Clinical Trial Protocol

Clinical Trial Protocol Number	MS700461-0035
Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
Phase	II
IND Number	122,043
EudraCT Number	2016-002262-31
Coordinating Investigator	PPD PPD PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt Germany and EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 US Medical Responsible: PPD

EMD Serono Research and Development Institute, Inc.
45A Middlesex Turnpike
Billerica, MA 01821
US

Mobile: PPD

Email: PPD

EMD Serono is a subsidiary of Merck KGaA

Clinical Trial Protocol Version	27 November 2018 / Version 5.0 amendment 4
Replaces Version	15 September 2017 / Version 4.0 amendment 3

[redacted]

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AESI	Adverse Event of Special Interest
APRIL	A Proliferation-Inducing Ligand
APRIL-SLE	Clinical Trial 27646 in Systemic Lupus Erythematosus
ARB	Angiotensin Receptor Blockers
BCM	B-Cell Malignancies
BLyS	B Lymphocyte Stimulator (also called B-cell activating factor or BAFF)
BP	Blood Pressure
CI	Coordinating Investigator
CIC	Circulating Immune Complexes
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	Contract Research Organization
CS	Corticosteroid(s)
CTP	Clinical Trial Protocol
DBPC	Double-Blind Placebo-Controlled
DFR	Dose Frequency Reduction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOW	Every Other Week
ESRD	End Stage Renal Disease
ET	Early Termination
FU	Follow-Up
GCP	Good Clinical Practice
Gd-IgA1	Galactose Deficient-IgA1
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IgA, G, M, G1	Immunoglobulins A, G, M, G1

IgAN	IgA Nephropathy
IMP	Investigational Medicinal Product
ISR	Injection site reaction
ITT	Intention To Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LN	Lupus Nephritis
MCP-Mod	Multiple Comparison Procedures with Modeling Techniques
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat
MS	Multiple Sclerosis
PD	Pharmacodynamic(s)
PGx	Pharmacogenetics
PK	Pharmacokinetic(s)
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
SoC	Standard of Care
SOP(s)	Standard Operating Procedure(s)
Subject ID	Subject Identification Number
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
UACR	Urine Albumin to Creatinine Ratio
UPCR	Urine Protein to Creatinine Ratio
UPEP	Urine Protein Electrophoresis
WOCBP	Women of Childbearing Potential

1 Synopsis

Clinical Trial Protocol Number	MS700461-0035
Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
Trial Phase	II
IND Number	122,043
FDA covered trial	Yes
EudraCT Number	2016-002262-31
Coordinating Investigator	PPD
Sponsor	Merck KGaA and EMD Serono Research and Development Institute, Inc. (US)
Trial centers/countries	Part A: The study will be conducted in approximately 20 sites in 3 countries (US, UK, Japan) Part B: The study will be conducted in approximately 44 sites in 6 countries
Planned trial period (first subject in-last subject out)	December 2016-December 2021
Trial Registry	ClinicalTrials.gov

Objectives:

<u>Part A (if Part B is not activated)</u>

Primary Objective

- Evaluate the safety and tolerability profiles of atacicept in subjects with IgA Nephropathy (IgAN) and persistent proteinuria (ie, urine protein to creatinine ratio [UPCR] ≥ 1 mg/mg) through Week 48, while on a stable dose of Angiotensin Converting Enzyme Inhibitor (ACEi) and/or Angiotensin Receptor Blockers (ARB), considered optimal by the Investigator.

Secondary Objectives

- Evaluate the pharmacodynamic (PD) effect of atacicept
- Evaluate the serum atacicept concentrations (pharmacokinetic [PK])
- Evaluate the safety and tolerability profiles of atacicept

- Evaluate the immunogenicity profile of atacicept.

Other Objectives

- Evaluate the effect of atacicept compared to placebo in reducing proteinuria
- Evaluate the effect of atacicept compared to placebo on achieving complete clinical remission and other measures of renal response
- Evaluate the effect of atacicept compared to placebo on renal function (ie, estimated glomerular filtration rate [eGFR])
- Evaluate the effect of atacicept compared to placebo on titers of antibodies to pneumococcal antigens, tetanus toxoid, and diphtheria toxoid.

Exploratory Objectives

- Evaluate the association of baseline serum levels of B Lymphocyte Stimulator (also called B-cell activating factor or BAFF) (BLyS) and A Proliferation-Inducing Ligand (APRIL) with clinical response and/or safety
- Evaluate the association of exploratory markers (eg, genetic variations, gene expression, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety
- Evaluate the association of renal histopathology at baseline (archival kidney biopsies if available) with clinical response and/or safety
- Evaluate the effect of atacicept compared to placebo on renal histopathology after treatment (optional repeat kidney biopsy).

Part B

Primary Objective

- Evaluate the efficacy and dose-response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria (ie, UPCR $\geq$ 1 mg/mg) while on a stable dose of ACEi and/or ARB, considered optimal by the Investigator, through Week 48.

Secondary Objectives

- Evaluate the effect of atacicept compared to placebo on proteinuria (ie, UPCR < 1 mg/mg) at Week 48
- Evaluate the effect of atacicept compared to placebo on renal function (ie, eGFR) at Week 156
- Evaluate the safety and tolerability profiles of atacicept.

Other Objectives

- Evaluate the effect of atacicept compared to placebo on proteinuria over 156 weeks

- Evaluate the effect of atacicept compared to placebo on achieving complete clinical remission and other measures of renal response
- Evaluate the effect of atacicept compared to placebo on renal function over 156 weeks
- Evaluate the serum atacicept concentrations (PK)
- Evaluate the PD effect of atacicept
- Evaluate the effect of atacicept compared to placebo on titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid
- Evaluate the immunogenicity profile of atacicept.

Exploratory Objectives

- Evaluate the association of baseline serum levels of BLyS and APRIL with clinical response and/or safety
- Evaluate the association of exploratory markers (eg, genetic variations, gene expression, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response and/or safety
- Evaluate the association of renal histopathology at baseline (archival kidney biopsies if available) with clinical response and/or safety
- Evaluate the effect of atacicept compared to placebo on renal histopathology after treatment (optional repeat kidney biopsy).

Methodology: This Phase II, multicenter, double-blind, placebo-controlled (DBPC) parallel arm study has 2 parts. The study will begin with 3 treatment arms in Part A; subjects will be randomized in a ratio of 1:1:1 to receive placebo, atacicept 25 mg, or atacicept 75 mg, given by subcutaneous (SC) injection once weekly. After at least 5 subjects per arm have had at least 12 weeks of treatment with Investigational Medicinal Product (IMP), assessments of the cumulative available safety data will be conducted, taking into account recommendations by an Independent Data Monitoring Committee (IDMC). After IDMC recommendation, an interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team. Following recommendation by the IDMC and decision by the Sponsor, enrollment may be opened for Part B, wherein the atacicept 150 mg arm, given by SC injection once weekly for 156 weeks, will begin enrollment and the study will proceed with 4 treatment arms. The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment), and so that the final sample size is ~25 subjects per arm (total n = 100 subjects) to receive placebo, atacicept 25 mg, 75 mg or 150 mg. If Part B is not activated, only Part A will be completed with ~10 subjects per arm treated up to 72 weeks; if Part B is activated, all subjects from Part A will roll into Part B and only Part B will be completed.

