

- Age (< 40 , ≥ 40)
- Sex (Male, Female)
- Region (Asia, Other)
- Country (US, ex-US)
- Race (White, Non-White)
- Baseline UPCR (< 1.5 g/g, ≥ 1.5 g/g)
- Baseline Proteinuria (< 2 g/day, ≥ 2 g/day)
- Baseline eGFR (< 60 mL/min/1.73 m², ≥ 60 mL/min/1.73 m²)
- Stable SGLT2 use at baseline (Yes, No)

The subgroup analyses will be conducted using the same imputed data sets and the same MMRM model as that of the primary analysis for each subgroup category, separately. If the subgroup is one of the covariates in the model, the covariate will be removed from the model statement when the model is performed for the particular subgroup. If the sample size for a subgroup at a particular category is too small, the analysis might not be conducted.

A forest plot with geometric mean ratios, standard errors, associated 2-sided 95% CIs for the above subgroups and overall, when appropriate, will be presented.

3.4.2 Key Secondary Endpoint

The key secondary endpoint is the annualized rate change in eGFR through Week 104.

3.4.2.1 Primary Analyses

The analysis of the key secondary endpoint will take place when all study subjects complete the double-blind portion of the study (i.e., Week 104 visits) or prematurely discontinue from the study, which is specified in Section 3.5.2.1.

3.4.2.2 Interim Analyses for eGFR

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.4.3 Analyses of Other Secondary Endpoints

For Phase 3 Week 36 Interim Analysis, selected other secondary endpoints will be evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment-policy strategy, except that data (i.e., Gd-IgA1 and Hematuria) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, and no multiple imputation is planned for other secondary endpoints.

3.4.3.1 Change from Baseline at Week 36 in Natural-log Transformed Gd-IgA1

Differences in percentage change from baseline in Gd-IgA1 in atacicept group compared to placebo group at Week 36 will be analyzed using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, will all be presented in summary table.

3.4.3.2 Hematuria Resolution at Week 36

Hematuria categories are defined based on urine dipstick (labelled as “occult blood” in laboratory database) results into 4 categories: Negative/Trace = Negative or 0.03; 1+ = 0.06 or 0.1; 2+ = 0.2 or 0.5; and 3+ = 1.0 or >1.0.

- Hematuria resolution is defined as hematuria improvement to Negative/Trace from those with hematuria 1+ to 3+ at baseline.

The following analyses will be conducted:

- The number and percentage of subjects with hematuria resolution by visit and treatment group for subjects with 1+ to 3+ hematuria at baseline.

A logistic regression model for repeated measures will be used to estimate the odds ratio of achieving hematuria resolution for subjects treated with atacicept versus subjects treated with the placebo for each post-baseline visit up to Week 36. The logistic regression model will include the indicator variable of whether a subject achieves hematuria resolution as the dependent variable, stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category, randomized treatment, visit, and treatment-by-visit interaction as fixed effects. The odds ratios for the treatment effect at each post-baseline visit up to Week 36, associated 2-sided 95% CIs, and 2-sided p-values will be presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment at each post-baseline visit, their associated 2-sided 95% CIs, will also be presented.

If the model does not converge, the covariates will be removed one by one until the model converges in the following sequential order: region, stable SGLT2i use at baseline, baseline total urine protein excretion category, and baseline eGFR category.

The sample SAS code for logistic regression analysis is provided in Appendix 8.6.3.

In addition, the number and percentage of subjects in each hematuria category will be summarized by visit and treatment group for the IAS population.

3.4.4 Exploratory Endpoints

For the Week 36 Interim Analysis, selected exploratory endpoints will be evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment policy strategy, except that data (i.e., [REDACTED], total urine protein, IgA, IgG, IgM, spot UPCr, and [REDACTED]) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, and no multiple imputation is planned for exploratory endpoints.

3.4.4.1 [REDACTED]

[REDACTED]

[REDACTED]

3.4.4.2 Proportion of Subjects Achieving Desirable Total Urine Protein Reduction from Baseline at Week 36

Proportion of subjects reaching both a total urine protein < 1 g/day and $\geq 25\%$ reduction from baseline at Week 36 will be evaluated based on IAS.

A logistic regression model for repeated measures will be used to analyze the proportion of subjects reaching the total urine protein reduction from baseline at each postbaseline visit up to Week 36 similar to the model used for hematuria resolution (see Section 3.4.3.2 for details).

3.4.4.3 Change from Baseline at Week 36 in IgA, IgG, IgM, Spot UPCr, [REDACTED]

For each immunoglobulin biomarkers (i.e., IgA, IgG, and IgM), lab parameters from spot urine samples (i.e., spot UPCr [REDACTED]), the differences in percentage change from baseline in atacicept group compared to placebo group up to Week 36 will be analyzed, separately, using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values will all be presented in summary tables.

3.4.5 Predictive Power for the Annualized eGFR Total Slope Through Week 104 Based on the Phase 3 Week 36 Interim Data

The predictive power for the annualized eGFR slope through Week 104 will be calculated following Week 36 Interim Analysis using the data available at that time.

Suppose $\hat{\mu}_{D,UPCR}$ is the sample estimator for the treatment effect in change from Baseline in log(UPCR) at Week 36, denoted by $\mu_{D,UPCR}$; while $\hat{\mu}_{D,eGFR}$ is the sample estimator for the treatment effect in eGFR slope through Week 104, denoted by $\mu_{D,eGFR}$. According to the Multivariate Central Limit Theorem, it is reasonable to assume (refer to Appendix 8.5 for details):

$$(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \sim N(\mu_{D,UPCR}, \mu_{D,eGFR}, \sigma_{D,UPCR}^2, \sigma_{D,eGFR}^2, \rho) \quad (4)$$

where,

- $\sigma_{D,UPCR}^2$ and $\sigma_{D,eGFR}^2$ are the variances for the treatment effect estimator of UPCR at Week 36 and the treatment effect estimator of eGFR slope through Week 104, respectively.
- ρ is the correlation between the treatment effect estimator of UPCR at Week 36 and the treatment effect estimator of eGFR slope through Week 104.

Therefore, the distribution of $\hat{\mu}_{D,eGFR}$ conditional on $\hat{\mu}_{D,UPCR} = x$ follows a normal distribution:

$$\hat{\mu}_{D,eGFR} | \hat{\mu}_{D,UPCR} = x \sim N\left(\mu_{D,eGFR} + \rho \frac{\sigma_{D,eGFR}}{\sigma_{D,UPCR}}(x - \mu_{D,UPCR}), \sigma_{D,eGFR}^2(1 - \rho^2)\right) \quad (5)$$

The power to reject $H_0: \mu_{D,eGFR} = 0$ conditional on $\hat{\mu}_{D,UPCR} = x$ would be:

$$\begin{aligned} CP(\hat{\mu}_{D,UPCR} = x) &= P(\text{Reject } H_0 | \hat{\mu}_{D,UPCR} = x) \\ &= 1 - \Phi(z_{\alpha/2} - z_{D,eGFR}) + \Phi(-z_{\alpha/2} - z_{D,eGFR}), \end{aligned} \quad (6)$$

where $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$, $z_{D,eGFR} = \left[\mu_{D,eGFR} + \rho \frac{\sigma_{D,eGFR}}{\sigma_{D,UPCR}}(x - \mu_{D,UPCR})\right] / \sigma_{D,eGFR} \sqrt{(1 - \rho^2)}$.

The predictive power to reject $H_0: \mu_{D,eGFR} = 0$ would be:

$$PP = \int CP(\hat{\mu}_{D,UPCR} = x) f(\hat{\mu}_{D,UPCR} = x) dx, \quad (7)$$

where $f(x)$ represents the probability density function of $\hat{\mu}_{D,UPCR}$.

At the time of Phase 3 Week 36 Interim, we will have the sample estimate for $\mu_{D,UPCR}$ as u_1 , and the sample estimate for $\sigma_{D,UPCR}^2$ as s_1^2 . According to the Central Limit Theorem, it is reasonable to say: $\hat{\mu}_{D,UPCR} \sim N(u_1, s_1^2)$.

A meta-analysis for the association of treatment effects on early change in urine protein and annualized eGFR total slope in IgAN patients (Inker et al 2021) is referenced to predict the true treatment effect on the annualized eGFR slope. Here it is assumed that there is a linear relationship between $\mu_{D,eGFR}$ and $\mu_{D,UPCR}$ following the formula from Figure S6 in the reference manuscript: $\mu_{D,eGFR} = -0.85 - 7.15 * \mu_{D,UPCR}$. Assuming $u_2 = -0.85 - 7.15u_1$, we can estimate $\mu_{D,eGFR}$ as u_2 .

Considering estimates for $\sigma_{D,eGFR}^2$ and ρ will not be available at the time of Phase 3 Week 36 Interim Analysis, we will use information from Phase 2b data to estimate them (refer to Appendix 8.5 for details). Therefore, we will have estimates for $\sigma_{D,eGFR}^2$ and ρ as s_2^2 and r , respectively.

Now we have the distribution of $\hat{\mu}_{D,eGFR}$ conditional on $\hat{\mu}_{D,UPCR} = x$ as:

$$\hat{\mu}_{D,eGFR} | \hat{\mu}_{D,UPCR} = x \sim N\left(u_2 + r * \frac{s_2}{s_1}(x - u_1), s_2^2(1 - r^2)\right) \quad (8)$$

The power to reject $H_0: \mu_{D,eGFR} = 0$ conditional on $\hat{\mu}_{D,UPCR} = x$ can be expressed as:

$$\begin{aligned} CP(\hat{\mu}_{D,UPCR} = x) &= P(\text{Reject } H_0 | \hat{\mu}_{D,UPCR} = x) \\ &= 1 - \Phi(z_{\alpha/2} - z_0) + \Phi(-z_{\alpha/2} - z_0) \end{aligned} \quad (9)$$

where $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$, $z_0 = \left[u_2 + r * \frac{s_2}{s_1}(x - u_1)\right] / \sqrt{s_2^2(1 - r^2)}$

We will draw 10,000 random values for $\hat{\mu}_{D,UPCR}$ based on the distribution $\hat{\mu}_{D,UPCR} \sim N(u_1, s_1^2)$, denoted by x_k where $k = 1, 2, \dots, 10,000$. The power to reject $H_0: \mu_{D,eGFR} = 0$ conditional on $\hat{\mu}_{D,UPCR} = x_k$ would be $CP(\hat{\mu}_{D,UPCR} = x_k)$. The predictive power would be the averaged $CP(\hat{\mu}_{D,UPCR} = x_k)$ value across all possible values for $\hat{\mu}_{D,UPCR}$, written as:

$$\text{Predictive Power} = \frac{1}{10,000} \sum_{k=1}^{10,000} CP(\hat{\mu}_{D,UPCR} = x_k) \quad (10)$$

3.5 Efficacy Assessment for Phase 3 Week 104 Interim Analysis

Phase 3 Week 104 Interim Analysis will take place when all subjects complete the double-blind portion of the study at Week 104 or prematurely discontinue from the study. For the Phase 3 Week 104 Interim Analysis, efficacy data will be summarized by randomized treatment based on the FAS population. Unless otherwise indicated, the FAS is the primary analysis population for efficacy endpoints in Phase 3 Week 104 Interim Analysis.

3.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR (i.e., $\log(\text{UPCR})$) at Week 36.

The primary efficacy endpoint would have been evaluated at Week 36 Interim Analysis based on IAS population and including all UPCR data up to Week 36. The change from baseline in natural-log transferred UPCR up to Week 104 will be evaluated at the Week 104 Interim Analysis based on FAS population. The same estimand framework as specified for the primary analysis of the primary efficacy endpoint will be followed (see details in Section 3.4.1.1) to estimate the treatment effect on UPCR by visit.

3.5.2 Key Secondary Endpoint

The key secondary endpoint is the annualized rate of change in eGFR through Week 104.

3.5.2.1 Primary Analyses

The estimand for the primary analysis of the key secondary endpoint is as follows:

- The population is defined in a similar manner as for the primary efficacy endpoint. The analysis population is based on the FAS population.
- The variable of interest is the annualized rate of change in eGFR through Week 104.
- The intercurrent events (ICEs) include (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplant, or death. The intercurrent events and missing data will be handled in the order as described below:
 - Step 1: Intercurrent Events Strategy
 - For subjects who discontinue treatment, all observed data will be used according to treatment policy strategy.
 - For subjects who initiate rescue/prohibited therapy, all observed data will be used according to treatment policy strategy.
 - For subjects who experience ICEs of dialysis, kidney transplant, or death, the data collected after the first occurrence of above ICEs will be deemed not-interpretable and will be excluded from the analysis.
 - Step 2: Intermittent Missing Data
 - Intermittent missing data will be imputed by multiple imputation based on MCMC Monotone option in SAS PROC MI by treatment group under the missing at random assumption with 100 imputations.
 - Step 3: Monotone Missing Data
 - After intermittent missing data were imputed in Step 2, the rest of the missing data mainly due to subjects who withdraw from the study, subjects who missed the last visit(s) while still ongoing in the study, or subjects experience dialysis, kidney transplant, or death. All these missing data will be imputed by “jump to reference” approach first according to the hypothetical strategy.

- For subjects who experience ICEs of dialysis, kidney transplant, or death, the values after the first occurrence of such ICEs will be imputed again (i.e., replaced) by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy. Some subjects may experience dialysis or kidney transplant first, then experience other ICEs (such as initiation of rescue therapy). The ICEs of dialysis, kidney transplant, or death will take the priority. The values after the ICE of dialysis, kidney transplant, or death will be replaced by the “worst case” approach regardless of whether other ICEs occurred or not. The sufficiently unfavorable value is defined as the 1 percentile of the eGFR values from all visits and both treatments using the observed data, since for eGFR endpoint, the lower the value is, the worse the renal function is. The random error is estimated by the residual error calculated from the same analysis model using observed data.
- Step 4: Statistical Analysis
 - Perform MMRIRS model for each imputation data set.
 - Combine MMRIRS model results using Rubin’s rule.
- The population level summary measure is the difference between atacicept and placebo group in the annualized rate of change in eGFR through Week 104, the associated 2-sided 95% CI, and the p-value.
- The analysis approach uses a MMRIRS to analyze the annualized rate of change in eGFR. In the model, eGFR will be the dependent variable, with random subject effects for intercepts and slopes, and fixed effects for stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category, randomized treatment, time, and the treatment-by-time interaction. The actual time measurements, in years after the first injection (i.e., total slope), will be included in the model as a continuous variable. The baseline eGFR value recorded per subject will be assigned a time value of 0. The analysis testing the differences between the treatment groups will be constructed using linear contrasts of the appropriate LS Means from the MMRIRS model, where the difference in eGFR slope corresponds to the parameter for the treatment-by-time interaction term.
- The sample SAS code for primary analysis of the key secondary efficacy endpoint is provided in Appendix 8.6.4.

3.5.2.2 Sensitivity Analyses

Sensitivity Analysis 1: While-On-Treatment Analysis

The first sensitivity analysis will investigate the effect of different intercurrent events handling approach on the estimation of treatment effect.

The estimand for the first sensitivity analysis is the same as that of the primary analysis with the following exceptions:

- While-on-treatment policy will be used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE will be used, and data collected after the first ICE will be treated as missing in the next step.

- After including all data collected on or prior to the first ICE, missing data will be imputed according to the hypothetical strategy.
 - Intermittent missing: multiple imputation will be used to impute the intermittent missing based on MCMC monotone option in SAS PROC MI by treatment group under the missing at random assumption with 100 imputations.
 - Missing after the last observed data on or prior to the first ICE: multiple imputation will be used to impute missing data by treatment group using the regression option from the monotone statement of SAS PROC MI.
 - Perform MMRIRS Analysis for each imputation data set.
 - Combine MMRIRS analysis results using Rubin's rule.

Sensitivity Analysis 2: Tipping Point Analysis

A second sensitivity analysis will be a two-dimensional tipping point analysis to assess the robustness of the “worst case” and “jump to reference” imputation strategies used in the primary analysis. The two-dimensional tipping point analysis is a delta-adjust method under the Missing Not At Random (MNAR) assumption. It explores the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis become non-significant.

Two different fixed and definite sets of shift parameters will be imposed on the multiply imputed missing data respectively for atacicept group and placebo group to encapsulate the annualized total slope in efficacy results. The shift parameters for total slope for both atacicept group and placebo group are ranged from -8 to 8 by 2 (i.e., -8, -6, ..., 6, 8). The range and increments of shift parameters may be adjusted if tipping points are not identified in the range. For each given pair of shift parameters, it adjusts the imputed eGFR values over time by the shift parameters for the atacicept and placebo groups, respectively. The tipping points are the shift needed to make the results become statistically non-significant, or in other words, they are the minimum deviation of the distribution of missing data needed to make the results become statistically non-significant. After the tipping points are identified, clinical judgement will be needed to assess the plausibility of the assumptions under the tipping points. The reverse of study conclusion under plausible tipping points indicates that the primary analysis assumption may not be reasonable.

The SAS sample code for the tipping point sensitivity analysis is provided in Appendix 8.6.5.

Sensitivity Analysis 3: Two-slopes MMRIRS

Sensitivity analysis may be conducted to estimate the annualized eGFR chronic slope if data suggests there is an acute eGFR effect, i.e., a noticeable acute increase/decrease in eGFR observed in atacicept group at an early post-baseline visit, such as Week 12.

Statistical analysis will be carried out using a MMRIRS model allowing for two slope parameters, corresponding to acute (or short-term) and chronic (or long-term) eGFR slope effects, in order to characterize longitudinal trends in the rate of eGFR decline. The model is formulated via the definition of a changepoint in time at which the chronic effect starts. The changepoint will be selected based on visualization of Phase 3 eGFR data and confirmed by fitting the model considering changepoints at Weeks 4 to 24 and selecting the changepoint corresponding to the best fitting model as determined by the Akaike's Information Criterion (AIC) using the observed data set.

This sensitivity analysis will use the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1). The two-slope MMRIRS model described below will be fitted on each imputed dataset and the results will be combined using Rubin's rules to obtain the estimates of the difference and its associated 95% CI in acute slope and total slope, respectively.

Let t^* denote the selected changepoint and let $time_cp = \max \{ time - t^*, 0 \}$ be the truncated time after the changepoint. In the two-slope MMRIRS model, eGFR will be the dependent variable, with random subject effects for intercepts and two slopes; Fixed effects include baseline eGFR category, baseline total urine protein excretion category, stable SGLT2i use at baseline, region, randomized treatment, time, time_cp, treatment-by-time interaction, and treatment-by-time_cp interaction. The actual *time* measurements, in years after the first injection, and the truncated *time_cp* measurement, in years after the changepoint, will be included in the model as continuous variables. The baseline eGFR value recorded per subject will be assigned a time value of 0. An unstructured covariance matrix will be used to model the within subject correlation of data. In case the model fails to converge using an unstructured covariance matrix at any stage, compound symmetric covariance matrix will be used. If convergence still fails, statistically insignificant (i.e., $p > 0.05$) stratification factors may be removed from the model to satisfy the convergence criteria. If issues persist, a modified single-slope MMRIRS excluding eGFR values prior to the changepoint will be fit.

The SAS sample code for the two-slope MMRIRS is provided in Appendix 8.6.6.

3.5.2.3 Supplementary Analyses

A supplementary analysis for the key secondary endpoint will be conducted using the Week 104 PP population using the observed data following the treatment-policy strategy, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis, whereas other elements of the estimand will be the same as that of primary analysis and the same MMRIRS will be repeated (see Section 3.5.2.1).

3.5.2.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the key secondary endpoint may be conducted for the following subgroups as appropriate based on FAS population:

- Age ($< 40, \geq 40$)
- Sex (Male, Female)
- Region (Asia, Other)

- Country (US, ex-US)
- Race (White, Non-White)
- Baseline UPCr (< 1.5 g/g, ≥ 1.5 g/g)
- Baseline Proteinuria (< 2 g/day, ≥ 2 g/day)
- Baseline eGFR (< 60 mL/min/1.73 m², ≥ 60 mL/min/1.73 m²)
- Stable SGLT2i use at baseline (Yes, No)

The subgroup analyses will be conducted using the same MMRIRS as that of primary analysis and the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1) for each subgroup category, separately. If the subgroup is one of the covariates in the model, the covariate will be removed from the model statement when the model is performed for the particular subgroup. If the sample size for a subgroup at a particular category is too small, the analysis might not be conducted.

A forest plot with total slope difference, standard errors, associated 2-sided 95% CIs obtained from the MMRIRS for the above subgroups, when appropriate, will be presented.

3.5.3 Analyses of Other Secondary Endpoints

For Phase 3 Week 104 Interim Analysis, selected other secondary endpoints will be formally evaluated according to the hierarchical multiple testing approach prespecified in Section 3.1.7 based on FAS and including all available data up to Week 104.

For the change from baseline in eGFR at Weeks [REDACTED] 104 endpoints, the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1) will be used to support this secondary endpoint.

All other secondary endpoints, excluding the change from baseline in eGFR at Weeks [REDACTED] and 104, will be analyzed following the treatment-policy strategy, except that data (e.g., Gd-IgA1, eGFR, and Hematuria) collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, and no multiple imputation is planned for other secondary endpoints.

3.5.3.1 Change from Baseline at Weeks [REDACTED] 104 in eGFR

For each imputed dataset, the differences in change from baseline in eGFR in atacicept group compared to placebo group at each post baseline visit will be analyzed using the MMRM model. Change from baseline in eGFR will be the dependent variable. Effects for stable SGLT2i use at baseline, Region, baseline total urine protein category, baseline eGFR, randomized treatment, visit, and treatment-by-visit interaction will be included as fixed effects, and subjects will be included as a random effect. The results will be combined using Rubin's rule to obtain the final result. The LSM differences, standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-values will be presented in the summary table.

The details on the strategies to handle intercurrent events and missing data for the analysis of the change from baseline in eGFR at Weeks [REDACTED] 104 are provided in Appendix 8.3.

3.5.3.2 Change from Baseline at Weeks 36, 52, and 104 in Gd-IgA1

Differences in percentage change from baseline in Gd-IgA1 in atacicept group compared to placebo group at each post-baseline visit up to Week 104 will be analyzed using MMRM similar to the one as described in Phase 3 Interim Analysis (see Section 3.4.3.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-value will all be presented in summary table. The details on the strategies to handle intercurrent events and missing data for the analysis of the change from baseline in Gd-IgA1 are provided in Appendix 8.3.

3.5.3.3 Hematuria Resolution at Weeks 36, 52, and 104

Hematuria resolution will be analyzed using logistic regression model with repeated measurements similarly as described in Phase 3 Week 36 Interim Analysis (see Section 3.4.3.2 for details) including subjects in the FAS population and with 1+ and above hematuria at Baseline and including data up to Week 104. The odds ratios for the treatment effect at each postbaseline visit up to Week 104, associated 2-sided 95% CIs, and 2-sided p-values will be presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment and by visit, their associated 2-sided 95% CIs, will also be presented. The details on the strategies to handle intercurrent events and missing data for the analysis of hematuria resolution are provided in Appendix 8.3.

3.5.3.4 Time from Randomization to the First Occurrence of a Sustained $\geq 30\%$ Decline in eGFR

Time to the first occurrence of a Sustained $\geq 30\%$ Decline in eGFR will be analyzed using a Cox proportional hazards model including stable SGLT2i use at baseline, Region, baseline eGFR category, baseline total urine protein category, and randomized treatment as fixed effects. The estimated hazard ratio, the corresponding 2-sided 95% CIs, and 2-sided p-values will be presented. Participants who have not had an event up to Week 104 will be censored in the analysis. Cumulative incidence curves will be presented by treatment group. The details on the strategies to handle intercurrent events and missing data for the analysis of time randomization to the first occurrence of a sustained $\geq 30\%$ decline in eGFR are provided in Appendix 8.3.

3.5.4 Exploratory Endpoints

For Week 104 Interim Analysis, all exploratory endpoints will be evaluated as supportive analyses similarly as they are analyzed in Phase 3 Week 36 Interim Analysis (see Section 3.4.4 for details) based on FAS and including all available data up to Week 104.

3.6 Safety Assessment

Safety data will be summarized by actual treatment received based on the Safety Population.

For the Phase 3 Week 36 Interim Analysis, as we expect a minimal number of subjects will complete the DB period and enter into the OLE period, safety assessments will be summarized for the DB period only.

For Phase 3 Week 104 Interim Analysis, safety assessments will be summarized for DB period, OLE period, and the entire study period, separately.

For both interim analyses, all safety data, regardless of being collected in DB period, OLE period, or follow-up period will be listed for Safety population.

3.6.1 Adverse Events (AEs)

All AEs occurring from the date of the first informed consent to the last safety follow-up visit will be collected and captured by eCRF. All AEs will be coded and categorized using SOC and PT using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The severity of AEs will be assessed by the Investigator as mild, moderate, or severe.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates occurring during the study period (i.e., on or after the first dose date/time until the subject's last study visit). TEAEs will be assigned to the most recently received treatment at the start of the AE.

AEs will be considered treatment-emergent during the DB period if they start on or after the first dose date/time of double-blinded study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. AEs will be considered treatment-emergent during the OLE period if they start on or after the first dose date/time of OLE study drug through the end of the study. If AEs cannot be decided as to which period they belong due to completely missing or partial AE onset dates, AEs will be considered treatment-emergent during both periods.

An overview summary of the number and percentage of subjects with the following TEAEs will be provided:

- TEAEs (overall and by severity)
- Study drug related TEAEs (overall and by severity)
- Treatment-emergent serious AEs (TESAEs)
- Study drug related TESAEs
- TEAEs of special interest (TEAESI) (overall and by severity)
- TEAEs of injection site reaction (ISR) defined by injection site reaction PT or by combined PTs (overall and by severity), combined PTs are listed in Appendix 8.4 to define injection site reaction.
- TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death

In addition, the following TEAEs will be summarized by SOC and/or PT separately:

- TEAEs by SOC and PT
- Study drug related TEAEs by SOC and PT
- TESAEs by SOC and PT
- Study drug related TESAEs by SOC and PT
- TEAESIs by Category and PT
- TEAEs leading to study drug interruption by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- Common TEAEs by PT ($\geq 5\%$ incident rate in either treatment arm)

A subject experienced multiple TEAEs within a SOC or PT will be counted only once for the SOC or PT. For tabulations that include classification by relationship to study treatment, TEAEs with missing relationship will be considered related to study drug. When summarized by severity, a subject with TEAEs with multiple severity categories will be summarized under the maximum severity category (severe > moderate > mild). If missing severity category exists, TEAEs with missing severity will be summarized under a missing category and displayed as the last category in severity summary table.

Adverse events of special interest (AESIs) include, hypersensitivity reactions, demyelination disorders, cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and infections.

For hypersensitivity reactions, demyelination disorders, and cardiac events, a list of preferred terms from the relevant Standardized MedDRA Query (SMQ) narrow scope will be used to flag these AESI in a systematic and objective way.

AESI of infections will be identified using two approaches: (1) a predefined list of preferred terms from the narrow scope of the “opportunistic infections” SMQ; and (2) serious or severe adverse events in the SOC of “infections and infestations”.

AESIs will be included for tabulation summary and listing.

Listings will be presented specifically for AEs, SAEs, AESIs, AEs leading to study drug discontinuation, AEs leading to study discontinuation, and AEs leading to death.

3.6.2 Clinical Laboratory Tests

Clinical laboratory tests in this study include hematology, clinical chemistry, urine sediment, routine urinalysis and other tests.

Summary statistics for selected hematology, clinical chemistry, urine sediment, and routine urinalysis at DB baseline, at all scheduled post-baseline visits, as well as for change from

baseline for all scheduled post baseline visits will be provided by treatment group. Results of clinical laboratory tests will be flagged as abnormal if they are out of normal ranges.

Listings of hematology, clinical chemistry, urine sediment, routine urinalysis and other tests will be provided respectively.

3.6.3 Vital Signs

Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, and at the scheduled visits.

Summary statistics for systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature at DB baseline, at all scheduled post baseline visits, as well as for change from baseline for all scheduled post-baseline visits will be provided by treatment group.

A listing of vital signs will be provided.

3.6.4 Electrocardiograms (ECG)

The overall interpretation of ECG results will be categorized as abnormal (further categorized as clinically significant abnormal or not clinically significant abnormal), indeterminate, normal, not evaluable, and unknown. The number and percentage of subjects with different categories of overall interpretation of ECG results will be summarized by visits (including baseline and scheduled post-baseline visits).

A listing of ECG will be provided.

3.6.5 Physical Examinations

A complete physical examination will include, at a minimum, assessment of the general appearance, skin, lymph nodes (cervical), head, ears, eyes, nose, throat (HEENT), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems. Complete physical examination will be performed at screening and Week 104 visits. On other visits, a symptom-driven physical examination will be performed and will include assessment of any new subject complaints or changes from baseline.

Findings from physical examinations will be categorized as clinically significant and not clinically significant. As physical examination findings are qualitative and there is significant inter-observer variation, no analyses will be performed on the physical examination data. All physical examination findings will be presented in a listing.

3.6.6

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.7 Anti-Drug Antibody Assessment

3.7.1 Classification of Subject ADA Status

For Week 36 Interim Analysis, only immunogenicity data collected on or prior to Week 36 will be used to determine ADA status for subjects in the Immunogenicity population as specified below.

ADA results from each sample are reported as either positive or negative based on the confirmatory assay. If the sample is positive, the ADA titer is reported as well. A subject is

defined as being ADA-positive if a positive ADA result is available at any time, including baseline or any post-baseline measurements. A subject is defined as being ADA-negative if the subject has no positive ADA assessments at all available assessments.

The subject ADA status of each evaluable subject is classified according to the following definitions:

- ADA positive at baseline or post-baseline: subjects with any positive ADA assessment at baseline or post-baseline. The percentage of these subjects in a population is known as ADA prevalence.
- Treatment-induced ADA positive: subjects who were ADA negative or missing at baseline and have at least 1 post-baseline ADA positive result with titer > 50.
- Treatment-boosted ADA positive: subjects who were ADA positive at both baseline and post-baseline but had a meaningful increase in ADA titer by at least 4-fold from baseline to post-baseline.
- Treatment-emergent ADA positive (TE-ADA+): subjects who were either treatment-boosted ADA positive or treatment-induced ADA positive. The percentage of these subjects in a population is known as ADA incidence.
- Non-TE-ADA+: subjects who were ADA positive but not fulfilling the criteria for being TE-ADA+.
- ADA positive at baseline only: subjects with at least 1 positive ADA sample at baseline and no positive ADA sample at any post-baseline assessment.
- ADA positive at both baseline and post-baseline: Subjects with positive ADA samples at both baseline and at least one post-baseline assessment.

Duration of ADA response:

- Treatment-emergent persistently ADA positive: TE-ADA+ subjects with at least 2 post-baseline ADA+ assessments with titer > 50 and at least 16 weeks (112 days) between the first and the last positive assessment with titer > 50 (irrespective of any negative results in between).
- Treatment-emergent transiently ADA positive: TE-ADA+ subjects with at least 1 post-baseline ADA positive assessment and not fulfilling the conditions for TE-persistently ADA positive.

For subjects randomized to the placebo group, only selected post-baseline ADA samples will be analyzed, except for a subgroup of placebo subjects (n~25), for whom all ADA available samples will be analyzed. Thus, the duration of ADA response will be derived for all subjects in the atacicept group, but only for the selected subset in the placebo group, whose ADA samples were analyzed for all post-baseline assessments.

ADA Response Summary

The number and percentage of subjects in each subject ADA status described above will be summarized by treatment for immunogenicity populations. In addition, the descriptive statistics

for maximum post-baseline ADA titers for each subject ADA status will be summarized by treatment.

Kinetics of ADA Response Summary

The number and percentage of subjects with ADA-negative or ADA-positive sample results will be summarized by visit and by treatment. Among subjects with ADA-positive sample, further breakdown will be provided for those with maximum post-baseline titers ≤ 50 (i.e., borderline positive) or 50 and those with titers >50 at the corresponding visit. Results will be summarized by visit (baseline and scheduled post-baseline visits up to the DB Week 36 visit) and by treatment group.

Additionally, descriptive statistics (minimum, Q1, median, Q3, and maximum) of titer results for subjects with ADA positive and titers >50 will be summarized by visit and treatment group.

ADA results at each visit and the corresponding efficacy endpoints (i.e., percentage change from baseline in UPCR and Gd-IgA1, and change from baseline in eGFR) will be presented in a subject listing for TE-ADA+ subjects. In addition, an adverse event listing will be produced for TE-ADA+ subjects.

4 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (iDMC) will monitor the safety and wellbeing of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority in all aspects. Details regarding the role, responsibilities, and data review requirements of the iDMC will be outlined in a separate iDMC charter.

5 MID-STUDY ANALYSIS AND FINAL ANALYSIS TIMING

5.1 Primary Endpoint Analysis at Week 36 Data Cut

The primary analysis of UPCR will be performed after approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study. This data cut will include all data from all subjects when approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study, including data from subjects who have completed visits beyond Week 36.

5.2 End of Part C Analysis at Week 104 Data Cut

An end of Part C analysis will be performed when all subjects complete the double-blind portion of the study at Week 104 or prematurely discontinue from the study. This data cut will include all data from all subjects when all subjects complete the Week 104 visit or prematurely discontinue from the study, including data from subjects who have completed visits beyond Week 104.

5.3 Final Analysis

A final analysis will be conducted once all subjects complete the OLE and safety follow-up visits or discontinue from the trial.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Based on the US FDA comments received on April 29th, 2025 and May 9th, 2025, the following updates were incorporated in SAP version 2.0.

- FDA recommended to pre-specify a plan to use the available interim data to assess the predictive power / positive predictive value for the annualized rate of change in eGFR through Week 104.
- FDA recommended to change the endpoint of “time to the composite kidney failure endpoint through Week 104” to “time to a sustained $\geq 30\%$ decline in eGFR”.
- FDA recommended to increase the number of imputations for missing data from 50 imputations to 100 imputations to account for uncertainty in the missing data.
- FDA recommended to remove “study withdrawal” from the list of intercurrent events per E9 (R1) Addendum.

The study team recommended to make the following updates in SAP Version 2.0:

- Percentage reductions in UPCR at Weeks 36 and 104 based on the FAS population were not specified as “secondary objectives” in Protocol Amendment 7. However, both endpoints are included in the multiple testing hierarchy (Figure 2) and will be formally tested at the time of the Phase 3 Week 104 interim analysis. These endpoints provide confirmatory and final estimates of the treatment effect on UPCR.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS[®] version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by treatment group, subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

8 APPENDICES

8.1 References

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med. 2009;150(9):604-612.
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4. Inker LA, Heerspink HJL, Tighiouart H. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Subject Meta-analysis. *Am J Kidney Dis*. 2021;78:340-349.e1.
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6. Richard L, Jens K, et al. Efficacy and Safety of a Targeted-release Formulation of Budesonide in Patients with Primary IgA Nephropathy (NefIgArd): 2-year Results From a Randomised Phase 3 Trial. *Lancet*. 2023.
7. [REDACTED]
8. [REDACTED]
9. Rubin, D. B.. Multiple Imputation for Nonresponse in Surveys. Wiley 1987.
10. <https://euroqol.org/information-and-support/resources/value-sets/>

8.2 Analysis Window Relative to DB Baseline

Analysis Visit	Target Analysis Day	Earliest Analysis Day	Latest Analysis Day
Screening	-1		-1
DB Baseline (Day 1)	1		prior to the first DB dose date/time
Week 2	15	On or after the first DB dose date/time	21
Week 4	29	22	56
Week 12	85	57	126
Week 24	169	127	210
Week 36	253	211	294
Week 48	337	295	350
Week 52	365	351	392
Week 60	421	393	462
Week 72	505	463	546
Week 84	589	547	630
Week 96	673	631	700
Week 104	729	701	735 for subjects not participating in OLE; prior to the OLE first dose date/time for subjects continuing in OLE
Week 106	743	On or after the OLE first dose date/time	784
Week 118	827	785	875
Week 132	925	876	966
Week 144	1009	967	1050
Week 156	1093	1051	1134
Week 168	1177	1135	1225
Week 182	1275	1226	NA

Note: Analysis Day = Event Date – First Date of Dosing in DB period +1 for events on first date of dosing in DB period and after. Analysis Day = Event Date – First Date of Dosing for events prior to first date of dosing in DB period.

8.3 Intercurrent Events and Missing Data Handling Strategy for Endpoints Included in the Multiple Testing Hierarchy

Endpoints	Intercurrent Events/ Missing Data	Handling Strategy in Primary Analysis	Implementation
Endpoint To be Tested in Week 36 Interim Analysis			
% Reduction in UPCR at Weeks 36 (IAS)	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapies	Treatment Policy	Use all observed data
	Initiation of prohibited medications	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded and imputed with worst change plus a random error
	Intermittent Missing Data	Hypothetical Policy	Imputed using MCMC assuming Missing at Random
	Monotone Missing Data	Hypothetical Policy	Imputed with Jump to Reference for missing due to study withdrawal including loss to follow-up, etc.
Endpoints To be Tested in Week 104 Interim Analysis			
eGFR Total Slope 	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapy	Treatment Policy	Use all observed data
	Initiation of prohibited medication	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded and imputed with worst value plus a random error
	Intermittent Missing Data	Hypothetical Policy	Imputed using MCMC assuming Missing at Random
	Monotone Missing Data	Hypothetical Policy	Imputed with Jump to Reference for missing due to study withdrawal including loss to follow-up, etc.
% Reduction in UPCR at Weeks 36 and 104 (FAS)	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapies	Treatment Policy	Use all observed data
	Initiation of prohibited medications	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded and imputed with worst change plus a random error
	Intermittent Missing Data	Hypothetical Policy	Imputed using MCMC assuming Missing at Random
	Monotone Missing Data	Hypothetical Policy:	Imputed with Jump to Reference for missing due to study withdrawal including loss to follow-up, etc.

Endpoints	Intercurrent Events/ Missing Data	Handling Strategy in Primary Analysis	Implementation
% Reduction in Gd-IgA1 at Weeks 36 and 104 (FAS)	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapy	Treatment Policy	Use all observed data
	Initiation of prohibited medication	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded and missing data were implicitly handled by MMRM assuming Missing at Random.
	Intermittent and Monotone Missing Data	Hypothetical Policy:	Missing data was implicitly handled by MMRM assuming Missing at Random,
% of Hematuria Resolution at Weeks 36 and 104 (FAS)	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapy	Treatment Policy	Use all observed data
	Initiation of prohibited medication	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded from logistic regression modeling
	Intermittent and Monotone Missing Data	Hypothetical Policy:	Excluded from logistic regression modeling
Time to a Sustained $\geq$ 30% Decline in eGFR (FAS)	Treatment Discontinuation	Treatment Policy	Use all observed data
	Initiation of rescue therapy	Treatment Policy	Use all observed data
	Initiation of prohibited medication	Treatment Policy	Use all observed data
	Dialysis; Kidney transplantation; Death	Hypothetical Policy	Data collected after ICEs were excluded.
	Intermittent and Monotone Missing Data	Hypothetical Policy:	Subjects without an event at the time of analysis were censored at their last available follow-up date. No imputation was performed for missing event time. Censoring was assumed to be non-informative.

IAS = Interim Analysis Set; ICE = Intercurrent Events; FAS = Full Analysis Set; MMRM = Mixed-effect Model for Repeated Measurement.