For each subject, the study is composed of a Screening Period, a DBPC treatment Period, and a Safety follow-up (FU) Period.

Screening Period: The first visit will be a Screening Visit and include review of the inclusion/exclusion criteria. The Day 1 Visit is the baseline visit. For all assessments except UPCR from 24-hour urine, the last non-missing value prior to randomization on Day 1 will be considered as the baseline value. Duration of the Screening Period will be up to 4 weeks, during which all screening assessments must be completed and reviewed to determine the subject's eligibility. Importantly, subjects should undergo the Day 1 Visit as soon as possible after all assessments for eligibility of the study have been confirmed. Archival renal tissues from previous kidney biopsies, if available, will be requested for central pathology review.

DBPC Treatment Period: For each subject, duration of the treatment period from randomization will be 72 weeks for Part A if Part B is not activated, or extended to a total of 156 weeks if Part B is activated. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be reviewed again on Day 1 prior to randomization. The Day 1 procedures will be performed up to, at most, 4 weeks after the Screening Visit if the subject is found to be eligible. The first dose of the IMP (atacicept or placebo) will be given while the subject is still on site for the Day 1 Visit. Subjects will be monitored at study visits at Weeks 1, 2 and 4, and every 4 weeks thereafter through Week 24, then every 8 weeks through Week 48, and then every 12 weeks.

Decision to Activate/Not to Activate Part B: After review of the cumulative safety data and recommendation by the IDMC, a decision will be made by the Sponsor to either initiate Part B or complete only the ongoing Part A study without initiating Part B. The 2 possible scenarios are as follows:

- **Begin Part B**: If Part B is activated, the atacicept 150 mg arm will be opened for enrollment and only Part B will be completed. All subjects will be scheduled to receive IMP treatment for 156 weeks. Subjects who are receiving IMP in Part A will be rolled over to the DBPC treatment period of Part B and complete 156 weeks of IMP treatment. Additional subjects will be enrolled into all 4 treatment arms. The randomization ratio will be adjusted such that 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment), and that the final sample size is approximately 25 subjects per arm. The Week 156 Visit is the end of IMP treatment for the study.
- **Complete only Part A**: If the decision is made not to proceed to Part B, then enrollment will continue into Part A until approximately 30 subjects have been enrolled (~ 10 subjects per arm). The study enrollment for the placebo and atacicept 25 mg and 75 mg arms will continue uninterrupted and subjects will receive IMP treatment until Week 72.

Safety FU Period:

After the last dose of the IMP, all subjects are required to enter a Safety FU period. For subjects who completed the treatment (72 weeks for Part A if Part B is not activated, or 156 weeks for Part B if Part B is activated), the Safety FU period is 24 weeks, with visits at Weeks 4, 12 and 24.

For each subject completing Part A only, the study is composed of an up-to-4 week Screening Period, a 72-week DBPC treatment Period, and a 24-week Safety FU period. Alternatively, if Part B is activated, the study is composed of an up-to-4 week Screening Period, a 156-week DBPC treatment Period, and a 24-week Safety FU period for all subjects. If early discontinuation occurs, subjects will complete an ET Visit, and a Safety FU period, with visits at 4, 12, 24 weeks and every 12 weeks thereafter, until the end of the planned DBPC treatment period (Week 72 for Part A if Part B is not activated, or Week 156 for Part B if Part B is activated). All visits will be conducted on an outpatient basis.

Planned number of subjects: Approximately 30 subjects (~10 per arm) for Part A if Part B is not activated, or a total of 100 subjects (~25 per arm) if Part B is activated, are planned to be enrolled.

<u>Part A</u> (if Part B is not activated)
Primary endpoint:

- Adverse Events (AEs), AEs of special interest (AESI), AEs leading to discontinuation, Serious AEs (SAE), AEs leading to death.

Secondary endpoints:

- Serum atacicept concentrations at pre-specified time points (additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects [~6 subjects per treatment group])
- Change from baseline levels in serum immunoglobulin (Ig) classes (IgG, IgA, and IgM) (g/L) at pre-specified time points
- Change from baseline in serum Galactose Deficient-IgA1 (Gd-IgA1) levels at pre-specified time points, if corresponding assay is available
- Change from baseline in serum complement C3 and C4 levels at pre-specified time points
- Change from baseline in immune cell subsets by flow cytometry analysis at pre-specified time points
- Change in urine immuno-electrophoresis pattern and quantitative analysis of urinary IgG, IgA and IgM levels at pre-specified time points
- Anti-drug antibody assessment at pre-specified time points
- Clinically significant vital signs, electrocardiograms (ECGs), and laboratory assessments.

Other endpoints:

- Change from baseline in proteinuria at pre-specified time points, determined by 4 different assessments:
    - Total protein (g/day) by 24-hour urine collection
    - UPCR (mg/mg) by 24-hour urine collection
    - UPCR (mg/mg) by spot urine collection
    - Urine Albumin to Creatinine Ratio (UACR) mg/mg by spot urine collection.
- Complete clinical remission at each time point. Complete clinical remission is defined as having UPCR < 0.3 mg/mg and urine Red Blood Cells < 5/high power field by spot urine over, at minimum, a 24-week period
- Complete proteinuria remission at each time point. Complete proteinuria remission is defined as UPCR < 0.3 mg/mg by spot urine
- Disease remission at each time point. Disease remission is defined as having UPCR < 0.2 mg/mg by spot urine and reduction of eGFR < 5 mL/min/1.73m^2 from the baseline level
- Complete renal response at each time point. Complete renal response is defined as having UPCR < 0.3 mg/mg by spot urine and ≤ 10% reduction of eGFR from the baseline level
- Partial renal response at each time point. Partial renal response is defined as having UPCR with > 50% reduction by spot urine and ≤ 25% reduction of eGFR from the baseline level
- Progressive kidney failure at each time point. Progressive kidney failure is defined as having ≥ 40% reduction of eGFR from the baseline level, the development of end stage renal disease (ESRD) (ie, a need for maintenance dialysis or kidney transplantation), or death due to kidney disease
- Change from baseline in eGFR at pre-specified time points through Week 72
- Change from baseline in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid at pre-specified time points.