8.4 AE of Injection Site Reaction Definition

Below Preferred Terms (Coded in MeDRA v27.1) under High-Level Term of “Injection Site Reactions” will be grouped as AE of Injection Site Reaction. This grouping will be used for adverse event summaries among all Atacicept studies.

High-Level Term	Preferred Terms
Injection Site Reactions	Injection site bruising
	Injection site coldness
	Injection site discolouration
	Injection site discomfort
	Injection site erythema
	Injection site haematoma
	Injection site haemorrhage
	Injection site induration
	Injection site irritation
	Injection site mass
	Injection site pain
	Injection site pruritus
	Injection site reaction
	Injection site recall reaction
	Injection site swelling
	Injection site urticaria
	Injection site warmth

8.5 Details for Calculating Predictive Power at Week 36 Interim Analysis

The predictive power for the annualized eGFR slope through Week 104 will be calculated following Week 36 Interim Analysis using the data available at that time.

Suppose $\hat{\mu}_{D,UPCR}$ is the sample estimator for the treatment effect in change from Baseline in $\log(UPCR)$ at Week 36, denoted by $\mu_{D,UPCR}$; while $\hat{\mu}_{D,eGFR}$ is the sample estimator for the treatment effect in eGFR slope through Week 104, denoted by $\mu_{D,eGFR}$. The following sections provide justification for assuming $(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$ follows a bivariate normal distribution.

Bivariate Normal Distribution of $(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$:

The sample estimator for $\mu_{D,UPCR} = \mu_{A,UPCR} - \mu_{P,UPCR}$ based on the Week 36 Interim data would be:

$$\begin{aligned}\hat{\mu}_{D,UPCR} &= \hat{\mu}_{A,UPCR} - \hat{\mu}_{P,UPCR} \\ &= \frac{1}{n_1} \sum_{i=1}^{n_1} [\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})] \\ &\quad - \frac{1}{m_1} \sum_{j=1}^{m_1} [\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})]\end{aligned}$$

where,

- $\mu_{A,UPCR}$ and $\mu_{P,UPCR}$ are the population means for the change from Baseline in $\log(UPCR)$ at Week 36 for the Atacicept 150mg and the Placebo groups, respectively;
- $UPCR_{A,i,W36}$ and $UPCR_{P,j,W36}$ are the Week 36 UPCR values for the i^{th} Atacicept 150 mg subject and j^{th} Placebo subject, respectively. Similarly, $UPCR_{A,i,Base}$ and $UPCR_{P,j,Base}$ are the Baseline UPCR values for the i^{th} Atacicept 150 mg subject and j^{th} Placebo subject, respectively;
- n_1 and m_1 are the numbers of subjects at Week 36 Interim Analysis for Atacicept 150 mg and Placebo groups, respectively.

The sample estimator for $\mu_{D,eGFR} = \mu_{A,eGFR} - \mu_{P,eGFR}$ based on the Week 104 Interim data would be:

$$\begin{aligned}\hat{\mu}_{D,eGFR} &= \hat{\mu}_{A,eGFR} - \hat{\mu}_{P,eGFR} \\ &= \frac{1}{n} \sum_{i=1}^n eGFR_Slope_{A,i} - \frac{1}{m} \sum_{j=1}^m eGFR_Slope_{P,j}\end{aligned}$$

where,

- $\mu_{A,eGFR}$ and $\mu_{P,eGFR}$ are the population means for the eGFR slope through Week 104 for the Atacicept 150 mg and the Placebo groups, respectively.

- $eGFR_Slope_{A,i}$ and $eGFR_Slope_{P,j}$ are the eGFR slope through Week 104 for the i^{th} Atacicept 150 mg subject and j^{th} Placebo subject, respectively.
- n and m are the numbers of subjects at Week 104 Interim Analysis for Atacicept 150 mg and Placebo groups, respectively.

Based on the Multivariate Central Limit Theorem, it is reasonable to assume:

$$(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \sim N(\mu_{D,UPCR}, \mu_{D,eGFR}, \sigma_{D,UPCR}^2, \sigma_{D,eGFR}^2, \rho)$$

Where $\mu_{D,UPCR}$, $\mu_{D,eGFR}$, and $\sigma_{D,UPCR}^2$ could be estimated from Phase 3 Week 36 Interim Analysis and the reference manuscript by Inker et al (refer to Section 3.4.5 for details). While $\sigma_{D,eGFR}^2$ and ρ cannot be estimated at the time of Phase 3 Week 36 Interim Analysis, the following two sections provide details regarding how to estimate $\sigma_{D,eGFR}^2$ and ρ using Phase 2b data.

Estimating $\sigma_{D,eGFR}^2$ (i.e., Variance of $\hat{\mu}_{D,eGFR}$) Based on Phase 2b Data:

The variance of $\hat{\mu}_{D,eGFR}$ is:

$$\sigma_{D,eGFR}^2 = \frac{1}{n} Var(eGFR_Slope_{A,i}) + \frac{1}{m} Var(eGFR_Slope_{P,j})$$

Assuming $Var(eGFR_Slope_{A,i}) = Var(eGFR_Slope_{P,j})$, we will use the following two ways to estimate $\sigma_{D,eGFR}^2$ based on Phase 2b data for eGFR slope through Week 96:

- Use the variance of eGFR slope through Week 96 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of Phase 2b study) to estimate both $Var(eGFR_Slope_{A,i})$ and $Var(eGFR_Slope_{P,j})$. Therefore, we can estimate $\sigma_{D,eGFR}^2$ as s_2^2 .
- Use the variance of eGFR slope through Week 96 within the Atacicept 150 mg group (only subjects who were randomized to Atacicept 150mg group at the beginning of Phase 2b study) to estimate both $Var(eGFR_Slope_{A,i})$ and $Var(eGFR_Slope_{P,j})$. Therefore, we can estimate $\sigma_{D,eGFR}^2$ as s_2^2 .

Estimating Correlation Coefficient ρ Based on Phase 2b Data:

We will use Phase 2b data to estimate the correlation coefficient ρ . To do this, we will have to estimate $\sigma_{D,UPCR}^2$ and ρ using the same data (Phase 2b data).

The variance of $\hat{\mu}_{D,UPCR}$ is:

$$\begin{aligned} \sigma_{D,UPCR}^2 = & \frac{1}{n_1} Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\} \\ & + \frac{1}{m_1} Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\} \end{aligned}$$

Similarly, we will use the following two ways to estimate $\sigma_{D,UPCR}^2$ based on Phase 2b data:

- Use the change from baseline in $\log(UPCR)$ at Week 36 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of the Phase 2b study) to estimate $Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\}$; while use the change from baseline in $\log(UPCR)$ at Week 36 within the Placebo group to estimate $Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\}$. Therefore, we can estimate $\sigma_{D,UPCR}^2$ as s_3^2 .
- Use change from baseline in $\log(UPCR)$ at Week 36 within the Atacicept 150 mg group (only subjects who were randomized to Atacicept 150mg group at the beginning of Phase 2b study) to estimate $Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\}$; while use the change from baseline in $\log(UPCR)$ at Week 36 within the Placebo group to estimate $Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\}$. Therefore, we can estimate $\sigma_{D,UPCR}^2$ as s_3^2 .

The covariance between $\hat{\mu}_{D,UPCR}$ and $\hat{\mu}_{D,eGFR}$ is:

$$\begin{aligned} & Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \\ &= \frac{1}{n} Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR_Slope_{A,i}\} \\ & \quad + \frac{1}{m} Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR_Slope_{P,j}\}. \end{aligned}$$

Assuming $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR_Slope_{A,i}\}$ is the same as $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR_Slope_{P,j}\}$, we will also use the following two ways to estimate $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$ based on Phase 2b data, which corresponds to the two ways for estimating $\sigma_{D,eGFR}^2$ and $\sigma_{D,UPCR}^2$:

- Use the Phase 2b data for the covariance between the change from baseline in $\log(UPCR)$ at Week 36 and the eGFR slope through Week 96 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of Phase 2b study) to estimate both $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR_Slope_{A,i}\}$ and $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR_Slope_{P,j}\}$. Therefore, we can estimate $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$ as c_0 .
- Use the covariance between the change from baseline in $\log(UPCR)$ at Week 36 and the eGFR slope through Week 96 within the Atacicept 150 mg group (subjects who were randomized to Atacicept 150 mg group at the beginning of Phase 2b study) to estimate both $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR_Slope_{A,i}\}$ and $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR_Slope_{P,j}\}$. Therefore, we can estimate $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$ as c_0 .

Finally, we can estimate ρ as $r = c_0 / (s_3 * s_2)$ based on phase 2 data.

8.6 Program Specifications

8.6.1 Primary Analysis for the Primary Efficacy Endpoint at Week 36 Interim Analysis

The sample SAS code for primary efficacy endpoint analysis is provided as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* VISIT = Post-baseline study visits (Week 12, Week 24, and Week 36)
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, and >=90 mL/min/1.73m2]
* BHEMA = Baseline hematuria category [Negative/Trace, 1+, 2+, and 3+]
* BASE = log (baseline UPCR)
* CHG = Change of natural logarithmic UPCR at each post-baseline visit calculated as AVAL-BASE.
      where AVAL= log transformed UPCR value at each visit
* WEEK12, WEEK24, WEEK36 = Natural-log transformed UPCR values at Week 12, Week 24 and Week 36
*****;
/*Take log-transformation for UPCR at each visit. BASE, AVAL, and CHG are the baseline, absolute value, and the
change from baseline in log(UPCR), respectively*/
/*Transpose the change from baseline in log-transformed UPCR (i.e., CHG) to wide format, one record per subject*/

/*Step 1: Intercurrent Event Strategy*/
/*Exclude values collected on and after ICEs of dialysis, kidney transplant */

/*Step 2: Intermittent Missing Data Imputation Using MCMC*/
proc mi data=in seed=123 nimpute=100 out=mono;
  by TRTN;
  var BASE WEEK12 WEEK24 WEEK36;
  mcmc impute=monotone nbiter=5000 niter=5000 chain=multiple;
run;

/*Step 3.1: Missing Data due to ICEs*/
/* All missing values should theoretically result from study withdrawal, dialysis, kidney transplant, or
death. However, there may occasionally be a few subjects with missing values at their last visits while still
remaining on-study. For simplicity, all missing values will be imputed using the 'Jump to reference' strategy. */
proc mi data=mono seed=123 nimpute=1 out=outmi;
  class TRTN SGLT2 REGION BGFR BHEMA;
  by _imputation_ ;
  monotone reg(/details);
  mnar model (WEEK12 / modelobs= (TRTN= '1'));
  mnar model (WEEK24 / modelobs= (TRTN= '1'));
  mnar model (WEEK36 / modelobs= (TRTN= '1'));
  var SGLT2 REGION BGFR BHEMA BASE WEEK12 WEEK24 WEEK36;
run;

/* Step 3.2: Missing Data due to Dialysis, Kidney transplant, or Death */
/* Impute values in visits on and after ICEs of dialysis, kidney transplant, and death*/
/* In each imputation, replace the values on and after the above ICEs with rand('normal',U,E); */
/* Where U and E are the mean and random error for the unfavorable values for change in ln(UPCR).*/

/*Step 4: Statistical Analysis*/
```

/*Analyze the imputation data sets after transposing to long format, one record per visit per subject per imputation*/
proc mixed data=efficacy (where=(CHG ne . and BASE ne.)) method=reml;

```
by imputation ;  
class TRTN USUBJID VISIT SGLT2 REGION BGFR;  
model CHG = SGLT2 REGION BGFR BASE TRTN VISIT TRTN*VISIT /ddfm=kr;  
repeated VISIT/ sub = USUBJID type = un;  
lsmean TRTN*VISIT / cl alpha=0.05 OM;  
estimate 'Week 36 Effect' TRTN -1 1 TRTN*VISIT 0 0 -1 0 0 1 / cl alpha=0.05;  
estimate 'Week 24 Effect' TRTN -1 1 TRTN*VISIT 0 -1 0 0 1 0 / cl alpha=0.05;  
estimate 'Week 12 Effect' TRTN -1 1 TRTN*VISIT -1 0 0 1 0 0 / cl alpha=0.05;  
ods output Estimates=Estimates;
```

run;

/*Combine the analysis results using Rubin's rule*/

```
proc mianalyze data=estimates;  
where Label = 'Week 36 Effect';  
modeleffects estimate;  
stderr stderr;  
ods output parameterestimates=diffs1;
```

run;

8.6.2 Sensitive Analysis for the Primary Efficacy Endpoint at Week 36 Interim Analysis: Tipping Point Analysis

The SAS sample code for the tipping point sensitivity analysis is provided as follows:

Step 1. Set a flag, imputed = Y, for Week 36 values which are imputed due to ICEs of dialysis, kidney transplant, death, or purely missing Week 36 UPCR while on study from the primary imputed analysis dataset. The shift parameters for both atacicept and placebo groups are ranged from -2.8 to 2.8 by 0.2 (i.e., -2.8, -2.6, -2.4, ..., 2.6, 2.8). The range and increments of shift parameters may be adjusted if tipping points are not identified in the range.

```
*****
* TRTN = treatment group (1=Placebo 2 =atacicept 150mg)
* WEEK36 = Natural-log transformed UPCR values at Week 36
* k1= -2.8, -2.6, ..., 2.6, 2.8
* k2= -2.8, -2.6, ..., 2.6, 2.8
*****;
```

Step 2. Add a pair of shift parameters (k1, k2) for each imputed data set generated from Step 1

```
if imputed ='Y' then do;
  if trtn= 1 then Week36 = Week36+ &k1;
  if trtn= 2 then Week36 = Week36+ &k2;
end;
```

Step 3. Apply MMRM model used for the primary analysis for each adjusted data set generated from Step 2.

Step 4. Obtain pooled results per Rubin's Rule for each pair of shift parameters (k1, k2).

```
proc mianalyze;
  by Label;
  modeleffects estimate;
  stderr stderr;
run;
```

8.6.3 Analysis for Hematuria Resolution

The sample SAS code for logistic regression analysis is provided as follows:

```
*****
* TRTN = Treatment group [1 = Placebo, 2 = Atacicept 150 mg]
* RESL = indicator variable of whether a participant achieves hematuria resolution [1 = Yes, 2 = No]
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, or >=90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, >=2 g/24h]
* VISIT = Visit Number [2, 4, 12, 24, 36]
*****.
PROC GENMOD data = efficacy;
  class USUBJID SGLT2 REGION BGFR BTUPE TRTN VISIT;
  model resl(event="1") = SGLT2 REGION BGFR BTUPE TRTN VISIT TRTN*VISIT / dist=binomial link=logit;
  repeated subject = USUBJID;
  lsmeans TRTN*VISIT / om cl exp ilink pdiff oddsratio;
  ods output Lsmeans = Lsmeans Diffs = diff;
run;
```

where *om* specifies the weighting scheme for LS-means computation as determined by the input data set; *cl* and *exp* compute and display estimate and confidence intervals for odds of subjects achieving hematuria resolution; *ilink* computes and displays estimate, standard error, and confidence intervals for probability of subjects achieving hematuria resolution; *pdiff* and *oddsratio* compute and display estimate and confidence intervals for odds ratio between atacicept and placebo.

8.6.4 Primary Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis

The sample SAS code for primary analysis of the key secondary efficacy endpoint is as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* VISIT = Post-baseline study visits (Week 2, Week 4, ..., and Week 104)
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, >=45 to <90, and >=90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, >=2 g/24h]
* BHEMA = Baseline hematuria category [n=Negative/Trace, 1+, 2+, and 3+]
* BASE = Baseline eGFR
* CHG = Change of eGFR at each post-baseline visit calculated as AVAL-BASE
* AVAL = eGFR value at each visit
* WEEK2, WEEK4, ..., WEEK104 = eGFR values at Week 2, Week 4, ..., and Week 104
* TIME = Time in years calculated as (study visit date - the first DB dose date + 1)/365.25
* For the imputed eGFR values without actual visit, TIME = (7X+1)/365.25 for Week X
*****
/*BASE, AVAL, and CHG are the baseline, absolute value, and the change from baseline in eGFR, respectively,
with ANL01FL = "Y"*/
/*Transpose the eGFR (i.e., AVAL) to wide format, one record per subject*/

/*Step 1: Intercurrent event strategy */
/*Exclude values collected after ICEs of dialysis, kidney transplant, and death*/

/*Step 2: Intermittent Missing Data Imputation Using MCMC. */
proc mi data=in seed=123 nimpute=100 out=mono
  minimum = . 0 0 0 0 0 0 0 0 0 0;
  by TRTN;
  var BASE WEEK2 - WEEK104;
  mcmc impute=monotone nbiter=5000 niter=5000 chain=multiple;
run;

/*Step 3.1: Missing Data due to ICEs*/
/* All missing values should theoretically result from study withdrawal, dialysis, kidney transplant, or
death. However, there may occasionally be a few subjects with missing values at their last visits while still
remaining on-study. For simplicity, all missing values will be imputed using the 'Jump to reference' strategy. */
proc mi data=mono seed=123 nimpute=1 out=outmi
  minimum = . . . . . 0 0 0 0 0 0 0 0 0 0;
  class TRTN SGLT2 REGION BTUPE BHEMA;
  by imputation ;
  monotone reg(/details);
  Mnar model (WEEK2 / modelobs= (TRTN= '1'));
  ...
  Mnar model (WEEK104 / modelobs= (TRTN= '1'));
  var SGLT2 REGION BTUPE BHEMA BASE WEEK2-WEEK104;
run;

/* Step 3.2: Missing Data due to Dialysis, Kidney Transplant, or Death */
/* Impute values in visits on and after ICEs of dialysis, kidney transplant, and death */
```

```
/*      In each imputation, replace the values on and after above ICEs with rand('normal',U,E); */  
/*      Where U and E are the mean and random error for the unfavorable values for eGFR. */
```

```
/*Step 4: Statistical Analysis*/
```

```
/*Transpose the imputed datasets into long format, one record per visit per subject per imputation*/
```

```
/*Pool transposed and imputed dataset with the rest eGFR data with ANL01FL = ""*/
```

```
/*Analyze the pooled data by random coefficient mixed-effect model*/
```

```
proc mixed data=efficacy method=reml;  
  by IMPUTATION ;  
  class TRTN USUBJID SGLT2 REGION BGFR BTUPE;  
  model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TRTN*TIME /solution ddfm=kr covb cl;  
  random INT TIME/ sub = USUBJID type = un;  
  estimate 'slope for placebo'      TIME 1 TRTN*TIME 1 0 / cl alpha=0.05;  
  estimate 'slope for atacicept'    TIME 1 TRTN*TIME 0 1 / cl alpha=0.05;  
  estimate 'slope difference'      TRTN*TIME -1 1 / cl alpha=0.05;  
  ods output covparms=covparms;  
  ods output estimates=estimates;  
run;
```

```
/*Combine the analysis results using Rubin's rule*/
```

```
proc mianalyze data=estimates;  
  by label;  
  modeleffects estimate;  
  stderr stderr;  
  ods output parameterestimates=diffs1;  
run;
```


8.6.5 Sensitivity Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis: Tipping Point Analysis

The SAS sample code for the tipping point sensitivity analysis is provided as follows:

Step 1. Set all post-baseline eGFR to missing for all subjects with ICEs of dialysis, kidney transplant, death, and study withdrawal from the primary imputed analysis dataset.

```
*****
* BASE = eGFR value at baseline
* WEEK 2, WEEK4, WEEK12, WEEK24, ... , WEEK104 = eGFR values at Week 2, Week 4, Week 12, Week 24,
... , and Week 104
* k1= -8, -6 , ..., 6, 8
* k2= -8, -6 , ..., 6, 8
*****;
```

Step 2. Apply MNAR assumption under each pair of shift parameters (k1, k2) to generate post-baseline eGFR values for subjects with ICE only in each imputed data set generated from Step 1, where `est_slope_trt` and `stderr` are the slope estimates from the primary analysis and associated standard error for specific treatment group. `Stddev` is from the sqrt of the model residual. For each treatment group, generate eGFR with below code using the corresponding treatment & shift parameter.

```
slope = &est_slope_trt + rand('normal', &shift, &stderr);
WEEK2 = base + 2/52*slope + rand('normal',0, &stddev);
WEEK4 = base + 4/52*slope + rand('normal',0, &stddev);
WEEK12 = base + 12/52*slope + rand('normal',0, &stddev);
WEEK24 = base + 24/52*slope + rand('normal',0, &stddev);
....
WEEK104 = base + 104/52*slope + rand('normal',0, &stddev);
```

Step 3. Apply MMIRS model used for the primary analysis for each adjusted data set generated from Step 2.

Step 4. Obtain pooled results per Rubin's Rule for each shift parameter pair.

```
proc mianalyze;
  by label;
  modeleffects estimate;
  stderr stderr;
run;
```

8.6.6 Sensitivity Analysis for the Key Secondary Efficacy Endpoint at Week 104 Interim Analysis: Two-Slope MMRIRS

The SAS sample code for the two-slope MMRIRS is provided as follows:

```
*****
* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* SGLT2 = Baseline stable SGLT2i use category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45, ≥ 45 to < 90, and ≥ 90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2, ≥2 g/24h]
* TIME = Time in years calculated as (study visit date – baseline date + 1)/365.25
* TIME_cp = Truncated time in years after changepoint calculated as max(TIME – Change Point, 0)
* AVAL = eGFR value at each visit including baseline visit
*****;
proc mixed data=efficacy;
  class TRTN USUBJID SGLT2 REGION BGFR BTUPE;
  model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TIME_CP TRTN*TIME TRTN*TIME_CP/s
  ddfm=kr;
  random INT TIME TIME_CP/ sub = USUBJID type = un;
  estimate "Acute Slope: Atacicept"  TIME 1 TIME_CP 0 TRTN*TIME  0 1 TRTN*TIME_CP 0 0 ;
  estimate "Acute Slope: Placebo"    TIME 1 TIME_CP 0 TRTN*TIME  1 0 TRTN*TIME_CP 0 0 ;
  estimate "Acute Slope: Diff"       TIME 0 TIME_CP 0 TRTN*TIME -1 1 TRTN*TIME_CP 0 0 ;
  estimate "Chronic Slope: Atacicept" TIME 1 TIME_CP 1 TRTN*TIME  0 1 TRTN*TIME_CP 0 1 ;
  estimate "Chronic Slope: Placebo"   TIME 1 TIME_CP 1 TRTN*TIME  1 0 TRTN*TIME_CP 1 0 ;
  estimate "Chronic Slope: Diff"      TIME 0 TIME_CP 0 TRTN*TIME -1 1 TRTN*TIME_CP -1 1 ;
  estimate "Slope Change: Atacicept"  TIME 0 TIME_CP 1 TRTN*TIME  0 0 TRTN*TIME_CP 0 1 ;
  estimate "Slope Change: Placebo"    TIME 0 TIME_CP 1 TRTN*TIME  0 0 TRTN*TIME_CP 1 0 ;
  estimate "Slope Change: Diff"       TIME 0 TIME_CP 0 TRTN*TIME  0 0 TRTN*TIME_CP -1 1 ;
  ods output estimates=estimates;
run;
```

8.6.7

[REDACTED]

[REDACTED]

[REDACTED]

```
data WORK.CAT;
  set WORK.CAT;
  if mobility eq 1 then disut_mo=0;
  else if mobility eq 2 then disut_mo=0.096;
  else if mobility eq 3 then disut_mo=0.122;
  else if mobility eq 4 then disut_mo=0.237;
  else if mobility eq 5 then disut_mo=0.322;

  if selfcare eq 1 then disut_sc=0;
  else if selfcare eq 2 then disut_sc=0.089;
  else if selfcare eq 3 then disut_sc=0.107;
  else if selfcare eq 4 then disut_sc=0.220;
  else if selfcare eq 5 then disut_sc=0.261;

  if activity eq 1 then disut_ua=0;
  else if activity eq 2 then disut_ua=0.068;
  else if activity eq 3 then disut_ua=0.101;
  else if activity eq 4 then disut_ua=0.255;
  else if activity eq 5 then disut_ua=0.255;

  if pain eq 1 then disut_pd=0;
  else if pain eq 2 then disut_pd=0.060;
  else if pain eq 3 then disut_pd=0.098;
  else if pain eq 4 then disut_pd=0.318;
  else if pain eq 5 then disut_pd=0.414;

  if anxiety eq 1 then disut_ad=0;
  else if anxiety eq 2 then disut_ad=0.057;
  else if anxiety eq 3 then disut_ad=0.123;
  else if anxiety eq 4 then disut_ad=0.299;
  else if anxiety eq 5 then disut_ad=0.321;

  disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
  EQindex=1-disut_total;
run;
```



STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with IgA Nephropathy (IgAN)

Protocol Number: VT-001-0050

Protocol Version / Date: Protocol Amendment 8 / 01 June 2026

Investigational Product: Atacicept (VT-001)

Sponsor: Vera Therapeutics, Inc.
2000 Sierra Point Parkway, Suite 1200
Brisbane, CA 94005

SAP Version/Date V 4.0 (Final) / 01 June 2026
Phase 3 [REDACTED] (End of Double-Blind
Period Analysis)
(for Regulatory Submission in the United States)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
APRIL	a proliferation-inducing ligand
BAFF	B-cell activating factor (also called "BLyS")
C _{max}	maximum concentration
ACEi	Angiotensin Converting Enzyme inhibitor
ADA	Anti-Drug Antibody
AESI	Adverse event of special interest
ARB	Angiotensin II Receptor Blocker
ATC	Anatomical therapeutic chemical class
BMI	Body mass index
BP	Bodily Pain
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case report form
CSR	Clinical Study Report
DB	Double-Blind
DNA	Deoxyribonucleic acid
EC	Exposure as Collected
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EDC	Electronic Data Capture
EOT	End of treatment
[REDACTED]	[REDACTED]
EQ VAS	EQ Visual Analog Scale
ET	Early Termination
EWB	Emotional Well-Being
[REDACTED]	[REDACTED]
FAS	Full analysis set
FS	Fatigue Subscale
FWB	Functional Well-Being
Gd-IgA1	Galactose-deficient IgA1
GH	General Health
GS	Glucocorticosteroids
HbA1c	Hemoglobin-A1c
HbcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HRQOL	Health-Related Quality of Life
IAS	Interim Analysis Set
ICEs	Intercurrent Events
iDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
Ig	Immunoglobulin
IgA, IgG, IgM	Immunoglobulin A, Immunoglobulin G, Immunoglobulin M
IgAN	IgA Nephropathy
IRT	Interactive Response Technology

Abbreviation	Definition
IS	Immunosuppressive
ISR	Injection site reaction
ITT	Intent to treat
IWRS	Interactive web response system
LS Means	Least Squares Means
LSMs	Least Squares Means
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Scores
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MI	Multiple Imputation
MMRM	Mixed-effects model for repeated measures
MNAR	Missing Not At Random
MRA	Mineralocorticoid Receptor Antagonists
OLE	Open-Label Extension
PCS	Physical Component Scores
PF	Physical Functioning
PGx	Pharmacogenetics
PK	Pharmacokinetics
PN	Preferred Name
PP	Per-protocol
PROs	Patient-Reported Outcomes
PT	Preferred Term
PWB	Physical Well-Being
Q1, Q3	First, Third quartile
RASi	Renin-Angiotensin System inhibitor
RE	Role-Emotional
REML	Restricted Maximum Likelihood
RP	Role-Physical
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Social Functioning
██████	████████████████████
SGLT2i	Sodium-glucose cotransporter-2 Inhibitor
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SWB	Social/Family Well-Being
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
TOI	Trial Outcome Index
TSH	Thyroid Stimulating Hormone
██████	████████████████████
UPCR	Urine protein to creatinine ratio
VAS	Visual Analog Scale
VT	Vitality
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis methods and data presentations to be implemented in tables, figures, and listings (TFLs) to support the primary endpoint analysis at Week 36 and the Week 52 Interim Analysis for study VT-001-0050 based on Protocol Amendment 8. The primary endpoint analysis at Week 36 (referred to as the “Phase 3 Week 36 Interim Analysis” in later sections) was performed after approximately the first 200 subjects enrolled for the Phase 3 part of this study complete their Week 36 visits or prematurely discontinue from the study. The End of Part C analysis (referred to as the “Phase 3 Week 52 Interim Analysis”) will be performed when all subjects enrolled for the Phase 3 part of this study complete their Week 52 visits or prematurely discontinue from the study. The SAP will be finalized prior to database lock for the Week 52 Interim Analysis. Any deviations from the SAP after database lock will be documented in the corresponding Clinical Study Report (CSR).

Separate SAPs were developed for the interim and final analyses for Phase 2b part of the study. Separate SAPs will be developed to support future interim and/or final analysis for the Phase 3 part of the study.

The following updates were incorporated in SAP version 4.0:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

- Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN at Week 36.

2.1.2 Key Secondary Objective

- Evaluate the effect of atacicept compared to placebo on change from baseline in eGFR [REDACTED]

2.1.3 Other Secondary Objectives

- Evaluate the effect of atacicept compared to placebo on the annualized rate of change in eGFR [REDACTED]
- Evaluate the effect of atacicept compared to placebo on change in proteinuria in adult subjects with IgAN [REDACTED]
- Evaluate the effect of atacicept compared to placebo on change in natural log transformed Gd-IgA1 [REDACTED].
- Evaluate the effect of atacicept compared to placebo on achieving hematuria resolution [REDACTED]
- Evaluate the effect of atacicept compared to placebo on time from the first dose to the first occurrence of a sustained $\geq 30\%$ decline in eGFR through Week 104.
- Evaluate the effect of atacicept compared to placebo on time from the first dose to the first occurrence of composite kidney disease progression event through Week 104.

2.1.4 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.1.5 Safety Objective

- Evaluate the safety and tolerability of atacicept during the entire study.

2.2 Study Design

2.2.1 Overview

This is a multi-part study comprising of the original Phase 2b study (i.e., Parts A and B) and the addition of a separate Phase 3 study (i.e., Parts C and D). The results from Phase 2b have been used to determine the dose selection and sample size for the Phase 3 study design.

The Phase 3 study is a multicenter, randomized, double-blinded, placebo-controlled study.

In Part C, approximately 376 subjects will be randomized 1:1 to atacicept 150 mg or placebo for 104 weeks:

- Atacicept 150 mg once weekly subcutaneous (SC) injections (N=188)
- Placebo once weekly SC injections (N=188)

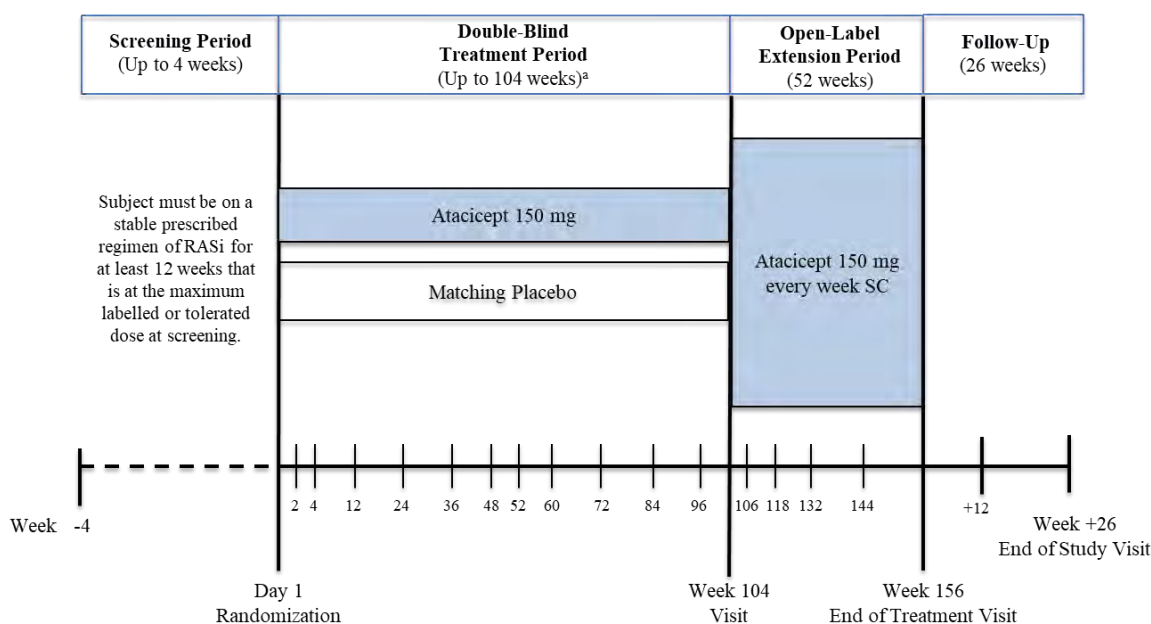
Subjects who have participated in Part A or B may not participate in Part C or D.

Subjects participating in the study will be stratified by screening eGFR values calculated by the central lab (<45 mL/min/ 1.73 m², or ≥ 45 to <90 mL/min/ 1.73 m², or ≥ 90 mL/min/ 1.73 m²), total urine protein excretion (<2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (yes or no), and Region (Asia or Other).

The Phase 3 study is composed of a (up to) 4-week Screening Period, an up to 104-week DB Treatment Period (Part C), a 52-week Open-Label Extension (OLE) (Part D), and a 26-week follow-up. Subjects who complete the DB period on treatment will be eligible for open-label atacicept 150 mg for an additional 52 weeks (OLE). Subjects who prematurely discontinue study drug prior to completion of the DB period should continue with study visits and assessments per protocol through the end of the DB period. After completion of the study, all patients will have a 26-week follow-up period except if the subject discontinued study drug more than 26 weeks before the end of the DB period.

The study will be conducted on an outpatient basis.

Figure 1: Phase 3 Study Schema



RASi= renin-angiotensin system inhibitor; SC=subcutaneous.

2.2.2 Investigational Medicinal Product(s)

In a blinded fashion, 150 mg atacicept or placebo are given as self-administered and once-weekly SC injections up to 104 weeks by prefilled syringe. For OLE, open-label 150 mg atacicept are given as self-administered and once-weekly SC injections for 52 weeks by prefilled syringe.

2.2.3 Randomization and Blinding

An interactive web response system (IWRS) will be used to randomize a subject to study drug assignment. Once a subject meets the eligibility criteria, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. In addition, the IWRS will allocate study drug to subjects at IMP dispensing study visit per the Schedule of Assessment (see Protocol Amendment 8.0 Table 3).

This study will be double-blinded for all subjects and Investigators through Part C. IMP packaging and labeling will be prepared to protect the blinded nature of the study. Study drug will be provided in treatment kits containing prefilled syringes. These prefilled syringes of study drug (atacicept or placebo) will not be distinguishable from each other. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication is atacicept or placebo. Blinded treatment kit numbers will be obtained through the IWRS. Part D of the study will be conducted in an open-label fashion.

2.2.4 Sample Size Determination

2.2.4.1 Sample Size Determination for the Primary Endpoint of UPCR

The primary efficacy endpoint is the ratio of UPCR at Week 36 compared with baseline, based on 24-hour urine collection. Due to the skewed distribution, UPCR will be natural log transformed. The primary efficacy endpoint is the change from baseline at Week 36 in natural log transformed UPCR. A two-sample t-test for ratio was used to determine the sample size for UPCR. It is assumed that the ratio of geometric mean ratio of Week 36 UPCR to baseline between atacicept and placebo groups is 0.67 (i.e., the percentage reduction is 33% higher for atacicept than placebo) and the standard deviation (SD) for the mean change of log (UPCR) from baseline is assumed to be 0.7 in both groups (based on the Origin Phase 2b Primary Endpoint Analysis [data on file]). Based on these assumptions, 100 subjects per group will provide 92% power to detect a ratio of 0.67 with a two-sided alpha of 0.01 when the ratio under the null hypothesis is 1 [PASS 2015: two-sided two sample t-test for ratios]. Missing data after subject withdrawals will be imputed and included in the primary efficacy endpoint analysis and therefore no overage of sample size for withdrawals is necessary.

Table 1 displays statistical power under different scenarios, accounting for uncertainty in estimating UPCR percentage reductions and standard deviations; 100 subjects per group will provide at least 78% power at two-sided significant level of 0.01 if the treatment effect on UPCR reduces from 33% to 30% and/or the standard deviation of the mean change of log (UPCR) from baseline increased from 0.7 to 0.75. A total of 100 subjects per group will provide at least 93% power at a two-sided significant level of 0.01 if the treatment effect on UPCR reduction is 35% (as observed in ORIGIN Phase 2b Week 36 Analysis).

Table 1: Power Calculation for Primary Endpoint of UPCR Under Different Assumptions

Sample Size per Group	Treatment Effect on UPCR		Standard Deviation	Alpha	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction			
100	0.67	33%	0.7	0.01	92%
			0.75	0.01	88%
	0.7	30%	0.7	0.01	84%
			0.75	0.01	78%
100	0.65	35%	0.7	0.01	96%
			0.75	0.01	93%

2.2.4.2 Sample Size Determination for the Annualized Rate of Change in eGFR Through Week 104

For the endpoint of eGFR total slope, a mixed-effects model with random intercept and random slope (MMRIRS) is planned for comparing 2 slopes, when we estimate the sample size for eGFR slope evaluation ([Ahn, Heo, and Zhang \[2014\]](#)). A difference in annualized slope in eGFR is assumed to be 2 mL/min/1.73m²/year, the variance of random slope is 27 and the variance of residuals is 32 based on the atacicept IgAN Phase 2a (JANUS) study. The follow-up period is approximately 2 years (i.e., 104 weeks) with 13 planned visits. Based on these assumptions, 171 subjects per group will provide at least 90% power to detect a difference in annualized slope of 2 mL/min/1.73m²/year throughout 104 weeks between the atacicept and placebo. Adjusting for approximately 10% dropout rate, 376 subjects in total (188 subjects per group) will be enrolled.

[Table 2](#) displays statistical power for annualized eGFR slope comparisons under different scenarios; 171 subjects per group will provide at least 87% power at two-sided significant level of 0.05 to detect an annualized slope difference of at least 2.0 mL/min/1.73m²/year, even if the variances of random slope and residuals increase by approximately 10% to 30 and 36, respectively. The power will be 77% if the expected annualized slope difference decreases to 1.67 mL/min/1.73m²/year.

Table 2: Power for Annualized eGFR Slope Comparison Under Different Assumptions (Alpha = 0.05)

Sample Size per Group	Treatment Effect on UPCR		Annualized Slope Difference in eGFR	Var (Slope)	Var (Residuals)	Power
	Ratio of Geometric Mean Ratios	Percentage Reduction				
171	0.7	30%	1.67	27	32	77%
	0.67	33%	2.0			90%
	0.65	35%	2.22			95%
	0.7	30%	1.67	30	36	73%
	0.67	33%	2.0			87%
	0.65	35%	2.22			93%

2.3 Study Endpoints for Week 36 Interim Analysis

The primary efficacy endpoint was formally evaluated with two-sided alpha of 0.01 at Phase 3 Week 36 Interim Analysis. Selected secondary and exploratory endpoints (detailed below) were evaluated at the Phase 3 Week 36 Interim Analysis as supportive analyses and no alpha spending is required.

2.3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

2.3.2 Key Secondary Endpoint

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

2.3.3

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

2.3.5 Safety Endpoints

Safety endpoints included evaluation of routine clinical and laboratory tests, adverse events and anti-drug antibodies (ADA) during the entire study.