<u>Exploratory Endpoints</u>

- Correlation of baseline serum BLyS and APRIL and change from baseline (if assay is available), with clinical response and/or safety
- Correlation of exploratory markers (eg, genetic variants [gene expression profiles, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety
- Scoring of renal tissues by immunohistochemistry using the Oxford-MEST classification of IgAN: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T)

- Glomerular IgG, IgA, Gd-IgA1, C3 and C4 deposition; measured by immunohistochemistry and/or immunofluorescence. BLyS and APRIL, expression in renal tissues
- Correlation of above histopathology parameters with clinical response (ie, proteinuria, eGFR) and/or safety.

Part B

Primary endpoint:

- Percent change in proteinuria from baseline at Week 48 (based on UPCR derived from 24-hour urine collections). The baseline value will be determined by the average of the values at Screening and Day 1 for UPCR.

Secondary endpoints:

- Proportion of subjects with UPCR < 1 mg/mg and ≥ 25% decrease from baseline (taken from the 24-hour urine collection) with stable eGFR (with < 15% reduction from the baseline level) at Week 48
- Change from baseline in eGFR at Week 156
- AEs, AESI, AEs leading to discontinuation, SAE, AEs leading to death
- Clinically significant vital signs, ECGs and laboratory assessments.

Other endpoints:

- For each of the following endpoints, proteinuria will be determined by 4 different assessments:

  1. Total protein (g/day) by 24-hour urine collection
  2. UPCR (mg/mg) by 24-hour urine collection
  3. UPCR (mg/mg) by spot urine collection
  4. UACR (mg/mg) by spot urine collection

  - Proportion of subjects with ≥ 25% decrease from baseline in proteinuria and to less than 1 (g/day for total protein or mg/mg for UPCR) with stable eGFR (with < 15% reduction compared to baseline level) at pre-specified time points
  - Proportion of subjects with ≥ 50% decrease in proteinuria with stable eGFR (with < 15% reduction compared to baseline level) at pre-specified time points
  - Proportion of subjects with proteinuria < 0.5 (g/day for total protein or mg/mg for UPCR) at pre-specified time points
  - Proportion of subjects with time-averaged proteinuria < 1 (g/day for total protein or mg/mg for UPCR) at pre-specified time points. Time averaged proteinuria is defined as the average proteinuria over a 24-week time window. At Week 156, time averaged proteinuria will also be computed as the average proteinuria over the 156-week treatment period

  - Change from baseline in proteinuria at pre-specified time points.

- Complete clinical remission at each time point. Complete clinical remission is defined as having UPCR < 0.3 mg/mg and urine Red Blood Cells < 5/high power field by spot urine over, at minimum, a 24-week period
- Complete proteinuria remission at each time point. Complete proteinuria remission is defined as UPCR < 0.3 mg/mg by spot urine
- Disease remission at each time point. Disease remission is defined as having UPCR < 0.2 mg/mg by spot urine and reduction of eGFR < 5 mL/min/1.73m^2 from the baseline level
- Complete renal response at each time point. Complete renal response is defined as having UPCR < 0.3 mg/mg by spot urine and ≤ 10% reduction of eGFR from the baseline level
- Partial renal response at each time point. Partial renal response is defined as having UPCR with > 50% reduction by spot urine and ≤ 25% reduction of eGFR from the baseline level
- Progressive kidney failure at each time point. Progressive kidney failure is defined as having ≥ 40% reduction of eGFR from the baseline level, the development of ESRD (ie, a need for maintenance dialysis or kidney transplantation), or death due to kidney disease
- Poor renal outcome, defined as at least one of the following criteria: ≥ 30% decrease in eGFR (sustained for at least 4 weeks), ESRD (eGFR ≤ 15 mL/min/1.73m^2, dialysis, or renal transplant), or who died from renal or cardiovascular causes up to and including Week 156; in addition, the proportion of subjects with individual components of this composite endpoint
- Change from baseline in eGFR at pre-specified time points
- Serum atacicept concentrations at pre-specified time points (additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects [approximately 6 subjects per treatment group])
- Change from baseline levels in serum Ig classes (IgG, IgA, and IgM) (g/L) at pre-specified time points
- Change from baseline in serum galactose deficient IgA1 (Gd-IgA1) levels at pre-specified time points, if corresponding assay is available
- Change from baseline in serum complement C3 and C4 levels at pre-specified time points
- Change from baseline in immune cell subsets by flow cytometry analysis at pre-specified time points
- Change in urine immuno-electrophoresis pattern and quantitative analysis of urinary IgG, IgA and IgM levels at pre-specified time points
- Change from baseline in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid at pre-specified time points
- Anti-drug antibody assessment at pre-specified time points.

Exploratory Endpoints

- Correlation of serum BLyS and APRIL (Day 1 as baseline and change from baseline, if assay is available) with clinical response and/or safety
- Correlation of exploratory markers (eg, genetic variants [gene expression profiles, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety
- Scoring of renal tissues by immunohistochemistry using the Oxford-MEST classification of IgAN: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T)
- Glomerular IgG, IgA, Gd-IgA1, C3 and C4 deposition; measured by immunohistochemistry and/or immunofluorescence. BLyS and APRIL (if an assay is available) expression in renal tissues
- Correlation of above histopathology parameters with clinical response (ie, proteinuria, eGFR) and/or safety.

Diagnosis and key inclusion and exclusion criteria: Eligible male and female subjects, 18 years of age or older who provide written informed consent, with IgAN as demonstrated by renal biopsy done within 60 months of the Screening Visit, with UPCR ≥ 0.75 and ≤ 6 mg/mg during screening, and on a stable, optimized ACEi and/or ARB for at least 8 weeks prior to the Screening Visit. Subjects are not eligible for this study if they have concomitant renal disease other than IgAN, severe renal impairment, history of tuberculosis (TB) or active or untreated latent TB, or positive hepatitis B or C serology, or concomitant immunosuppressant use.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule: Atacicept 25 mg, 75 mg or 150 mg in pre-filled 1 mL syringes, administered as once weekly SC injection.

Reference therapy: dose/mode of administration/dosing schedule: Matching placebo in pre-filled 1 mL syringes, administered as once weekly SC injection.

Planned study and treatment duration per subject: A total of 72 weeks for Part A (if Part B is not activated) or 156 weeks if Part B is activated followed by a 24-week Safety FU Period.

Statistical methods:

Part A for this Phase II study is designed to evaluate safety, PK, and PD during the 72-week treatment period with atacicept compared to placebo in subjects with IgAN with persistent proteinuria ≥ 1 mg/mg by UPCR at Screening or within 12 months prior to the Screening Visit, or ≥ 0.75 mg/mg during Screening, while on a stable dose of ACEi and/or ARB (considered optimal by the Investigator). There is no hypothesis tested in the Safety analyses (sample size in part A is not based on statistical power).