2.4 [REDACTED]

[REDACTED]

[REDACTED]

2.4.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample.

The primary efficacy endpoint has been evaluated based on the Interim Analysis Set (IAS) population and included all UPCR data up to Week 36.

2.4.2 Key Secondary Endpoint

The key secondary efficacy endpoint is the change from baseline in eGFR at Week 52.

2.4.3 Other Secondary Endpoints

Other secondary endpoints include:

- The annualized rate of change in eGFR [REDACTED].
- Change from baseline [REDACTED] in natural-log transformed UPCR.
- Change from baseline [REDACTED] in natural-log transformed Gd-IgA1.
- Hematuria resolution (i.e., achieving hematuria of negative or trace) [REDACTED] for subjects with hematuria of 1+ or above at baseline.
- Time from the first dose to the first occurrence of a sustained $\geq 30\%$ decline in eGFR through Week 104.
- Evaluate the effect of atacicept compared to placebo on time from the first dose to the first occurrence of composite kidney disease progression event through Week 104.

2.4.4

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.4.5 Safety Endpoints

Safety endpoints include evaluation of routine clinical and laboratory tests, adverse events, serum trough pharmacokinetics (PK), and anti-drug antibodies (ADA) during the double blinded period.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Day

Study day will be calculated from the date of the first dose of study drug. The study day of the first dose of study drug will be Day 1, and the study day immediately before Day 1 will be Day -1. There will be no Day 0.

- For dates before Day 1, study day = date of assessment/event – date of Day 1.
- For dates on or after Day 1, study day = date of assessment/event – date of Day 1 + 1.

3.1.2 Definition of Period

Analysis for the double-blinded (DB) period will include data collected during the screening and DB periods: (1) all available data for subjects who prematurely discontinued the blinded study drug and/or did not receive any dose of open-label atacicept in the OLE period; (2) all available data prior to the first dose data/time of open-label atacicept for subjects who completed the double-blinded drugs and received at least 1 dose of open-label atacicept.

3.1.3 Definition of Baseline, the First Dose, and the Last Dose

Baseline for DB period (labeled as DB baseline for future reference) will be defined as the last available measurement prior to the first dose of double-blinded study drug (i.e., it is generally the pre-dose assessment on Day 1), except for UPCR, [REDACTED], and other lab tests from 24-hour urine samples or spot urine samples. For UPCR, [REDACTED], and other lab tests from 24-hour urine samples or spot urine samples, the geometric mean of all measurements during the screening period and prior to the first dose of double-blinded study drug will be used as baseline. DB baseline is the default baseline and will be used interchangeably with baseline.

The first dose date for the DB period is the first injection date of blinded study drug. The last dose date for the DB period is the last injection of blinded study drug.

3.1.4 Analysis Visits

All efficacy and safety assessments, regardless collected on schedule or unscheduled visits and regardless collected while on-treatment or off-treatment, will be allocated to analysis visits as defined in Appendix 8.2. If more than one postbaseline measurements are recorded within a visit window, the following rule will be applied, while baseline is defined in Section 3.1.3:

- If there are multiple measurements collected on the same day (even if some measurements are collected as unscheduled measurements or off-treatment measurements), the arithmetic or geometric mean of all measurements will be used for that day. The mean of all measurements collected on that day will be treated as on-treatment measurement if at least one measurement is collected as an on-treatment measurement. Otherwise, it will be treated as an off-treatment measurement. For subjects who don't complete the End of Treatment eCRF (i.e., still receiving study drug), all postbaseline measurements will be considered as on-treatment. For subjects who complete the End of Treatment eCRF, a measurement will be considered as an on-treatment measurement if it is collected on or after the first dose date/time and prior to the last dose date/time + 10.
- If a test is collected in multiple days within a visit window, the measurement taken at the day closest to the target day will be used. If there are multiple days with equidistance from the target day, the latest one will be used.

3.1.5 Stratification

Subjects will be stratified by screening eGFR values calculated by the central laboratory (< 45 mL/min/1.73 m², or ≥ 45 to < 90 mL/min/1.73 m², or ≥ 90 mL/min/1.73 m² by CKD-EPI), screening total urine protein excretion (< 2 g/24h or ≥ 2 g/24h), stable SGLT2i use at screening (Yes or No) and Region (Asia or Other). Screening eGFR and total urine protein excretion will be imported from central laboratory into IRT directly to assign the stratification category, while subject with/without stable SGLT2i use at screening will be manually entered into IRT. Subjects with/without stable SGLT2i use at screening will also be derived based on prior/concomitant medication data from EDC. Any discrepancies in SGLT2i screening stratification categories between IRT and EDC will be listed. In addition, eGFR category and total urine protein excretion category at baseline and stable SGLT2i use at baseline will be derived and used for statistical modeling. Any difference between derived stratification categories at screening and these at baseline will be listed.

3.1.6 Statistical Hypotheses

Hypothesis for Primary Study Objective

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR. The primary comparison of interest is a 2-sided test comparing the atacicept 150 mg dose to placebo at an alpha level of 0.01. The statistical hypothesis for the primary efficacy endpoint is:

$$H_{10}: \mu_{\text{placebo}} = \mu_{\text{ATC}} \text{ vs. } H_{11}: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.005.

$$H_{10}: \mu_{\text{placebo}} \leq \mu_{\text{ATC}} \text{ vs } H_{11}: \mu_{\text{placebo}} > \mu_{\text{ATC}}$$

Where:

μ_{placebo} = the change from baseline at Week 36 in natural-log transformed UPCR for placebo group;

μ_{ATC} = the change from baseline at Week 36 in natural-log transformed UPCR for atacicept 150 mg group.

Hypothesis for Key Secondary Study Objective

For the efficacy endpoint of change from Baseline in eGFR [REDACTED], the comparison of interest is a 2-sided test comparing the atacicept 150 mg to placebo at an alpha level of 0.05, since the superiority of the primary endpoint has been established at the time of developing SAP Version 4.0. The statistical hypothesis for this efficacy endpoint is:

$$H_{20}: \mu_{\text{placebo}} = \mu_{\text{ATC}} \text{ vs. } H_{21}: \mu_{\text{placebo}} \neq \mu_{\text{ATC}}$$

The above hypothesis expression could also be written as follows for 1-sided test of superiority at an alpha level of 0.025:

$$H_{20}: \mu_{\text{placebo}} \geq \mu_{\text{ATC}} \text{ vs. } H_{21}: \mu_{\text{placebo}} < \mu_{\text{ATC}}$$

Where:

μ_{placebo} = the change from baseline in eGFR [REDACTED] for placebo group;

μ_{ATC} = the change from baseline in eGFR [REDACTED] for atacicept 150 mg group.

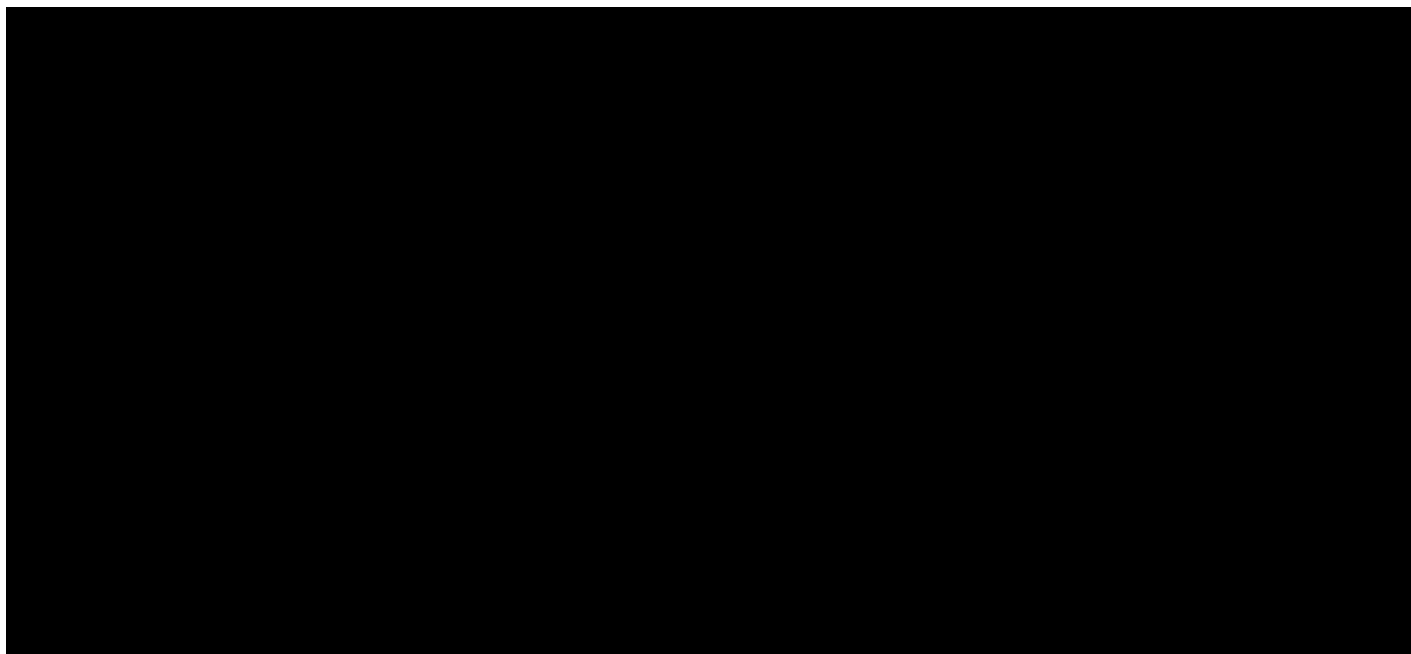
3.1.7 Multiple Comparisons

The primary efficacy endpoint is the change from baseline at Week 36 in natural-log transformed UPCR based on 24-hour urine sample. The key secondary efficacy endpoint is the change from baseline in eGFR [REDACTED].

To control the overall type 1 error rate in the evaluation of the primary and key secondary efficacy endpoints at a two-sided alpha of 0.05, the plan was to perform the hypothesis testing in sequential order by fallback procedure. The primary efficacy endpoint was tested first at a two-sided alpha of 0.01 at the Week 36 Interim Analysis. If superiority for the primary endpoint is established, the key secondary efficacy endpoint would then be tested at a two-sided alpha of 0.05 [REDACTED]. If the statistical significance is not met for the primary endpoint at the Week 36 Interim Analysis, the key secondary efficacy endpoint would be tested

at a two-sided alpha of 0.04 [REDACTED]. After statistical significances are tested for both the primary and the key secondary endpoints, the sequential testing approach would be used to test other selected secondary endpoints with a two-sided alpha of 0.05, 0.04, or 0 [REDACTED] based on the hypotheses testing results from the primary and key secondary efficacy endpoints (see details in [Figure 2](#)).

Figure 2: Multiple Testing Hierarchy



3.1.8 Data Summaries and Conventions

All endpoints will be summarized using descriptive statistics. Continuous variables will be summarized descriptively using the number of observations, mean, SD and/or SE, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and population being presented, unless otherwise specified. All available data will be presented in the data listings by treatment group and subject number.

Mean, median, Q1, Q3, as well as their corresponding confidence intervals (CI) (if applicable) will be reported to one decimal place more than the data reported on the eCRF or by the laboratory/vendor. SD will be reported to two decimal places more than the original data reported. Minimum and maximum will be reported to the same number of decimal places displayed on eCRF or by the laboratory/vendor. P values will be reported to four decimal places. If a p value of “0” or “1” is obtained, display them as “<0.0001” and “>0.9999”, respectively. In general, the number of decimal places should not exceed four.

All tabular summaries will be presented by treatment group (atacicept 150 mg group or placebo group) and/or for overall.

Formal statistical comparisons will be conducted for the data collected in DB period. Strategies for alpha control for multiple comparisons are specified in Section 3.1.7.

3.1.9 Handling of Dropouts and Missing Data

For prior and concomitant medications/procedures, if a medication/procedure has incomplete start or end dates, dates will be imputed to determine whether a medication/procedure should be considered prior or concomitant. If a medication/procedure start date is incomplete and the start date is in the same year and month as the first dose date, the first dose date will be used to impute the incomplete start date. Otherwise, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a medication/procedure end date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. If the imputed end date is later than the death date, then the end date will be imputed with the death date. Incomplete start and end dates will be listed as collected without imputation.

If it is not possible to determine whether an AE is or is not treatment emergent, or whether an AE starts in the on-treatment period, due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent, i.e., starting in the treatment period. Detailed imputation rule will be documented in ADaM mapping specification.

Descriptive summaries of efficacy and safety measures will be based on observed data. Imputation of missing data for modeling will be detailed in later sections.

3.2 Populations

Screening Population

The Screening Population consists of all subjects who sign informed consent.

Intention -to-treat Population

The ITT Population consists of all randomized subjects. Subjects will be analyzed according to randomized treatment.

Full Analysis Set (FAS) Population

The FAS Population consists of all randomized subjects who have received at least 1 dose of treatment. Subjects will be analyzed according to randomized treatment.

Safety Population

The Safety Population consists of all randomized subjects who receive at least 1 dose of treatment. Subjects will be analyzed according to the actual treatment received during the DB period. Unless otherwise indicated, the Safety Population is the primary analysis population for safety endpoints.

Interim Analysis Set (IAS) Population

The IAS Population consists of a subset of subjects in the FAS population who were randomized and dosed on or prior to Sep 12th, 2024 (i.e., 203 subjects were randomized and dosed on or prior to Sep 12th, 2024) or subjects who completed the Week 36 visit at the time of the data cut for the Week 36 Interim Analysis. Unless otherwise indicated, the IAS is the primary analysis population for efficacy endpoints in the Week 36 Interim Analysis, where subjects were analyzed according to randomized treatment. In addition, selected safety endpoints were analyzed using IAS Population according to actual treatment received during the DB period.

Week 36 Per-protocol (PP) Population

The Week 36 PP Population consists of all subjects in the IAS Population who did not have any special events that may affect the validity of the primary efficacy endpoint evaluation.

Subjects who experience any CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation were excluded from the Week 36 PP population. CSR reportable protocol deviations that may affect the validity of the primary efficacy endpoint evaluation include but are not limited to:

- Eligibility criteria violations that may affect the validity of the primary efficacy endpoint (e.g., screening eGFR < 30 mL/min/1.73m²),
- Study drug compliance outside of 80-120% up to the Week 36 visit, and
- Other substantial CSR reportable protocol violations prior to the Week 36 visit.

Subjects who experienced any of the following events that may affect the validity of the primary efficacy endpoint evaluation were excluded from the Week 36 PP population:

- Use of rescue / prohibited concomitant medication that could have impacted on the efficacy of study treatment prior to the Week 36 visit,
- Change the background medication (i.e., RASi, MRA, or SGLT2i) that could have impacted the efficacy of study treatment within 6 weeks prior to the Week 36 visit,
- Premature discontinuation of study drug prior to the Week 36 visit and with missing Week 36 on-treatment UPCR, and
- Unblinding of the patient prior to the Week 36 visit.

Week 36 PP Population was determined through blinded review prior to Week 36 database lock. Week 36 PP population was used as a supportive analysis on the primary efficacy endpoint for Phase 3 Week 36 Interim Analysis. Subjects were analyzed according to the actual treatment received during the DB period.

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

Pharmacokinetics Population

The PK Population consists of all randomized subjects who receive at least 1 dose of treatment and have at least 1 evaluable PK concentration. All PK evaluations will be based on this population. PK concentration will be measured for subjects randomized to Atacicept 150 mg only.

Immunogenicity Population

The Immunogenicity Population consists of all subjects in the FAS population who receive at least 1 dose of treatment and have at least 1 evaluable ADA measurement. Subjects will be analyzed according to the actual treatment received during the DB period.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented for Screening Population:

- Subjects who failed screening and were not randomized
- Subjects who were randomized

Subjects who failed the screen will be tabulated by primary reason for screen failure/not randomized. The number and percentage of subjects who failed the screen/not randomized due to COVID-19 will also be presented.

The number and percentage of subjects in each of the following disposition categories as recorded on the CRF will be presented by treatment group and in total using ITT Population:

- Subjects randomized (ITT Population)
- Subjects treated (FAS/Safety Population)
- Subjects who prematurely discontinued study drug in the DB period by reason
- Subjects who prematurely discontinued the study by reason

The following disposition categories were not included in Week 36 Interim Analysis, but will be included in [REDACTED]

- Subjects who completed study drug in the DB period
- Subjects who completed study drug in the DB period and continued to OLE period

3.3.2 Protocol Deviations

The number and percentages of subjects with CSR reportable and CSR non-reportable protocol deviations by deviation category will be summarized by treatment group and in total using ITT Population. CSR reportable protocol deviations are deviations related to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment that impact the safety of the subjects or jeopardize the quality of study data. Protocol deviation categories are described in the protocol deviation plan.

All protocol deviations (CSR reportable and CSR non-reportable) will be listed by deviation categories.

3.3.3 Analysis Populations

The number and percentages of subjects in each analysis population will be summarized by treatment group and in total using ITT Population.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics include, but are not limited to

- Age collected at Screening (years)
- Age collected at Screening categories (years): (1) $< 40, \geq 40$; and (2) $< 45, \geq 45$ to $< 65, \geq 65$
- Sex: female, male
- Childbearing potential (female only): yes, no
- Race: (1) American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other pacific islander, White, Other, Unknown or Not Reported, Not Permitted; and (2) White, Non-White, Not Reported or Not Permitted.
- Ethnicity: Hispanic or Latino, not Hispanic or Latino, Unknown or Not Reported, Not Permitted.

- Country: (1) by country; and (2) US, ex-US.
- Region Categories: (1) Asia, Europe, North America, South America; and (2) Asia, Other.
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline body mass index (BMI) (kg/m²)
- Screening eGFR (mL/min/1.73 m²)
- Screening eGFR Categories (IRT) (mL/min/1.73 m²): <45, ≥45 to <90, ≥90
- Baseline eGFR (mL/min/1.73 m²)
- Baseline eGFR Categories (mL/min/1.73 m²): (1) <45, ≥45 to <90, ≥90; and (2) <15, ≥15 to <30, ≥30 to <45, ≥45 to <60, ≥60 to <90, ≥90; (3) <45, ≥45; (4) <60, ≥60.
- Baseline Hematuria (%): Negative/Trace, 1+, 2+, 3+
- Baseline UPCR (g/g)
- Baseline UPCR Category (g/g): <1.5, ≥1.5
- [REDACTED]
- Screening Proteinuria (g/day)
- Screening Proteinuria Category (IRT) (g/day): <2, ≥2
- Baseline Proteinuria (g/day)
- Baseline Proteinuria Categories (g/day): (1) <2, ≥2; and (2) <2, ≥2 to <3.5, ≥3.5
- Baseline Gd-IgA1 (ug/L), IgA (mg/dL), IgG (mg/dL), IgM (mg/dL), BAFF (ng/L), APRIL (ug/L)
- Baseline Systolic Blood Pressure (mmHg)
- Baseline Diastolic Blood Pressure (mmHg)
- Duration from IgAN Diagnosis (years)
- Time since Biopsy (years)
- Stable SGLT2i Use at Screening (IRT): yes, no
- Stable SGLT2i Use at Screening (EDC Derived): yes, no
- Stable SGLT2i Use at Baseline (EDC Derived): yes, no
- SGLT2i Use at Baseline (for subjects not on stable SGLT2i use at baseline only): Never Used, Less than 12 Weeks.
- Stable MRA Use at Baseline; yes, no
- MRA Use at Baseline (for subjects not on stable MRA use at baseline only): Never Used, Less than 12 Weeks.
- RASi Medication Use at Baseline by Category: No RASi, ACEi only, ARB only, ACEi + ARB.
- Number of Anti-hypertension Medication(s) Used at Baseline: None, At least 1 (further break down by 1, 2, 3, 4+).
- Anti-hypertension Medication Used at Baseline by Class: ACEi, ARB, MRA, Diuretic, Calcium Channel Blocker, Beta Blocker, Direct Renin Inhibitors, Other.
- Medical History of Hypertension

- Medical History of Diabetes
- Prior GS or IS IgA nephropathy treatments: yes, no
- Prior GS or IS IgA nephropathy treatments type: glucocorticosteroids (by subcategory), mycophenolate mofetil, azathioprine, cyclophosphamide, hydroxychloroquine, other
- Kidney Biopsy Results Reported in eCRF: yes, no
- Number of Glomeruli on Biopsy (n)
- Number of Glomeruli on Biopsy Category (n): < 8 , ≥ 8
- Classification Used for Kidney Biopsy Results: Kidney Biopsy Not Reported, Other, OXFORD MEST-C (by Subclassification)

Demographic and baseline characteristics relative to DB baseline will be summarized with descriptive statistics or number and percentages of subjects as appropriate by treatment group and in total for FAS Populations [REDACTED].