The sample size in Part B is planned to primarily support the dose-response testing. The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of

interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment); the final sample size is ~25 subjects per arm (total n = 100 subjects). Given a maximum effect size assumption of 40% on proteinuria reduction over placebo, a SD assumption of 40% for proteinuria change from baseline at Week 48, and 20% non-evaluable subjects by Week 156, it is estimated that 20 evaluable subjects per arm for an equal randomization ratio will provide at least 80% power to demonstrate a statistically significant dose-response at the 2-sided 5% alpha level. Randomization will be stratified according to the following stratification factors: baseline proteinuria (UPCR < 2 mg/mg vs ≥ 2 mg/mg, based on the Screening 24-hour urine collection) and race (Asian vs non-Asian).

Planned analyses:

Analyses, where indicated below, will be performed depending on whether or not Part B of the study is activated. For either Part A or Part B, the primary analysis will be performed when all subjects have completed the scheduled Week 48 Visit or have discontinued from study. Analyses at Weeks 96 and 156 of Part B will support long-term treatment evidence for safety and efficacy.

- Interim analysis (Part A): may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team.
- Interim futility analysis (if Part B is activated): performed by an independent statistical center after 60 randomized subjects (60% of total subjects) have completed 24 weeks of treatment. Proteinuria and other biomarker changes from baseline at Week 24 will be evaluated for futility by the IDMC and the Sponsor's internal unblinded Firewall team.
- Week 48 analysis (primary analysis, Part A or Part B): performed after all randomized subjects have completed the scheduled Week 48 Visit or have discontinued from study. After the Week 48 analysis, the sites and subjects will remain blinded while the trial is ongoing.
- Week 96 analysis (if Part B is activated): performed after all randomized subjects have completed the scheduled Week 96 Visit or have discontinued from study.
- Week 156 analysis (if Part B is activated): performed after all randomized subjects have completed the scheduled Week 156 Visit or have discontinued from study.
- Final analysis (Part A or Part B): will be performed after all randomized subjects have completed the Safety FU Period or have discontinued from study.

Table 1 Schedule of Assessments Part A (if Part B is not activated)

Study Period	Screening (Baseline)	Treatment Period																Safety FU			Early Terminators				
																						Safety FU			
Week	-4	0	0	0	1	2	4	8	12	16	20	24	32	40	48	60	72	+4	+12	+24	ET Visit	+4	+12	+24	+12
Study Day	-28 to -1	1	2	3	8	15	29	57	85	113	141	169	225	281	337	421	505	From Week 72				From ET			until 72 weeks
Visit window (±day)	-	-	-	-	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																								
PK subgroup informed consent[a]	X																								
PGx informed consent[b]	X																								
Inclusion/exclusion criteria Review[c]	X	X																							
Archival renal tissue request consent form[d]	X																								
Optional pre-treatment biopsy consent form[e]	X																								
Optional post-treatment biopsy consent form[e]		X																							
Randomization		X																							
Demographic data	X																								
IgAN clinical diagnosis medical Hx, medications previous vaccinations, surgery/procedures[f]	X																								
Assessments																									
Vital signs, height[g]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X														X		X				X				
12-lead ECG	X	X					X		X			X			X		X				X				
Complete physical examination	X														X		X				X				
Physical examination disease-focused		X			X	X	X	X	X	X	X	X	X	X		X		X	X	X		X	X	X	X
Chest X-ray[h]	X																								
Tuberculosis assessment	X																								
Laboratory Assessments																									
Routine hematology, chemistry, urinalysis[i]	X	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	X																								
Serum pregnancy test[j]	X																								

Study Period	Screening (Baseline)	Treatment Period																Safety FU			Early Terminators				
																						Safety FU			
Week	-4	0	0	0	1	2	4	8	12	16	20	24	32	40	48	60	72	+4	+12	+24	ET visit	+4	+12	+24	+12
Study Day	-28 to -1	1	2	3	8	15	29	57	85	113	141	169	225	281	337	421	505	From Week 72				From ET			until 72 weeks
Visit window (±day)	-	-	-	-	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Urine pregnancy test[j]		X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[w]
24-hour urine collection[k]	X	X										X			X		X				X				
Spot Urine Sample[k]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UPEP[l]		X										X			X						X				
Archival kidney biopsy[m]		X																							
Pre-treatment kidney biopsy (optional)[n]	X																								
Post-treatment kidney biopsy (optional)[n]															X										
Pharmacokinetics																									
Serum atacicept[o]		X	X[a]	X[a]	X	X	X	X	X	X		X		X	X		X	X	X	X	X	X	X	X	
Anti-drug antibodies		X										X			X		X		X	X	X		X	X	
Pharmacodynamics																									
Serum BLyS & APRIL level[p]	X	X					X		X			X			X		X			X	X			X	
Vaccine immunization titers[q]		X													X		X				X				
Immunoglobulins (IgG,IgA,IgM)[r]	X[r]	X			X	X	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
Complement (C3, C4)		X							X			X			X		X		X	X	X		X	X	X
PGx blood sample[s]		X																							
Sample for blood gene expression profiling[s]		X			X		X		X			X			X		X			X	X			X	X[w]
Sample for circulating proteins[s]	X	X					X		X			X			X		X			X	X			X	X[w]
Urine for exploratory markers[t]		X					X		X			X			X		X			X	X			X	X[w]
Flow Cytometry of immune cell subsets (selected sites)		X					X		X			X			X		X			X	X			X	
Safety																									
Prior/Concomitant medications and procedures	Continuous																								
Adverse events	Continuous																								
Local injection tolerability		Continuous																			X				
IMP accountability							X	X	X	X	X	X	X	X	X	X	X				X				
IMP administration[u]		X[v]			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									

APRIL=a proliferation-Inducing ligand; BLyS=B-lymphocyte stimulator; C=complement component; ECG=electrocardiogram; ET=early termination; FU=follow-up; Gd-IgA1=galactose deficient IgA1; HBV=hepatitis B virus serologies; HCV=hepatitis C virus; HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; PGx=pharmacogenetics; PK=pharmacokinetics; TSH=Thyroid stimulating hormone; UACR=Urine Albumin to Creatinine Ratio; UPCR=urine protein: creatinine ratio; UPEP= urine protein electrophoresis.

a. Additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects (approximately 6 subjects per treatment group).
b. Pharmacogenetics (PGx) informed consent is only for those subjects who agree to participate in this optional testing.
c. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization. All baseline study assessments on Study Day 1 are to be performed pre-dose.
d. Archival renal tissue request consent form is only for subjects who agree to release those results for study use.
e. Only for subjects who agree to participate in this optional procedure.
f. Documentation of IgAN on biopsy within 5 years. Pneumococcal and seasonal injectable influenza virus vaccine should be administered if needed (at least 2 weeks prior to randomization).
g. Vital signs include blood pressure (see Section 7.5.4.1), pulse rate, and oral temperature. Height to be measured at screening only.
h. Chest X-ray will be performed locally. The results of a chest X-ray performed within 3 months of the Screening Visit (if available) are acceptable, provided there is no reason to suspect any clinical changes.
i. Urinalysis requires a random spot urine sample obtained from clean-catch midstream collection at the study visit.
j. Women of childbearing potential (WOCBP) only.
k. 24-hour urine collection: As soon as possible after the Screening Visit, the subject will return one of the two 24-hour urine containers dispensed during the Screening Visit, and one of the two mid-stream clean-catch spot urine first morning void cups that were dispensed on the same occasion. Spot urine collection: Early first morning void spot urine sample is required for spot UPCR and UACR. Subject will need specimen cup before morning of collection. Subject will collect first morning void, clean-catch midstream sample in AM of clinic visit and bring to the visit.
l. UPEP with immuno-electrophoresis.
m. When available.
n. Pre-treatment optional kidney biopsy is to be performed at the discretion of the site Principal Investigator as a standard of care procedure. This is to be performed immediately after the urine collections planned for the Screening Visit. Evaluations of renal histopathology in archival kidney biopsy specimens before treatment and in the post-treatment optional kidney biopsy up to a maximum of 4 weeks after 48 weeks of IMP treatment (or at least 24 weeks of IMP treatment for ET) are included in this study.
o. Beginning with Week 1: Blood sample for PK analysis will be collected within 25 hours before the next scheduled dose of IMP to assess trough levels of serum atacicept.
p. BLyS/APRIL: Day 1 sample to be obtained prior to first dose of atacicept. Samples post-baseline will be analysed if assay is available.
q. Evaluation of titers of previous vaccinations: tetanus toxoid, pneumococcus and diphtheria.
r. At Screening, IgG only.
s. Blood samples for PGx, gene expression, and circulating proteins will be acquired at the timepoints outlined above and may be processed and evaluated after the primary results of the study are available.
t. Urine samples for exploratory markers including but not limited to IgG, IgA, IgM, Gd-IgA1, cytokine proteins (BLyS, APRIL); cell pellet for cytospin and/or gene expression will be acquired at the timepoints outlined above and may be processed if assay is available and evaluated after the primary results of the study are available.
u. See Section 7.1.2.1. IMP to be administered once weekly unless site investigator receives notification to adjust dosing frequency.

v. Subjects should receive emergency contact number(s) before leaving the site on Day 1.
w. Only at last FU Visit.

Table 2 Schedule of Assessments Part B

Study Period	Screening	Treatment Period																						
Week	-4	0	0	0	1	2	4	8	12	16	20	24	32	40	48	60	72	84	96	108	120	132	144
Study Day	-28 to -1	1	2	3	8	15	29	57	85	113	141	169	225	281	337	421	505	589	673	757	841	925	1009
Visit window (±day)	-	-	-	-	± 3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																						
PK subgroup informed consent[a]	X																						
PGx informed consent[b]	X																						
Inclusion/exclusion criteria Review[c]	X	X																					
Archival renal tissue request consent form[d]	X																						
Optional pre-treatment kidney biopsy consent form[e]	X																						
Optional post-treatment kidney biopsy consent form[e]		X																					
Randomization		X																					
Demographic data	X																						
Clinical diagnosis of IgAN & other medical history, medications, previous vaccinations, surgery/procedures[f]	X																						
Assessments																							
Vital signs, height[g]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X														X		X		X				
12-lead ECG	X	X					X		X			X			X		X		X				
Complete physical examination	X														X		X		X				
Physical examination disease-focused		X			X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X
Chest X-ray[h]	X																						
Tuberculosis assessment	X																						
Laboratory Assessments																							
Routine hematology, chemistry, urinalysis[i]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X																						
Serum virology (HIV,HCV,HBV)	X																						
Serum pregnancy test[j]	X																						

Study Period	**Screening**	**Treatment Period**																					
Week	-4	0	0	0	1	2	4	8	12	16	20	24	32	40	48	60	72	84	96	108	120	132	144
Study Day	-28 to -1	1	2	3	8	15	29	57	85	113	141	169	225	281	337	421	505	589	673	757	841	925	1009
Visit window (±day)	-	-	-	-	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	±7
Urine pregnancy test[j]		X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine collection[k]	X	X										X			X		X		X				
Spot Urine Sample[k]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UPEP[l]		X										X			X				X				
Archival kidney biopsy[m]		X																					
Pre-treatment kidney biopsy (optional)[n]	X																						
Post-treatment kidney biopsy (optional)[n]															X								
Pharmacokinetics																							
Serum atacicept[o]		X	X[a]	X[a]	X	X	X	X	X	X		X		X	X		X		X				
Anti-drug antibodies		X										X			X		X		X				
Pharmacodynamics																							
Serum BLyS and APRIL level[p]	X	X					X		X			X			X		X		X				
Vaccine immunization titers[q]		X													X		X						
Immunoglobulins (IgG,IgA,IgM)[r]	X[r]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gd-IgA1 (if assay is available)		X					X		X			X			X		X		X				
Complement (C3, C4)		X							X			X			X		X		X				
PGx blood sample[s]		X																					
Sample for blood gene expression profiling[s]		X			X		X		X			X			X		X		X				
Sample for circulating proteins[s]	X	X					X		X			X			X		X		X				
Urine for exploratory markers[t]		X					X		X			X			X		X		X				
Flow Cytometry of immune cell subsets (at selected sites only)		X					X		X			X			X		X		X				
Safety																							
Prior/Concomitant medications and procedures	Continuous																						
Adverse events	Continuous																						
Local injection tolerability		Continuous																					
IMP accountability							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration[u]		X[v]			X	X	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	X	X

Study Period	Treatment Period	Safety FU			Early Terminators				
						Safety FU			
Week	156	+4	+12	+24	ET visit	+4	+12	+24	+12
Study Day	1093	From Week 156				From ET			until 156 weeks
Visit window (±day)	±7	±7	±7	±7	±7	±7	±7	±7	±7
Vital signs, height[g]	X	X	X	X	X	X	X	X	X
Weight	X				X				
12-lead ECG	X				X				
Complete physical exam	X				X				
Physical examination disease-focused		X	X	X		X	X	X	X
Laboratory assessments									
Routine hematology, chemistry, urinalysis[i]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[j]	X	X	X	X	X	X	X	X	X[w]
24-hour urine collection	X				X				
Spot Urine Sample[k]	X	X	X	X	X	X	X	X	X
UPEP[l]	X				X				
Pharmacokinetics									
Serum atacicept[o]	X	X	X	X	X	X	X	X	
Anti-drug antibodies	X		X	X	X		X	X	
Pharmacodynamics									
Serum BLyS and APRIL level[p]	X			X	X			X	
Vaccine immunization titers[q]	X				X				
Immunoglobulins (IgG, IgA, and IgM)	X	X	X	X	X	X	X	X	X
Gd-IgA1	X		X	X	X		X	X	X
Complement (C3, C4)	X		X	X	X		X	X	X
Sample for blood gene expression profiling[s]	X			X	X			X	X[w]
Sample for circulating proteins[s]	X			X	X			X	X[w]
Urine sample for exploratory markers[t]	X			X	X			X	X[w]
Flow Cytometry: B cell and plasma cell subsets (at selected sites only)	X			X	X			X	
Safety									
Prior/Concomitant medications and procedures	Continuous								
Adverse events	Continuous								
Local injection tolerability	X				X				
IMP accountability	X				X				
IMP administration[u]									
IMP dispensing to subject									