3.3.5 Medical History

Medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The number and percentages of subjects with medical history by SOC and PT will be summarized by treatment group and in total based on the Safety Population.

3.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical class (ATC) and preferred name (PN) using the World Health Organization (WHO) Drug Dictionary (B3 Global, September 2024 or later). For summary purposes, medications will be considered prior medications if they ended prior to the first dose of study drug and concomitant medications if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Medications will be considered concomitant medications during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. If medications cannot be decided as to which period they belong due to completely missing or partial start dates, medications will be considered concomitant during the DB period.

In the case where a medication has incomplete start or end dates and cannot be determined as whether the medication should be considered as prior or concomitant medication, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects taking prior and concomitant medications by ATC2 and PN will respectively be summarized and will be summarized by treatment group and in total based on the Safety Population.

3.3.7 Prior and Concomitant Procedures

Prior and Concomitant procedures will be coded to SOC and PT using MedDRA (version 27.1 or later). For summary purposes, procedures will be considered prior procedures if they ended prior to the first dose of study drug and concomitant procedures if they were taken at any time on or after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started on or after the first dose of study drug).

Procedures will be considered concomitant procedures during the DB period if they were taken at any time on or after the first dose of study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. If procedures cannot be decided as to which period they belong due to completely missing or partial start dates, procedures will be considered concomitant during the DB period.

In the case where a procedure has incomplete start or end dates and cannot be determined as whether the procedure should be considered as prior or concomitant procedure, dates will be imputed as described in Section 3.1.9.

The number and percentages of subjects with prior and concomitant procedures by SOC and PT will respectively be summarized and will be summarized by treatment group based on the Safety Population.

3.3.8 Study Drug Exposure and Compliance

Days of exposure to study drug will be defined for DB period as follows:

- Days of exposure during the DB period = date of the last dose during the DB period – date of the first dose during the DB period + 7.

For the calculation of the study drug exposure, the data cut date will be used to impute the corresponding last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized in weeks by treatment group based on the Safety Population. Descriptive statistics and the number and percentages of subjects with exposure in the following categories will be presented:

- DB Period
 - ≤12 weeks (≤84 days)
 - >12 - ≤24 weeks (>84 to ≤168 days)
 - >24 - ≤36 weeks (>168 to ≤252 days)
 - >36 - ≤48 weeks (>252 to ≤336 days)
 - >48 - ≤52 weeks (>336 to ≤364 days)
 - >52 - ≤60 weeks (>364 to ≤420 days)
 - >60 - ≤72 weeks (>420 to ≤504 days)
 - >72 - ≤84 weeks (>504 to ≤588 days)
 - >84 - ≤96 weeks (>588 to ≤672 days)
 - >96 - ≤104 weeks (>672 to ≤728 days)
 - >104 weeks (>728 days)

Percent compliance to study drug regimen will be defined for DB period. Percent compliance will be calculated as $100 \times \text{actual number of drug syringe injected} / \text{number of expected drug syringe injected}$. The actual and expected number of drug syringes injected will be calculated as follows:

- For the DB period, the actual number of syringes injected will be the number of records in “Weekly Injection Diary” eCRF with answers indicate dose (i.e., injection) was taken and with date of injection on or prior to the last DB EC record date. The number of syringes expected will be the ceiling of $\{(\text{the last DB EC record date} - \text{the first DB dose date} + 1) / 7\}$.
- Answers in “Weekly Injection Diary” eCRF indicate dose (i.e., injection) was taken including:
 - “Yes, Dose in Clinic” or “Yes, Dose off site” is selected for question “Did you dose this week?”, or
 - “Yes” is selected for question “Was the entire dose administered?”, or
 - Date or time is entered for “Please enter the date of this dose” or “Please enter the time of this dose”, or
 - Location is entered for “Please record the injection location by tapping the number associated with your injection site”.

Descriptive statistics of percent compliance for DB period will be presented using Safety Population. In addition, the number and percentages of subjects with compliance in the following categories $\leq 80\%$, 80% to $\leq 90\%$, 90% to $\leq 100\%$, 100% to $\leq 120\%$, and $> 120\%$ will be presented.

3.4 Efficacy Assessment for Week 36 Interim Analysis

The Phase 3 Week 36 Interim Analysis took place when approximately the first 200 subjects had completed their Week 36 visits or had prematurely discontinued from the study. For Phase 3 Week 36 Interim Analysis, efficacy data were summarized by randomized treatment based on the IAS. Unless otherwise indicated, the IAS was the primary analysis population for efficacy endpoints in Phase 3 Week 36 Interim Analysis.

3.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural-log transformed UPCR (i.e., $\log(\text{UPCR})$) at Week 36.

3.4.1.1 Primary Analysis

The primary efficacy endpoint was analyzed by mixed-effects model for repeated measures (MMRM) including UPCR data up to Week 36 for IAS population. Formal statistical comparisons was performed to compare the percentage change in UPCR between atacicept and placebo at each visit up to Week 36.

The estimand for the primary analysis of the primary efficacy endpoint was as follows:

- The population for the trial was defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The analysis population was based on the IAS population.
- The variable of interest was the change from baseline in log (UPCR).
- The intercurrent events (ICEs) included (1) treatment discontinuation; (2) initiation of rescue therapy (e.g., due to disease progression); (3) initiation of prohibited therapy; (4) dialysis, kidney transplant, or death. The intercurrent events and missing data were handled in the order as described below:
 - Step 1: Intercurrent Events Strategy
 - For subjects who discontinued treatment, all observed data were used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who initiated rescue/prohibited therapy, all observed data were used according to the intention-to-treat principle or treatment policy strategy.
 - For subjects who experienced ICEs of dialysis, kidney transplant, or death, the data collected after the first occurrence of the above ICEs were deemed not interpretable and were excluded from the analysis.
 - Step 2: Intermittent Missing Data
 - Intermittent missing data were imputed by multiple imputation based on MCMC Monotone option in SAS PROC MI by treatment group under the missing at random assumption with 100 imputations.
 - Step 3: Monotone Missing Data
 - After intermittent missing data were imputed in Step 2, the rest of the missing data mainly due to subjects who withdrew from the study, subjects who missed the last visit(s) while still ongoing in the study, or subjects experience dialysis, kidney transplant, or death. All these data were imputed by “jump to reference” approach first according to the hypothetical strategy.
 - For subjects who experienced ICEs of dialysis, kidney transplant, or death, the values after the first occurrence of such ICEs were imputed again (i.e., replaced) by a sufficiently unfavorable value plus a random error (“worst case” approach) for both treatment arms according to the hypothetical strategy. Some subjects may experience dialysis or kidney transplant first, then experience other ICEs (such as initiation of rescue therapy). The ICEs of dialysis, kidney transplant, or death took the priority. The values after the ICE of dialysis, kidney transplant, or death were replaced by the “worst case” approach regardless of whether other ICEs occurred or not. The sufficiently unfavorable value was defined as the 99 percentiles of the change from baseline in log (UPCR) from all postbaseline visits and both treatments using the observed data from Step 1, since for UPCR endpoint, the higher the value is, the worse the IgAN disease status is. The random error was estimated by the residual error calculated from the same analysis model using the observed data from Step 1.
 - Step 4: Statistical Analysis
 - Performed MMRM Analysis for each imputation data set.
 - Combined MMRM analysis results using Rubin’s rule (Rubin 1987).

- The population level summary measure was the reduction in the geometric mean ratio of UPCR relative to baseline in atacicept group compared to placebo group at Week 36, the associated 2-sided 95% confidence intervals (CI), and the p-value.

Baseline value for UPCR was derived as the geometric mean of all measurements prior to the first dose of study drug. All UPCR data (including baseline and post-baseline) were natural-log transformed prior to multiple imputation and analysis.

Following the above specified ICEs and missing data handling strategies, the statistical analysis method for the primary estimand was as follows. The primary efficacy endpoint was analyzed using a MMRM model. Change from baseline in log (UPCR) was the dependent variable. Effects for stable SGLT2i use at baseline (Yes, No), Region (Asia, Other), baseline eGFR category (< 45, ≥ 45 and < 90, or ≥ 90 mL/min/1.73m²), baseline natural-log transformed (UPCR), randomized treatment (atacicept, placebo), visit (Week 12, 24 and 36), and treatment-by-visit interaction was included as independent fixed effects. An unstructured covariance matrix was used to model the within-subject correlation of data. In case some of the MMRM models fail to converge, the results based on these imputed datasets were excluded from calculating the combined results using Robin's rule.

The primary comparison tested the mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week 36. The statistical comparison was based on linear contrasts of the Least Square Means (LSMs) estimated by the MMRM model.

Let T_{0i} and T_{1i} be the baseline UPCR and UPCR at Week v for the i subject in atacicept group, P_{0i} and P_{1i} be the baseline UPCR and UPCR at Week v for the i subject in placebo group, $i = 1, 2, 3, \dots, n$ and $v = 12, 24, 36$.

Mean difference in change from baseline in log (UPCR) between atacicept and placebo groups at Week v can be expressed as:

$$\frac{\sum(\log T_{1i} - \log T_{0i})}{n} - \frac{\sum(\log P_{1i} - \log P_{0i})}{n} = \log\left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}}\right] \quad (1)$$

The exponentiation of (1) is the ratio of geometric mean ratio of UPCR at Week v to baseline between atacicept and placebo groups:

$$\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n} \times P_{01} \times P_{02} \times \dots \times P_{0n}}{T_{01} \times T_{02} \times \dots \times T_{0n} \times P_{11} \times P_{12} \times \dots \times P_{1n}}\right)^{\frac{1}{n}} = \left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}} \quad (2)$$

The percentage reduction of the geometric mean ratio of UPCR at Week v relative to baseline for atacicept group vs. placebo group can be obtained as follow:

$$1 - \left[\left(\frac{T_{11} \times T_{12} \times \dots \times T_{1n}}{T_{01} \times T_{02} \times \dots \times T_{0n}}\right)^{\frac{1}{n}} \div \left(\frac{P_{11} \times P_{12} \times \dots \times P_{1n}}{P_{01} \times P_{02} \times \dots \times P_{0n}}\right)^{\frac{1}{n}}\right] \quad (3)$$

The LSM differences in natural-log scale, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values obtained from the MMRM model, while the relative reduction of geometric mean ratio or the estimated percentage reduction from baseline (i.e., $1 - \exp(\text{LSM difference})$), associated standard errors, associated 2-sided 95% CIs, were all presented in the summary table.

The sample SAS code for primary efficacy endpoint analysis is provided in an independent Programming Specifications document.

3.4.1.2 Sensitivity Analyses

Sensitivity Analysis 1: While-On-Treatment Analysis

The first sensitivity analysis investigated the effect of different intercurrent events handling approaches on the estimation of treatment effect.

The estimand for the first sensitivity analysis was the same as that of the primary analysis with the following exceptions:

- While-on-treatment policy was used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE was used, and data collected after the first ICE were treated as missing in the next step.
- After including all data collected on or prior to the first ICE, missing data were imputed according to the hypothetical strategy.
 - Intermittent missing: multiple imputation was used to impute the intermittent missing based on MCMC monotone option in SAS PROC MI by treatment group under the missing at random assumption.
 - Missing after the last observed data on or prior to the first ICE: multiple imputation was used to impute missing data by treatment group using the regression option from the monotone statement of SAS PROC MI.
 - Performed MMRM Analysis for each imputation data set.
 - Combined MMRM analysis results using Rubin's rule.

Sensitivity Analysis 2: Tipping Point Analysis

The second sensitivity analysis was a two-dimensional tipping point analysis to assess the robustness of the “worst case” and “jump to reference” imputation strategies used in the primary analysis. The two-dimensional tipping point analysis was a delta-adjust method under the Missing Not At Random (MNAR) assumption. It explored the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis became non-significant.

Two different fixed and definite sets of shift parameters were imposed on the multiply imputed missing data respectively for the atacicept and placebo groups to encapsulate the change in efficacy results. For each given pair of shift parameters, adjusted the imputed values by the shift parameters for atacicept group and placebo group respectively.

The pairs of shift parameters where the test results changed from significant to non-significant were the tipping points. The shift parameters, the corresponding LS mean for each treatment, treatment difference, and associated p-value will be presented in a table. A heat map was plotted for shift parameters and p-values.

The SAS sample code for the tipping point sensitivity analysis is provided in an independent Programming Specifications document.

3.4.1.3 Supplementary Analyses

A supplementary analysis for the primary endpoint was conducted by using the Week 36 PP population using the observed data following the treatment-policy strategy, except that data collected after dialysis or kidney transplant were deemed not interpretable and were excluded from analysis, whereas other elements of the estimand were the same as that of primary analysis, and the same MMRM model was used (see Section 3.4.1.1).

3.4.1.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the primary endpoint were conducted for the following subgroups as appropriate based on IAS population:

- Age (< 40 , ≥ 40)
- Sex (Male, Female)
- Region (Asia, Other)
- Country (US, ex-US)
- Race (White, Non-White)
- Baseline UPCr (< 1.5 g/g, ≥ 1.5 g/g)
- Baseline Proteinuria (< 2 g/day, ≥ 2 g/day)
- Baseline eGFR (< 60 mL/min/1.73 m², ≥ 60 mL/min/1.73 m²)
- Stable SGLT2 use at baseline (Yes, No)

The subgroup analyses were conducted using the same imputed data sets and the same MMRM model as that of the primary analysis for each subgroup category, separately. If the subgroup was one of the covariates in the model, the covariate was removed from the model statement when the model was performed for the particular subgroup. If the sample size for a subgroup at a particular category was too small, the analysis was not conducted.

A forest plot with geometric mean ratios, standard errors, associated 2-sided 95% CIs for the above subgroups and overall, when appropriate, was presented.

3.4.2

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]

- [REDACTED]

- ```

* TRTN = Treatment group [1=Placebo, 2=Atacicept 150 mg]
* USUBJID = Patient ID
* TIME = Time in years calculated as (study visit date – the first DB dose date + 1)/365.25
* SGLT2 = Baseline stable SGLT2iuse category [Yes, No]
* REGION = Region category [Asia, Other]
* BGFR = Baseline eGFR category [<45 , ≥ 45 to < 90 , and ≥ 90 mL/min/1.73m2]
* BTUPE = Baseline total urine protein excretion category [<2 , ≥ 2 g/24h]
* AVAL = eGFR value at each visit including baseline visit
*****.
proc mixed data=efficacy method=reml;
 class TRTN USUBJID SGLT2 REGION BGFR BTUPE;
 model AVAL = SGLT2 REGION BGFR BTUPE TRTN TIME TRTN*TIME /solution cl ddfm=kr;
 random INT TIME/ sub = USUBJID type = un;
 estimate 'Total Slope in Placebo' TIME 1 TRTN*TIME 1 0 / cl alpha=0.05;
 estimate 'Total Slope in Atacicept' TIME 1 TRTN*TIME 0 1 / cl alpha=0.05;
 estimate 'Total Slope Difference' TRTN*TIME -1 1 / cl alpha=0.05;
ods output estimates=estimates;
run;
```

For Phase 3 Week 36 Interim Analysis, selected other secondary endpoints were evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment-policy strategy, except that data (i.e., Gd-IgA1 and Hematuria) collected after dialysis or kidney transplant were deemed not interpretable and were excluded from analysis. Missing data were handled implicitly by the statistical model, and no multiple imputation was performed for other secondary endpoints.

### 3.4.3.1 Change from Baseline at Week 36 in Natural-log Transformed Gd-IgA1

Differences in percentage change from baseline in Gd-IgA1 in atacicept group compared to placebo group at Week 36 were analyzed using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values were obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, were all presented in summary table.

### 3.4.3.2 Hematuria Resolution at Week 36

Hematuria categories were defined based on urine dipstick (labelled as “occult blood” in laboratory database) results into 4 categories: Negative/Trace = Negative or 0.03; 1+ = 0.06 or 0.1; 2+ = 0.2 or 0.5; and 3+ = 1.0 or >1.0.

- Hematuria resolution was defined as hematuria improvement to Negative/Trace from those with hematuria 1+ to 3+ at baseline.

The following analyses were conducted:

- The number and percentage of subjects with hematuria resolution by visit and treatment group for subjects with 1+ to 3+ hematuria at baseline.

A logistic regression model for repeated measures was used to estimate the odds ratio of achieving hematuria resolution for subjects treated with atacicept versus subjects treated with the placebo for each post-baseline visit up to Week 36. The logistic regression model included the indicator variable of whether a subject achieves hematuria resolution as the dependent variable, stable SGLT2i use at baseline, region, baseline eGFR category, baseline total urine protein excretion category, randomized treatment, visit, and treatment-by-visit interaction as fixed effects. The odds ratios for the treatment effect at each post-baseline visit up to Week 36, associated 2-sided 95% CIs, and 2-sided p-values were presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment at each post-baseline visit, their associated 2-sided 95% CIs, were also presented.

If the model did not converge, the covariates were removed one by one until the model converges in the following sequential order: region, stable SGLT2i use at baseline, baseline total urine protein excretion category, and baseline eGFR category.

The sample SAS code for logistic regression analysis was provided in an independent Programming Specifications document.

In addition, the number and percentage of subjects in each hematuria category were summarized by visit and treatment group for the IAS population.

### 3.4.4 Exploratory Endpoints

For the Week 36 Interim Analysis, selected exploratory endpoints were evaluated as supportive analyses (i.e., not included in the multiple testing strategy) based on IAS and including all available data up to Week 36 following the treatment policy strategy, except that data (i.e., [REDACTED], total urine protein, IgA, IgG, IgM, spot UPCr, [REDACTED]) collected after dialysis or kidney transplant were deemed not interpretable and were excluded from analysis. Missing data were handled implicitly by the statistical model, and no multiple imputation was performed for exploratory endpoints.

#### 3.4.4.1 [REDACTED]

[REDACTED]

#### 3.4.4.2 Proportion of Subjects Achieving Desirable Total Urine Protein Reduction from Baseline at Week 36

Proportion of subjects reaching both a total urine protein  $< 1$  g/day and  $\geq 25\%$  reduction from baseline at Week 36 was evaluated based on IAS.

A logistic regression model for repeated measures was used to analyze the proportion of subjects reaching the total urine protein reduction from baseline at each postbaseline visit up to Week 36 similar to the model used for hematuria resolution (see Section 3.4.3.2 for details).

#### 3.4.4.3 Change from Baseline at Week 36 in IgA, IgG, IgM, Spot UPCr, [REDACTED]

For each immunoglobulin biomarkers (i.e., IgA, IgG, and IgM), lab parameters from spot urine samples (i.e., spot UPCr [REDACTED]), the differences in percentage change from baseline in atacicept group compared to placebo group up to Week 36 were analyzed, separately, using MMRM similar to that for the primary analysis for the primary endpoint (see Section 3.4.1.1). The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values were obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, and 2-sided p-values were all presented in summary tables.