APRIL=a proliferation-Inducing ligand; BLyS=B-lymphocyte stimulator; C=complement component; ECG=electrocardiogram; ET=early termination; FU=follow-up; Gd-IgA1=galactose deficient IgA1; HBV=hepatitis B virus serologies; HCV=hepatitis C virus; HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; PGx=pharmacogenetics; PK=pharmacokinetics; TSH=Thyroid stimulating hormone; UACR=Urine Albumin to Creatinine Ratio; UPCR=urine protein: creatinine ratio; UPEP= urine protein electrophoresis.

a. Additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects (approximately 6 subjects per treatment group).
b. Pharmacogenetics (PGx) informed consent is only for those subjects who agree to participate in this optional testing.
c. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization. All baseline study assessments on Study Day 1 are to be performed pre-dose.
d. Archival renal tissue request consent form is only for subjects who agree to release those results for study use.
e. Only for subjects who agree to participate in this optional procedure.
f. Documentation of IgAN on biopsy within 5 years. Pneumococcal and seasonal injectable influenza virus vaccine should be administered if needed (at least 2 weeks prior to randomization).
g. Vital signs include blood pressure (see Section 7.5.4.1), pulse rate, and oral temperature. Height to be measured at screening only.
h. Chest X-ray will be performed locally. The results of a chest X-ray performed within 3 months of the Screening Visit (if available) are acceptable, provided there is no reason to suspect any clinical changes.
i. Urinalysis requires a random spot urine sample obtained from clean-catch midstream collection at the study visit.
j. Women of childbearing potential (WOCBP) only.
k. 24-hour urine collection: As soon as possible after the Screening Visit, the subject will return one of the two 24-hour urine containers dispensed during the Screening Visit, and one of the two mid-stream clean-catch spot urine first morning void cups that were dispensed on the same occasion. Spot urine collection: Early first morning void spot urine sample is required for spot UPCR and UACR. Subject will need specimen cup before morning of collection. Subject will collect first morning void, clean-catch midstream sample in AM of clinic visit and bring to the visit.
l. UPEP with immuno-electrophoresis.
m. When available.
n. Pre-treatment optional kidney biopsy is to be performed at the discretion of the site Principal Investigator as a standard of care procedure. This is to be performed immediately after the urine collections planned for the Screening Visit. Evaluations of renal histopathology in archival kidney biopsy specimens before treatment and in the post-treatment optional kidney biopsy up to a maximum of 4 weeks after 48 weeks of IMP treatment (or at least 24 weeks of IMP treatment for ET) are included in this study.
o. Beginning with Week 1: Blood sample for PK analysis will be collected within 25 hours before the next scheduled dose of IMP to assess trough levels of serum atacicept.
p. BLyS/APRIL: Day 1 sample to be obtained prior to first dose of atacicept. Samples post-baseline will be analysed if assay is available.
q. Evaluation of titers of previous vaccinations: tetanus toxoid, pneumococcus and diphtheria.
r. At Screening, IgG only.
s. Blood samples for PGx, gene expression, and circulating proteins will be acquired at the timepoints outlined above and may be processed and evaluated after the primary results of the study are available.

t. Urine samples for exploratory markers including but not limited to IgG, IgA, IgM, Gd-IgA1, cytokine proteins (BLyS, APRIL); cell pellet for cytospin and/or gene expression will be acquired at the timepoints outlined above and may be processed if assay is available and evaluated after the primary results of the study are available.
u. See Section 7.1.2.1. IMP to be administered once weekly unless site investigator receives notification to adjust dosing frequency.
v. Subjects should receive emergency contact number(s) before leaving the site on Day 1.
w. Only at last FU Visit.

2 Sponsor, Investigators and Study Administrative Structure

Sponsors:

This clinical trial will be sponsored by:

- Merck KGaA
  Frankfurter Strasse 250
  64293 Darmstadt
  Germany

EMD Serono Research and Development Institute, Inc.
45A Middlesex Turnpike
Billerica, MA 01821
US

Part A: The study will be conducted in approximately 20 sites in 3 countries (US, UK, Japan)

Part B: The study will be conducted in approximately 44 sites in 6 countries

Investigators will be nephrologists practicing within these sites.

The Coordinating Investigators (CIs) PPD represent all Investigators for decisions and discussions regarding this study, consistent with the International Council for Harmonization (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The CIs will provide expert medical input and advice relating to study design and execution and are responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the CIs as well as a list of Sponsor responsible persons are in Appendix I.

The study will appear in the following clinical trial registries: ClinicalTrials.gov.

Merck KGaA (the Sponsor) will enlist the support of several contract research organizations (CROs) to undertake specific study-related activities. The Sponsor will supervise all outsourced activities. The George Institute, Sydney, Australia has been engaged to provide medical and scientific support to the design and execution of the study.

A global CRO, PPD, has been engaged to conduct the clinical part of the study including study set-up, coordination, monitoring, data capture, data management, and statistical analysis.

Central laboratory services will be provided by PPD Laboratories. The location will vary depending on region (PPD).

Exploratory biomarkers will be analyzed by laboratories selected by the Sponsor.

Central randomization and treatment allocation using an Interactive Web Response System (IWRS) has been delegated by the Sponsor to PPD .

Packaging, labelling, and distribution of the Investigational Medicinal Product (IMP) will be the responsibility of the Clinical trial Supply Department at Merck KGaA, Darmstadt, Germany.

An Independent Data Monitoring Committee (IDMC) will be formed to monitor interim safety on a regular basis to ensure ongoing surveillance of subject safety in this trial and will also be responsible to monitor both safety and efficacy for the futility analysis. The IDMC will consist of at least the following core members: 2 nephrologists and 1 biostatistician. The IDMC will also review interim safety data from the placebo and 25 mg and 75 mg atacicept treatment arms once at least 5 subjects in each arm have had at least 12 weeks of treatment, in order to make a determination on whether opening enrollment in the atacicept 150 mg arm is recommended. In addition, the IDMC will monitor and make recommendations for adjusting the dose frequency reduction (DFR) criteria, should the need arise.

An Unblinded Firewall Team, composed of senior members from the Sponsor's departments in Clinical, Safety, Biostatistics, and Quantitative Pharmacology will review the futility analysis data for Part B, and make the final decision regarding the continuation of the study.

Regulatory submissions will be the responsibility of PPD (except submissions to the Food and Drug Administration [FDA]).

Study drug safety and global drug safety will be the responsibility of the Sponsor and PPD .