### 3.4.5 Predictive Power for the Annualized eGFR Total Slope Through Week 104 Based on the Phase 3 Week 36 Interim Data

The predictive power for the annualized eGFR slope through Week 104 was calculated following Week 36 Interim Analysis using the data available at that time.

Suppose  $\hat{\mu}_{D,UPCR}$  is the sample estimator for the treatment effect in change from Baseline in log(UPCR) at Week 36, denoted by  $\mu_{D,UPCR}$ ; while  $\hat{\mu}_{D,eGFR}$  is the sample estimator for the treatment effect in eGFR slope through Week 104, denoted by  $\mu_{D,eGFR}$ . According to the Multivariate Central Limit Theorem, it is reasonable to assume (refer to Appendix 8.5 for details):

$$(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \sim N(\mu_{D,UPCR}, \mu_{D,eGFR}, \sigma_{D,UPCR}^2, \sigma_{D,eGFR}^2, \rho) \quad (4)$$

where,

- $\sigma_{D,UPCR}^2$  and  $\sigma_{D,eGFR}^2$  are the variances for the treatment effect estimator of UPCR at Week 36 and the treatment effect estimator of eGFR slope through Week 104, respectively.
- $\rho$  is the correlation between the treatment effect estimator of UPCR at Week 36 and the treatment effect estimator of eGFR slope through Week 104.

Therefore, the distribution of  $\hat{\mu}_{D,eGFR}$  conditional on  $\hat{\mu}_{D,UPCR} = x$  follows a normal distribution:

$$\hat{\mu}_{D,eGFR} | \hat{\mu}_{D,UPCR} = x \sim N\left(\mu_{D,eGFR} + \rho \frac{\sigma_{D,eGFR}}{\sigma_{D,UPCR}}(x - \mu_{D,UPCR}), \sigma_{D,eGFR}^2(1 - \rho^2)\right) \quad (5)$$

The power to reject  $H_0: \mu_{D,eGFR} = 0$  conditional on  $\hat{\mu}_{D,UPCR} = x$  would be:

$$\begin{aligned} CP(\hat{\mu}_{D,UPCR} = x) &= P(\text{Reject } H_0 | \hat{\mu}_{D,UPCR} = x) \\ &= 1 - \Phi(z_{\alpha/2} - z_{D,eGFR}) + \Phi(-z_{\alpha/2} - z_{D,eGFR}), \end{aligned} \quad (6)$$

where  $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$ ,  $z_{D,eGFR} = \left[\mu_{D,eGFR} + \rho \frac{\sigma_{D,eGFR}}{\sigma_{D,UPCR}}(x - \mu_{D,UPCR})\right] / \sigma_{D,eGFR} \sqrt{(1 - \rho^2)}$ .

The predictive power to reject  $H_0: \mu_{D,eGFR} = 0$  would be:

$$PP = \int CP(\hat{\mu}_{D,UPCR} = x) f(\hat{\mu}_{D,UPCR} = x) dx, \quad (7)$$

where  $f(x)$  represents the probability density function of  $\hat{\mu}_{D,UPCR}$ .

At the time of Phase 3 Week 36 Interim, we will have the sample estimate for  $\mu_{D,UPCR}$  as  $u_1$ , and the sample estimate for  $\sigma_{D,UPCR}^2$  as  $s_1^2$ . According to the Central Limit Theorem, it is reasonable to say:  $\hat{\mu}_{D,UPCR} \sim N(u_1, s_1^2)$ .



A meta-analysis for the association of treatment effects on early change in urine protein and annualized eGFR total slope in IgAN patients (Inker et al 2021) is referenced to predict the true treatment effect on the annualized eGFR slope. Here it is assumed that there is a linear relationship between  $\mu_{D,eGFR}$  and  $\mu_{D,UPCR}$  following the formula from Figure S6 in the reference manuscript:  $\mu_{D,eGFR} = -0.85 - 7.15 * \mu_{D,UPCR}$ . Assuming  $u_2 = -0.85 - 7.15u_1$ , we can estimate  $\mu_{D,eGFR}$  as  $u_2$ .

Considering estimates for  $\sigma_{D,eGFR}^2$  and  $\rho$  will not be available at the time of Phase 3 Week 36 Interim Analysis, we will use information from Phase 2b data to estimate them (refer to Appendix 8.5 for details). Therefore, we will have estimates for  $\sigma_{D,eGFR}^2$  and  $\rho$  as  $s_2^2$  and  $r$ , respectively.

Now we have the distribution of  $\hat{\mu}_{D,eGFR}$  conditional on  $\hat{\mu}_{D,UPCR} = x$  as:

$$\hat{\mu}_{D,eGFR} | \hat{\mu}_{D,UPCR} = x \sim N\left(u_2 + r * \frac{s_2}{s_1}(x - u_1), s_2^2(1 - r^2)\right) \quad (8)$$

The power to reject  $H_0: \mu_{D,eGFR} = 0$  conditional on  $\hat{\mu}_{D,UPCR} = x$  can be expressed as:

$$\begin{aligned} CP(\hat{\mu}_{D,UPCR} = x) &= P(\text{Reject } H_0 | \hat{\mu}_{D,UPCR} = x) \\ &= 1 - \Phi(z_{\alpha/2} - z_0) + \Phi(-z_{\alpha/2} - z_0) \end{aligned} \quad (9)$$

where  $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$ ,  $z_0 = \left[u_2 + r * \frac{s_2}{s_1}(x - u_1)\right] / \sqrt{s_2^2(1 - r^2)}$

We drew 10,000 random values for  $\hat{\mu}_{D,UPCR}$  based on the distribution  $\hat{\mu}_{D,UPCR} \sim N(u_1, s_1^2)$ , denoted by  $x_k$  where  $k = 1, 2, \dots, 10,000$ . The power to reject  $H_0: \mu_{D,eGFR} = 0$  conditional on  $\hat{\mu}_{D,UPCR} = x_k$  would be  $CP(\hat{\mu}_{D,UPCR} = x_k)$ . The predictive power was the averaged  $CP(\hat{\mu}_{D,UPCR} = x_k)$  value across all possible values for  $\hat{\mu}_{D,UPCR}$ , written as:

$$\text{Predictive Power} = \frac{1}{10,000} \sum_{k=1}^{10,000} CP(\hat{\mu}_{D,UPCR} = x_k) \quad (10)$$

### 3.5

#### 3.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in natural log transformed UPCR (i.e., log (UPCR)) at Week 36. The primary efficacy endpoint has been evaluated at the Week 36 Interim Analysis based on the IAS population and including all UPCR data up to Week 36.

### 3.5.2 Key Secondary Endpoint

The key secondary endpoint is the change from baseline in eGFR [REDACTED]

#### 3.5.2.1 Primary Analyses

The key secondary endpoint will be analyzed by a mixed-effects model for repeated measures (MMRM) based on the FAS population and include all data up to [REDACTED]. Formal statistical comparisons will be performed to compare the change in eGFR at [REDACTED] between atacicept and placebo groups.

The estimand framework for analyzing the key secondary endpoint is defined as:

- The population is defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval.
- The variable of interest is the change from baseline in eGFR [REDACTED]
- The intercurrent events (ICEs) include (1) treatment discontinuation; (2) initiation of rescue/prohibited therapy (except immunosuppressive treatments which have acute effects on eGFR); (3) initiation of immunosuppressive treatments which have acute effects on eGFR; (4) dialysis, kidney transplant, or death.  
Treatment policy strategy will be used for ICE (1) and ICE (2), where eGFR values collected in the study after ICE (1) or ICE (2) will be used. For ICE (3), the jump to reference strategy will be used considering the acute influences of immunosuppressive treatments on eGFR values. The hypothetical strategy will be used for ICE (4), where data after ICE (4) will be imputed by a sufficiently unfavorable value (“worst case” approach) as described in an independent Programming Specifications document.
- The population level summary measure is the difference between atacicept and placebo group in mean change from baseline in eGFR [REDACTED]

Missing data following ICE (1) and ICE (2) will be imputed by the jump to reference strategy. Other missing data will be handled under the assumption of missing at random (MAR).

Detailed algorithms are provided in an independent Programming Specifications document.

A similar MMRM model used for the primary endpoint will be adopted for the primary analysis of the key secondary endpoint. Change from baseline in eGFR will be the dependent variable. Effects for stable SGLT2i use at baseline, region, baseline total urine protein excretion category, baseline eGFR, randomized treatment, visit, and treatment-by-visit interaction will be included as fixed effects. An unstructured covariance structure will be used to model the within-subject errors. MMRM model results from the 100 imputed dataset will then be combined using Rubin’s rule. The estimated treatment effect (atacicept 150mg vs. placebo) at each visit with their 2-sided 95% confidence intervals and P-values will be provided.

The sample SAS code is provided in an independent Programming Specifications document.

### 3.5.2.2 Sensitivity Analyses

#### **Sensitivity Analysis 1: ICE and Missing Data Analysis**

The first sensitivity analysis will use the treatment policy strategy to handle ICE (3) and jump to reference assumption to replace the MAR assumption for missing data imputation to assess the impact of different missing data imputation algorithms on the estimation of treatment effect. The approach of “worst case” for ICEs will remain the same and won’t be impacted.

The other estimand framework, the analysis population, and the analysis method for this sensitivity analysis are the same as the primary analysis.

The sample SAS code is provided in an independent Programming Specifications document.

#### **Sensitivity Analysis 2: While-On-Treatment Analysis**

The second sensitivity analysis will investigate the effect of different intercurrent events handling approach on the estimation of treatment effect.

The estimand framework for this sensitivity analysis is the same as that of the primary analysis with the following exception:

- While-on-treatment policy will be used to handle all ICEs: all data collected on or prior to the first occurrence of any ICE will be used, and data collected after the first occurrence of ICE (1), (2), and (3) will be imputed according to the hypothetical strategy, which is based on the assumption of MAR.

The missing data imputation method, the analysis population, and the analysis method are the same as the primary analysis.

#### **Sensitivity Analysis 3: Tipping Point Analysis**

The third sensitivity analysis will be a two-dimensional tipping point analysis to assess the robustness of the MAR imputation strategies used in the primary analysis. The approach of “worst case” for ICEs will remain the same and won’t be impacted.

The estimand framework, the analysis population, and the analysis method are the same as the primary analysis.

For missing data [REDACTED], the two-dimensional tipping point analysis will be used. It is a delta-adjust method under the Missing Not At Random (MNAR) assumption, which explores the influence of missingness on the overall conclusion from statistical inference by shifting the multiple imputed missing data until the statistically significant results in the primary analysis become non-significant.

Two different fixed and definite sets of shift parameters will be imposed on the multiply imputed missing data respectively for atacicept group and placebo group to encapsulate the change in efficacy results. The shift parameters for both atacicept group and placebo group are ranged from -16 to 16 by 2 (i.e., -16, -14, ..., 14, 16). The range and increments of shift parameters will be adjusted if tipping points are not identified in the currently specified range. For each given pair



of shift parameters, the imputed values will be adjusted for the values defined by the shift parameters for atacicept group and placebo group respectively. The pairs of shift parameters where the test results changed from significant to non-significant will be the tipping points. After the tipping points are identified, clinical judgement will be needed to assess the plausibility of the assumptions under the tipping points.

The SAS sample code for the tipping point sensitivity analysis is provided in an independent Programming Specifications document.

### 3.5.2.3 Supplementary Analyses

A supplementary analysis for the key secondary endpoint will be conducted using the [REDACTED] PP population and using the observed data up to [REDACTED]. The estimand framework is the same as the primary analysis for the key secondary endpoint with the following exception:

- Treatment-policy strategy will be used for all ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis.

Missing data will be handled implicitly by the statistical model, and no imputation will be performed. The same MMRM will be repeated (see Section 3.5.2.1).

### 3.5.2.4 Subgroup Analyses

To evaluate the treatment effect in different subgroups of subjects, subgroup analyses for the key secondary endpoint may be conducted for the following subgroups as appropriate based on the FAS population and include data up to [REDACTED]:

- Age ( $< 40$ ,  $\geq 40$ )
- Sex (Male, Female)
- Region (Asia, Other)
- Country (US, ex-US)
- Race (White, Non-White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline UPCR ( $< 1.5$  g/g,  $\geq 1.5$  g/g)
- Baseline Proteinuria ( $< 2$  g/day,  $\geq 2$  g/day)
- Baseline eGFR ( $< 45$  mL/min/1.73 m<sup>2</sup>,  $\geq 45$  mL/min/1.73 m<sup>2</sup>)
- Baseline eGFR ( $< 60$  mL/min/1.73 m<sup>2</sup>,  $\geq 60$  mL/min/1.73 m<sup>2</sup>)
- Stable SGLT2i use at baseline (Yes, No)

The subgroup analyses will be conducted using the same MMRM as that of primary analysis and the same imputed datasets generated for the key secondary endpoint (see Section 3.5.2.1) for each subgroup category, separately. If the subgroup is one of the covariates in the model, the covariate will be removed from the model statement when the model is performed for the specific subgroup. If the sample size for a subgroup at a particular category is too small, the analysis might not be conducted.

A forest plot with treatment difference, standard errors, associated 2-sided 95% CIs obtained from the MMRM for the above subgroups, when appropriate, will be presented.

### 3.5.3 Analyses of Other Secondary Endpoints

For the Phase 3 [REDACTED], selected other secondary endpoints will be formally evaluated according to the hierarchical multiple testing approach prespecified in Section 3.1.7.

#### 3.5.3.1 The Annualized Rate of Change in eGFR [REDACTED]

The annualized rate of change [REDACTED] in eGFR will be analyzed including data up to Week 104 based on the FAS population.

The estimand framework for the analysis of the annualized rate of change through Week 104 in eGFR is the same as the primary analysis of the key secondary endpoint with the following exceptions:

- The variable of interest is the annualized rate of change in eGFR through Week 104.
- The population level summary measure is the difference between the atacicept and placebo group in the mean value of the annualized rate of change in eGFR through Week 104.

Missing data following ICE (1) and ICE (2) will be imputed by the jump to reference strategy. Other missing data will be handled implicitly by the statistical model, and no imputation will be performed.

Similar as the primary analysis for the key secondary endpoint, the multiple imputation approach will be used in the analysis for the annualized rate of change [REDACTED] in eGFR (100 sets of imputed eGFR data). For each imputed dataset, the differences in the annualized rate of change through [REDACTED] in eGFR in atacicept group compared to placebo group will be analyzed using the MMRIRS model. The eGFR value will be the dependent variable with random subject effects for intercepts and slopes. Effects for stable SGLT2i use at baseline, Region, baseline total urine protein category, baseline eGFR category, randomized treatment, time, and treatment-by-time interaction will be included as fixed effects. The actual time measurements, in years after the first injection (i.e., total slope), will be included in the model as a continuous variable. The baseline eGFR value recorded per subject will be assigned a time value of 0. The analysis testing the differences between the treatment groups will be constructed using linear contrasts of the appropriate LS Means from the MMRIRS model, where the difference in eGFR total slope corresponds to the parameter for the treatment-by-time interaction term. The results will be combined using Rubin's rule to obtain the final result. The LSM differences, standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-values will be presented in the summary table.

#### 3.5.3.2 Change from Baseline [REDACTED] in natural log transformed UPCR

Change from Baseline in natural log transformed UPCR in the atacicept group compared to the placebo group [REDACTED] will be analyzed based on the FAS population using MMRM similar to the analysis described in Phase 3 Week 36 Interim Analysis (see Section 3.4.1.1). The analysis will include all available data [REDACTED] following the treatment-policy strategy for ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will be handled implicitly by the statistical model, and no imputation will be performed. The LSM differences, standard errors, associated 2-sided 95% CIs, and 2-sided p-values will be obtained from the MMRM model, while the relative reduction of geometric mean ratio or the percentage reduction from baseline, associated standard errors, associated 2-sided 95% CIs, and nominal 2-sided p-value will all be presented in summary table.

### **3.5.3.3 Change from Baseline [REDACTED] in natural log transformed Gd-IgA1**

An MMRM model similar to the one specified in Section 3.5.3.2 will be used. The analysis will include all available data [REDACTED] following the treatment-policy strategy for ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis.

### **3.5.3.4 Hematuria Resolution [REDACTED]**

Hematuria resolution will be analyzed using logistic regression model with repeated measurements similarly as described in Phase 3 Week 36 Interim Analysis (see Section 3.4.3.2 for details) including subjects in the FAS population and with 1+ and above hematuria at Baseline. The analysis will include all available data up to Week 52 following the treatment-policy strategy for ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will not be imputed. The odds ratios for the treatment effect at each postbaseline visit up to Week 52, associated 2-sided 95% CIs, and 2-sided p-values will be presented. The odds and its corresponding probability of subjects achieving hematuria resolution by treatment and by visit, their associated 2-sided 95% CIs, will also be presented. The details on the strategies to handle intercurrent events and missing data for the analysis of hematuria resolution are provided in Appendix 8.3.

### **3.5.3.5 Time from the First Dose to the First Occurrence of a Sustained $\geq 30\%$ Decline in eGFR [REDACTED]**

Time from the first dose to the first occurrence of a sustained  $\geq 30\%$  decline in eGFR through Week 104 will be analyzed using a Cox proportional hazards model including stable SGLT2i use at baseline, Region, baseline eGFR category, baseline total urine protein category, and randomized treatment as fixed effects. The analysis will be based on the FAS population and include all available data [REDACTED] following the treatment-policy strategy for ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will not be imputed. The estimated hazard ratio, the corresponding 2-sided 95% CIs, and 2-sided p-values will be presented. Cumulative incidence curves will be presented by the treatment group. The details on the strategies to handle intercurrent events and missing data are provided in Appendix 8.3.



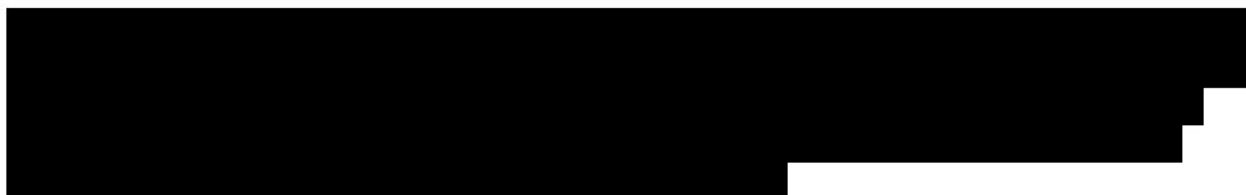
### **3.5.3.6 Time from the First Dose to the First Occurrence of Composite Kidney Disease Progression Event through Week 104**

The composite kidney disease progression endpoint is defined as experiencing at least one of the following events during the study:

- At least a 30% reduction relative to baseline in eGFR sustained for at least 30 days
- eGFR <15 mL/min/1.73m<sup>2</sup>, sustained for at least 30 days
- Chronic dialysis ≥30 days
- Kidney transplant
- Death

Time to the first occurrence of composite kidney disease progression event will be analyzed using a similar Cox proportional hazards model as the one specified in Section 3.5.3.5. The analysis will be based on the FAS population and include all available data up to Week 104 following the treatment-policy strategy for ICEs, except that data collected after dialysis or kidney transplant are deemed not interpretable and will be excluded from analysis. Missing data will not be imputed.

### **3.5.4 Exploratory Endpoints**



## **3.6 Safety Assessment**

Safety data will be summarized by actual treatment received based on the Safety Population.

For Phase 3 Week 36 Interim Analysis, no subjects completed the DB period and entered the OLE period, safety assessments were summarized for the DB period only.

For Phase 3 Week 52 Interim Analysis, safety assessments will be summarized for DB period only.

### **3.6.1 Adverse Events (AEs)**

All AEs occurring from the date of the first informed consent to the last safety follow-up visit will be collected and captured by eCRF. All AEs will be coded and categorized using SOC and PT using Medical Dictionary for Regulatory Activities (MedDRA) (version 27.1 or later). The severity of AEs will be assessed by the Investigator as mild, moderate, or severe.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset dates occurring during the study period (i.e., on or after the first dose date/time until the subject's last study visit). TEAEs will be assigned to the most recently received treatment at the start of the AE.

AEs will be considered treatment-emergent during the DB period if they start on or after the first dose date/time of double-blinded study drug through the completion of the DB period or prior to the first dose date/time of study drug in the OLE period. If AEs cannot be decided as to which period they belong due to completely missing or partial AE onset dates, AEs will be considered treatment-emergent during the DB period.

An overview summary of the number and percentage of subjects with the following TEAEs will be provided:

- TEAEs (overall and by severity)
- Study drug related TEAEs (overall and by severity)
- Treatment-emergent serious AEs (TESAEs)
- Study drug related TESAEs
- TEAEs of special interest (TEAESI) (overall and by severity)
- TEAEs of injection site reaction (ISR) defined by injection site reaction PT or by combined PTs (overall and by severity), combined PTs are listed in Appendix 8.4 to define injection site reaction.
- TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation
- TEAEs leading to study discontinuation
- TEAEs leading to death

In addition, the following TEAEs will be summarized by SOC and/or PT separately:

- TEAEs by SOC and PT
- Study drug related TEAEs by SOC and PT
- Study drug related TEAEs by PT
- TESAEs by SOC and PT
- Study drug related TESAEs by SOC and PT
- TEAESIs by Category and PT
- Study drug related TEAEs associated with ISR by PT
- TEAEs leading to study drug interruption by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- Study drug related TEAEs leading to study drug discontinuation by PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- Common TEAEs by PT ( $\geq 5\%$  incident rate in either treatment arm)

A subject who experienced multiple TEAEs within a SOC or PT will be counted only once for the SOC or PT. For tabulations that include classification by relationship to study treatment, TEAEs with missing relationship will be considered related to study drug. When summarized by severity, a subject with TEAEs with multiple severity categories will be summarized under the maximum severity category (severe > moderate > mild). If missing severity category exists, TEAEs with missing severity will be summarized under a missing category and displayed as the last category in severity summary table.

Adverse events of special interest (AESIs) include hypersensitivity reactions, demyelination disorders, cardiac events (specifically cardiac failure, cardiac arrhythmia, and ischemic heart disease), and infections.

For hypersensitivity reactions, demyelination disorders, and cardiac events, a list of preferred terms from the relevant Standardized MedDRA Query (SMQ) narrow scope will be used to flag these AESI in a systematic and objective way.

AESI of infections will be identified using two approaches: (1) a predefined list of preferred terms from the narrow scope of the “opportunistic infections” SMQ; and (2) serious or severe adverse events in the SOC of “infections and infestations”.

AESIs will be included for tabulation summary and listing.

Listings will be presented specifically for AEs, SAEs, AESIs, AEs leading to study drug discontinuation, AEs leading to study discontinuation, and AEs leading to death.

### **3.6.2 Clinical Laboratory Tests**

Clinical laboratory tests in this study include hematology, clinical chemistry, urine sediment, routine urinalysis and other tests.

Summary statistics for selected hematology, clinical chemistry, urine sediment, and routine urinalysis at DB baseline, at all scheduled post-baseline visits, as well as for change from baseline for all scheduled post baseline visits will be provided by treatment group. Results of clinical laboratory tests will be flagged as abnormal if they are out of normal ranges.

Listings of hematology, clinical chemistry, urine sediment, routine urinalysis and other tests will be provided respectively.

### **3.6.3 Vital Signs**

Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature), weight and height (at screening only) will be measured prior to any other study-related procedures, and at the scheduled visits.

Summary statistics for systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature at DB baseline, at all scheduled post baseline visits, as well as for change from baseline for all scheduled post-baseline visits will be provided by treatment group.

A listing of vital signs will be provided.

### 3.6.4 Electrocardiograms (ECG)

The overall interpretation of ECG results will be categorized as abnormal (further categorized as clinically significant abnormal or not clinically significant abnormal), indeterminate, normal, not evaluable, and unknown. The number and percentage of subjects with different categories of overall interpretation of ECG results will be summarized by visits (including baseline and scheduled post-baseline visits).

A listing of ECG will be provided.

### 3.6.5 Physical Examinations

A complete physical examination will include, at a minimum, assessment of the general appearance, skin, lymph nodes (cervical), head, ears, eyes, nose, throat (HEENT), neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems. Complete physical examination will be performed at screening and Week 104 visits. On other visits, a symptom-driven physical examination will be performed and will include assessment of any new subject complaints or changes from baseline.

Findings from physical examinations will be categorized as clinically significant and not clinically significant. As physical examination findings are qualitative and there is significant inter-observer variation, no analyses will be performed on the physical examination data. All physical examination findings will be presented in a listing.

### 3.6.6 [REDACTED]

#### 3.6.6.1 [REDACTED]

■ [REDACTED]

■ [REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



**Table 3:** [REDACTED]

|            |            |            |            |
|------------|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |
|            | [REDACTED] |            | [REDACTED] |

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]  
[REDACTED]  
[REDACTED]

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\_\_\_\_\_

[REDACTED]

\_\_\_\_\_

### Serum trough concentration of Atacicept (PK) Assessment

Serum trough concentration of Atacicept will be summarized descriptively for Atacicept treatment group based on PK Population.

Number of observations, mean and standard deviation, CV%, median, minimum and maximum, geometric mean and geometric CV% will be presented for all postbaseline visits occurring in DB period.

Individual PK concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the data listings. For by-visit descriptive summary statistics, BLQ values will be excluded from the calculation of summary statistics.

### Anti-Drug Antibody Assessment

The analyses for the summary of immunogenicity are detailed in a separate Statistical Analysis Plan (SAP).

## **4 INDEPENDENT DATA MONITORING COMMITTEE**

An independent data monitoring committee (iDMC) will monitor the safety and wellbeing of the study subjects. The iDMC will meet at designated intervals to review accumulated safety data and may make recommendations regarding the conduct of the study based on the accumulated data. Vera retains final decision-making authority in all aspects. Details regarding the role, responsibilities, and data review requirements of the iDMC will be outlined in a separate iDMC charter.

## **5 MID-STUDY ANALYSIS AND FINAL ANALYSIS TIMING**

### **5.1 Phase 3 Week 36 Interim Analysis Data Cut**

The primary analysis of UPCR will be performed after approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study. This data cut will include all data from all subjects when approximately the first 200 subjects complete the Week 36 visit or prematurely discontinue from the study, including data from subjects who have completed visits beyond Week 36.

### **5.2**

[REDACTED]

### **5.3 Final Analysis**

A final analysis will be conducted once all subjects complete the OLE and safety follow-up visits or discontinue from the trial.

## **6**

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## **7 PROGRAMMING SPECIFICATIONS**

Analyses will be performed using SAS<sup>®</sup> version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by treatment group, subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

## 8 APPENDICES

### 8.1 References

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4. Inker LA, Heerspink HJL, Tighiouart H. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Subject Meta-analysis. *Am J Kidney Dis*. 2021;78:340-349.e1.
5. Brad HR, Jonathan B, et al. Efficacy and Safety of Sparsentan Versus Irbesartan in Patients with IgA Nephropathy (PROTECT): 2-year Results from a Randomized, Active-controlled, Phase 3 trial. *Lancet*. 2023.
6. Richard L, Jens K, et al. Efficacy and Safety of a Targeted-release Formulation of Budesonide in Patients with Primary IgA Nephropathy (NefIgArd): 2-year Results From a Randomised Phase 3 Trial. *Lancet*. 2023.
7. [REDACTED]
8. [REDACTED]
9. Rubin, D. B.. Multiple Imputation for Nonresponse in Surveys. Wiley 1987.
10. <https://euroqol.org/information-and-support/resources/value-sets/>  
[REDACTED]

\_\_\_\_\_

[illegible]

period.

### 8.3 Intercurrent Events Strategy for Endpoints Included in the Multiple Testing Hierarchy

| Endpoints                        | Intercurrent Events/<br>Missing Data                                                                           | Handling Strategy<br>in Primary Analysis | Implementation                                                                                                                    |
|----------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| • Change in log(UPCR) at Week 36 | Treatment Discontinuation                                                                                      | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of rescue therapies                                                                                 | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of prohibited medications                                                                           | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Dialysis; Kidney transplantation;<br>Death                                                                     | Hypothetical Policy                      | Data collected after ICEs were excluded and imputed with worst change plus a random error.                                        |
| • [REDACTED]                     | Treatment Discontinuation                                                                                      | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of rescue/prohibited therapy (except immunosuppressive treatments which have acute effects on eGFR) | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of immunosuppressive treatments which have acute effects on eGFR                                    | Jump to Reference Policy                 | Data collected after ICEs were excluded and imputed based on a trajectory aligned with that observed in placebo-treated patients. |
|                                  | Dialysis; Kidney transplantation;<br>Death                                                                     | Hypothetical Policy                      | Data collected after ICEs were excluded and imputed with worst change plus a random error.                                        |
| • [REDACTED]                     | Treatment Discontinuation                                                                                      | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of rescue/prohibited therapy (except immunosuppressive treatments which have acute effects on eGFR) | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Initiation of immunosuppressive treatments which have acute effects on eGFR                                    | Treatment Policy                         | Use all observed data                                                                                                             |
|                                  | Dialysis; Kidney transplantation;<br>Death                                                                     | Hypothetical Policy                      | Data collected after ICEs were excluded                                                                                           |

ICE = Intercurrent Events

## 8.4 AE of Injection Site Reaction Definition

Below Preferred Terms (Coded in MeDRA v27.1) under High-Level Term of “Injection Site Reactions” will be grouped as AE of Injection Site Reaction. This grouping will be used for adverse event summaries among all Atacicept studies.

| High-Level Term          | Preferred Terms                |
|--------------------------|--------------------------------|
| Injection Site Reactions | Injection site bruising        |
|                          | Injection site coldness        |
|                          | Injection site discolouration  |
|                          | Injection site discomfort      |
|                          | Injection site erythema        |
|                          | Injection site haematoma       |
|                          | Injection site haemorrhage     |
|                          | Injection site induration      |
|                          | Injection site irritation      |
|                          | Injection site mass            |
|                          | Injection site pain            |
|                          | Injection site pruritus        |
|                          | Injection site reaction        |
|                          | Injection site recall reaction |
|                          | Injection site swelling        |
|                          | Injection site urticaria       |
|                          | Injection site warmth          |



## 8.5 Details for Calculating Predictive Power at Week 36 Interim

The predictive power for the annualized eGFR slope through Week 104 will be calculated following Week 36 Interim Analysis using the data available at that time.

Suppose  $\hat{\mu}_{D,UPCR}$  is the sample estimator for the treatment effect in change from Baseline in  $\log(UPCR)$  at Week 36, denoted by  $\mu_{D,UPCR}$ ; while  $\hat{\mu}_{D,eGFR}$  is the sample estimator for the treatment effect in eGFR slope through Week 104, denoted by  $\mu_{D,eGFR}$ . The following sections provide justification for assuming  $(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$  follows a bivariate normal distribution.

### Bivariate Normal Distribution of $(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$ :

The sample estimator for  $\mu_{D,UPCR} = \mu_{A,UPCR} - \mu_{P,UPCR}$  based on the Week 36 Interim data would be:

$$\begin{aligned}\hat{\mu}_{D,UPCR} &= \hat{\mu}_{A,UPCR} - \hat{\mu}_{P,UPCR} \\ &= \frac{1}{n_1} \sum_{i=1}^{n_1} [\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})] \\ &\quad - \frac{1}{m_1} \sum_{j=1}^{m_1} [\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})]\end{aligned}$$

where,

- $\mu_{A,UPCR}$  and  $\mu_{P,UPCR}$  are the population means for the change from Baseline in  $\log(UPCR)$  at Week 36 for the Atacicept 150 mg and the Placebo groups, respectively;
- $UPCR_{A,i,W36}$  and  $UPCR_{P,j,W36}$  are the Week 36 UPCR values for the  $i^{th}$  Atacicept 150 mg subject and  $j^{th}$  Placebo subject, respectively. Similarly,  $UPCR_{A,i,Base}$  and  $UPCR_{P,j,Base}$  are the Baseline UPCR values for the  $i^{th}$  Atacicept 150 mg subject and  $j^{th}$  Placebo subject, respectively;
- $n_1$  and  $m_1$  are the numbers of subjects at Week 36 Interim Analysis for Atacicept 150 mg and Placebo groups, respectively.

The sample estimator for  $\mu_{D,eGFR} = \mu_{A,eGFR} - \mu_{P,eGFR}$  based on the Week 104 Interim data would be:

$$\begin{aligned}\hat{\mu}_{D,eGFR} &= \hat{\mu}_{A,eGFR} - \hat{\mu}_{P,eGFR} \\ &= \frac{1}{n} \sum_{i=1}^n eGFR\_Slope_{A,i} - \frac{1}{m} \sum_{j=1}^m eGFR\_Slope_{P,j}\end{aligned}$$

where,

- $\mu_{A,eGFR}$  and  $\mu_{P,eGFR}$  are the population means for the eGFR slope through Week 104 for the Atacicept 150 mg and the Placebo groups, respectively.

- $eGFR\_Slope_{A,i}$  and  $eGFR\_Slope_{P,j}$  are the eGFR slope through Week 104 for the  $i^{th}$  Atacicept 150 mg subject and  $j^{th}$  Placebo subject, respectively.
- $n$  and  $m$  are the numbers of subjects at Week 104 Interim Analysis for Atacicept 150 mg and Placebo groups, respectively.

Based on the Multivariate Central Limit Theorem, it is reasonable to assume:

$$(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \sim N(\mu_{D,UPCR}, \mu_{D,eGFR}, \sigma_{D,UPCR}^2, \sigma_{D,eGFR}^2, \rho)$$

Where  $\mu_{D,UPCR}$ ,  $\mu_{D,eGFR}$ , and  $\sigma_{D,UPCR}^2$  could be estimated from Phase 3 Week 36 Interim Analysis and the reference manuscript by Inker et al (refer to Section 3.4.5 for details). While  $\sigma_{D,eGFR}^2$  and  $\rho$  cannot be estimated at the time of Phase 3 Week 36 Interim Analysis, the following two sections provide details regarding how to estimate  $\sigma_{D,eGFR}^2$  and  $\rho$  using Phase 2b data.

### Estimating $\sigma_{D,eGFR}^2$ (i.e., Variance of $\hat{\mu}_{D,eGFR}$ ) Based on Phase 2b Data:

The variance of  $\hat{\mu}_{D,eGFR}$  is:

$$\sigma_{D,eGFR}^2 = \frac{1}{n} Var(eGFR\_Slope_{A,i}) + \frac{1}{m} Var(eGFR\_Slope_{P,j})$$

Assuming  $Var(eGFR\_Slope_{A,i}) = Var(eGFR\_Slope_{P,j})$ , we will use the following two ways to estimate  $\sigma_{D,eGFR}^2$  based on Phase 2b data for eGFR slope through Week 96:

- Use the variance of eGFR slope through Week 96 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of Phase 2b study) to estimate both  $Var(eGFR\_Slope_{A,i})$  and  $Var(eGFR\_Slope_{P,j})$ . Therefore, we can estimate  $\sigma_{D,eGFR}^2$  as  $s_2^2$ .
- Use the variance of eGFR slope through Week 96 within the Atacicept 150 mg group (only subjects who were randomized to Atacicept 150 mg group at the beginning of Phase 2b study) to estimate both  $Var(eGFR\_Slope_{A,i})$  and  $Var(eGFR\_Slope_{P,j})$ . Therefore, we can estimate  $\sigma_{D,eGFR}^2$  as  $s_2^2$ .

### Estimating Correlation Coefficient $\rho$ Based on Phase 2b Data:

We will use Phase 2b data to estimate the correlation coefficient  $\rho$ . To do this, we will have to estimate  $\sigma_{D,UPCR}^2$  and  $\rho$  using the same data (Phase 2b data).

The variance of  $\hat{\mu}_{D,UPCR}$  is:

$$\begin{aligned} \sigma_{D,UPCR}^2 = & \frac{1}{n_1} Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\} \\ & + \frac{1}{m_1} Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\} \end{aligned}$$

Similarly, we will use the following two ways to estimate  $\sigma_{D,UPCR}^2$  based on Phase 2b data:

- Use the change from baseline in  $\log(UPCR)$  at Week 36 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of the Phase 2b study) to estimate  $Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\}$ ; while use the change from baseline in  $\log(UPCR)$  at Week 36 within the Placebo group to estimate  $Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\}$ . Therefore, we can estimate  $\sigma_{D,UPCR}^2$  as  $s_3^2$ .
- Use change from baseline in  $\log(UPCR)$  at Week 36 within the Atacicept 150 mg group (only subjects who were randomized to Atacicept 150 mg group at the beginning of Phase 2b study) to estimate  $Var\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base})\}$ ; while use the change from baseline in  $\log(UPCR)$  at Week 36 within the Placebo group to estimate  $Var\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base})\}$ . Therefore, we can estimate  $\sigma_{D,UPCR}^2$  as  $s_3^2$ .

The covariance between  $\hat{\mu}_{D,UPCR}$  and  $\hat{\mu}_{D,eGFR}$  is:

$$\begin{aligned} & Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR}) \\ &= \frac{1}{n} Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR\_Slope_{A,i}\} \\ & \quad + \frac{1}{m} Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR\_Slope_{P,j}\}. \end{aligned}$$

Assuming  $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR\_Slope_{A,i}\}$  is the same as  $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR\_Slope_{P,j}\}$ , we will also use the following two ways to estimate  $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$  based on Phase 2b data, which corresponds to the two ways for estimating  $\sigma_{D,eGFR}^2$  and  $\sigma_{D,UPCR}^2$ :

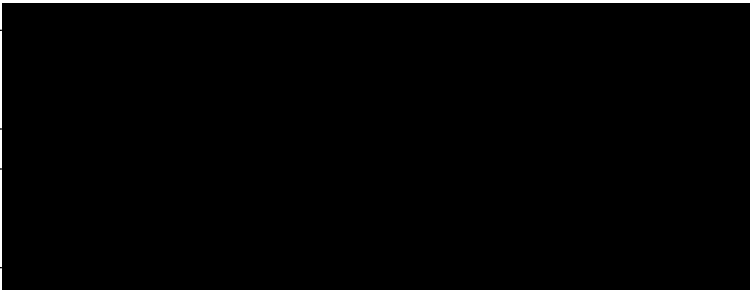
- Use the Phase 2b data for the covariance between the change from baseline in  $\log(UPCR)$  at Week 36 and the eGFR slope through Week 96 within the pooled Atacicept group (including subjects who were randomized to Atacicept 25 mg, 75 mg, and 150 mg groups at the beginning of Phase 2b study) to estimate both  $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR\_Slope_{A,i}\}$  and  $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR\_Slope_{P,j}\}$ . Therefore, we can estimate  $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$  as  $c_0$ .
- Use the covariance between the change from baseline in  $\log(UPCR)$  at Week 36 and the eGFR slope through Week 96 within the Atacicept 150 mg group (subjects who were randomized to Atacicept 150 mg group at the beginning of Phase 2b study) to estimate both  $Cov\{\log(UPCR_{A,i,W36}) - \log(UPCR_{A,i,Base}), GFR\_Slope_{A,i}\}$  and  $Cov\{\log(UPCR_{P,j,W36}) - \log(UPCR_{P,j,Base}), GFR\_Slope_{P,j}\}$ . Therefore, we can estimate  $Cov(\hat{\mu}_{D,UPCR}, \hat{\mu}_{D,eGFR})$  as  $c_0$ .

Finally, we can estimate  $\rho$  as  $r = c_0 / (s_3 * s_2)$  based on phase 2 data.

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