Quality Assurance (QA) will be the responsibility of the Sponsor and PPD .

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background Information

3.1 IgA Nephropathy

Immunoglobulin (Ig) A nephropathy (IgAN) or Berger's disease, is considered the most common cause of glomerulonephritis (GN) worldwide (Cattran 2009, Coppo 2010). The prevalence of IgAN is difficult to ascertain because of regional variability in screening and renal biopsy practices, however, it reportedly accounts for 35-45% of all GN cases in renal biopsy registries (Rychlik 2004, Li 2004). IgAN is more common in Asian and Caucasian populations compared with persons of African descent (Donadio 2002). The estimated incidence is 10 cases per million people per year in the US, and 20-40 cases per million people per year in Asia, although the former is likely to be something of an underestimate due to differences in biopsy thresholds. Consistent with differences in incidence based on ethnicity and genetic predisposition, the prevalence of IgAN varies geographically, with higher prevalence in East Asia and Northern European countries, compared with Southern Europe and Africa (Kiryluk 2012).

IgAN is highly variable, both clinically and pathologically. The classic presentation of IgAN is gross hematuria following an infection, but, more typically, IgAN presents as asymptomatic microscopic hematuria, with or without proteinuria. Renal impairment and hypertension are often present in subjects with older age at presentation (Barratt 2005). IgAN has generally been considered to be a relatively benign disease, however, up to 40% of all subjects with IgAN will progress to end stage renal disease (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).

The pathogenesis of IgAN remains unclear. However, there are new insights into the contribution of aberrant IgA antibodies, other auto-antibodies, circulating immune complexes (CIC), and novel mesangial cell proteins. A histopathological hallmark of IgAN is deposition of aberrant Galactose Deficient-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 CIC containing Gd-IgA1 (Czerkinsky 1986). Subsequent studies demonstrated that these Gd-IgA1 antibodies are defective due to aberrant glycosylation; resulting in deficiency of galactose on the O-linked glycans of the hinge region (Novak 2008, Tomana 1997). Circulating immune complex-containing Gd-IgA1 proteins were later shown to be the target antigens for IgG antibodies with specificity for the 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.

3.1.1 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. Subjects with IgAN with persistent proteinuria > 1 g/day are at increased risk of progression to ESRD (60%-70% over 20 years) (Reich 2007, Lee 2012, Moriyama 2014, Berthoux 2011). 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, recently in the STOP-IgAN study, IgAN patients with proteinuria (UPCR) ≥ 0.75 mg/mg had ongoing decline in renal function (decrease in eGFR) (Rauen 2015). Thus, the lowered threshold of proteinuria ≥ 0.75 mg/mg is deemed to be clinically relevant.

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) (International Society of Nephrology 2012). The use of ACEis 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-Latascha 2004). Used in combination, ACEis and ARBs may have an additive effect in decreasing proteinuria. However,

subjects on combination therapy require close monitoring for hyperkalemia, and combination therapy should be avoided in subjects with advanced kidney disease.

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 recommended 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 (Lv 2012).

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 some cases fish oil in proteinuric subjects, and CS in more severe cases, in combination with cyclophosphamide if there is crescentic GN (Kidney International Supplement 2012). In some regions, tonsillectomy is sometimes performed (Liu 2015). There are insufficient data supporting the use of most of the above listed therapies for IgAN, with the possible exception of RAS blockade. Reviews of randomized controlled trials suggest benefit from RAS blockade in reducing proteinuria and improving renal outcomes, but it is unclear whether this latter is beyond the benefit expected from the control of hypertension alone (Hotta 2013, Reid 2011, Cheng 2009). 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.

3.2 Scientific Background on Atacicept

Atacicept is a novel immunomodulator with B-cell targeting properties. The molecule is a fusion protein comprising the fragment crystallizable (Fc) portion of human IgG1 and the extracellular domain of the tumor necrosis factor receptor superfamily member TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor). Two TNF homologs, B Lymphocyte Stimulator (also called B-cell activating factor or BAFF) (BLyS) and A Proliferation-Inducing Ligand (APRIL), bind with high affinity and specificity to TACI and represent vital cytokines for B-cell homeostasis and function. Atacicept, an antagonist for all known conformations of BLyS and APRIL (ie, homotrimeric, heterotrimeric, multimeric, and soluble or membrane-expressed), deprives B cells of essential survival signals (Gross 2000). Blocking the activity of BLyS and APRIL consequently leads to a diminution in B-cell numbers and interferes with the maturation, differentiation, and effector function of these cells (Gross 2000, Dillon 2006, Moore 1999, Schneider 2005, Schneider 1999).

Atacicept is currently being investigated by the Sponsor for the treatment of systemic lupus erythematosus (SLE) and IgAN.

3.3 Nonclinical Experience with Atacicept

The binding of BLyS and APRIL by atacicept inhibits the respective cognate receptor interactions and results in substantial decreases in peripheral and secondary lymphoid tissue B-cell numbers over time, with naïve follicular B cells, marginal zone B cells, and long-lived plasma cells in bone marrow being particularly affected. In essence, in vivo atacicept treatment impedes the germinal center reaction while leaving immature B cells and memory B cells intact (Dillon 2006, Moore 1999, Schneider 2005, Schneider 1999, Dillon 2010, Gross 2001).

Mouse and cynomolgus monkey studies demonstrate atacicept's intended PD effects, including suppression of serum Igs, decreased circulating B-cell numbers, and reduced splenic and lymph node B-cell areas at doses as low as 0.4 mg/kg every second day in mice or every third day in monkeys administered for at least 13 weeks. Therapeutic benefit of atacicept was also demonstrated in a collagen-induced arthritis model and in SLE mouse models.

In addition, due to reduced antigen-specific immune responses observed in some atacicept mouse studies (Studies RES-10211, RES-10212, and RES-10213), further mouse studies were carried out using viral and bacterial host resistance models to directly assess the functional reserve of the immune system (Studies BRT 20030103 and ZGI 1493-007). Results showed atacicept reduced circulating B cells, and total and pathogen-specific IgG and IgM levels, but without affecting the host's ability to clear the viral or bacterial infection.

Subcutaneous (SC) safety pharmacology experiments in mice and monkeys did not reveal any pathophysiologically relevant effects on the cardiovascular, respiratory, or central nervous systems (Studies 24149, 24127, and 24128).

No signs of systemic toxicity were observed in single- or repeat-dose experiments conducted in mice (up to 26 weeks; Study 24924) or in monkeys (up to 39 weeks; Study 24951). In most animal studies, atacicept was administered SC, ie, the route utilized in the Phase II/III human clinical trials. PD effects were long-lasting and consistent with the mechanism of action of atacicept, including dose-dependent, reversible decreases in B lymphocytes in the circulation and in tissues (ie, total and mature B cell subsets), and in total serum immunoglobulin levels (IgG, IgM, and IgA).

Atacicept was shown to be non-genotoxic after in vitro and in vivo genotoxicity testing.

Reproductive toxicity studies indicate the potential of atacicept to negatively affect the early phases of pregnancy (eg, decrease in implantation frequency) without affecting male fertility (Studies 25129 and 26352). No fetal malformations were induced by atacicept (Studies 24967 and 25324); however, fetal resorption rates were increased compared to controls both in mice and rabbits. In a pre and postnatal development study in mice, atacicept produced the expected PD effects on the mothers without adversely affecting maternal function or development of the offspring (Study 25918).

Atacicept was well tolerated locally at the site of intravenous (IV) and SC administrations. The histological reactions observed in the general toxicity studies in mice and monkeys after repeat

dosing or in the dedicated local tolerance studies in rabbits after single doses, were mild in severity and resolved after an off-treatment period of several days.

The comprehensive toxicological evaluation of atacicept in appropriate animal models did not yield significant findings other than those predicted by the pharmacological mechanism of action. In view of the pharmacological effects observed in subacute and chronic toxicity studies, the no observed adverse effect level corresponded to the highest administered dose, ie, 80 mg/kg administered every second day in mice or every third day in monkeys for 4 weeks, and 10 mg/kg administered every second day for up to 26 weeks in mice or every third day for up to 39 weeks in monkeys. Results obtained from animal studies support the conduct of clinical trials investigating atacicept in healthy volunteers and in subjects with SLE, Lupus Nephritis (LN), or IgAN.

Refer to the current Investigator's Brochure (IB) for further details of the nonclinical studies described above.

3.4 Clinical Experience with Atacicept

As of 15 October 2015, a total of 1625 subjects (healthy volunteers and subjects with rheumatoid arthritis (RA), SLE, LN, MS and optic neuritis (ON), and B-cell malignancies(BCM) had been enrolled into completed and ongoing atacicept clinical studies. Approximately 1125 subjects were exposed to at least 1 dose of atacicept. Treatment remains blinded for 306 subjects who were randomized into the Phase IIb SLE Study EMR700461-023 and its extension study, EMR700461-024.

The current and previous versions of the IB provide details of the clinical experience with atacicept in RA, MS, ON, and BCM. It should be noted that based on the results of these trials, atacicept is no longer being evaluated for the treatment of RA or BCM due to lack of sufficient efficacy. In addition, due to the observation that exposure to atacicept correlated with worsening of MS, atacicept is no longer being pursued as a potential treatment for MS, ON or any other demyelinating disease. Consequently, SLE, LN and IgAN are the current focus of the atacicept clinical development program.

As indicated in Section 3.4.3, two previous clinical trials of atacicept in LN, another proteinuric renal disease (Trials 28113 [APRIL-LN] and EMR700461-014) raised safety concerns and demonstrated significant decreases in Ig levels that may be a risk for subjects with > 2 g/day and/or decreased estimated eGFR (ie, < 40 mL/min/1.73m^2). Both of these trials were terminated early.

3.4.1 Healthy Volunteer Trial (Trial 24675)

In 19 healthy volunteers (Trial 24675), single SC doses of atacicept up to 630 mg were investigated and found to be safe and well-tolerated. Specifically, single SC atacicept injections of 70, 210 and 630 mg produced reductions in IgM levels (approximately 20% in the 70 mg and 210 mg dose groups after 2-3 weeks, and 23% in the 630 mg dose group after 5 weeks, respectively). Recovery to baseline values was considered complete after 210 days. There were no apparent treatment effects on IgG or lymphocyte subpopulations following single doses of atacicept in healthy

subjects. No SAEs, or increased risk of infections were reported, and no subject was withdrawn due to an adverse event (AE).

3.4.2 Healthy Volunteer Trial (Trial 700461-022)

In 37 (19 Japanese subjects and 18 Caucasian subjects) healthy volunteers (Trial 700461-022), single SC doses atacicept up to 150 mg were investigated and found to be safe and well-tolerated. Single SC atacicept injections of 25, 75 and 150 mg doses showed no clinically significant differences in the safety profiles of Japanese and Caucasian subjects. A less than dose-proportional increase in exposure with increasing dose was observed, as indicated by a decrease in dose-normalized AUC_{0-t} and C_{max}, respectively, with increasing doses. A comparable slight transient decrease in IgA and IgM was seen in both ethnicities in the 75 mg and 150 mg dose groups. The dose by ethnic group interaction was not statistically significant at the 5% level for either AUC_{0-t} or C_{max} ($p = 0.24$ and $p = 0.29$), respectively indicating no differences in the PK parameter dose relationship between Japanese and Caucasian subjects. No SAEs, or other significant AEs were reported, and no subject was withdrawn due to an AE.

3.4.3 Clinical Data in Systemic Lupus Erythematosus and Lupus Nephritis

Five clinical trials of atacicept in SLE and LN have been completed (Trials 25050, 25842, 27646, 28113, and 700461-014). Two Phase IIb trials in SLE (Trials 700461-023 and 700461-024) are ongoing.

Refer to the current IB for details of the safety, efficacy, and PK findings from the clinical program in SLE and LN. Key safety findings are summarized below.

Trial 700461-014

Trial 700461-014 was a Phase Ib, open-label, multicenter, dose-escalation, and repeat-dose trial to assess the safety, tolerability, PK, and PD of atacicept in subjects with LN on a stable mycophenolate mofetil (MMF) regimen, with or without CS. The primary objective of the trial was to characterize the safety and tolerability of atacicept and to establish the PK and PD profiles of atacicept in subjects with LN taking a stable regimen of MMF.

PPD

Across other trials in SLE, RA, and MS, in which over 1000 subjects have been exposed to atacicept, there has been no increased risk of thrombotic events and atacicept is considered by the Sponsor to be unlikely to have contributed to this single cardiac death. However, due to the close temporal association, causality cannot be ruled out and the Sponsor has incorporated appropriate risk mitigation strategies into all current and future atacicept trials.

Trial 28113 (APRIL-LN)

Trial 28113 (APRIL-LN) was a Phase II/III, randomized, double-blind, multicenter, placebo-controlled trial to evaluate the safety and efficacy of atacicept in combination with MMF and high-dose CS in subjects with LN. The primary objective of the trial was to evaluate the efficacy of atacicept compared with placebo in subjects with LN receiving or requiring MMF immunosuppressive therapy and high-dose CS. The trial was discontinued prematurely because of unexpectedly large decreases in IgG levels. Data from the trial revealed rapid decreases in the levels of Ig following the initiation of MMF and CS in 4 of the 6 subjects enrolled. These 4 subjects with large Ig decreases all had nephrotic range proteinuria, whereas the other 2 subjects did not. Following 2 weeks of MMF and CS during the Screening Period, these 4 subjects with large IgG decreases were all randomized to receive atacicept and continued decreases in serum IgG. In 3 of these 4 subjects, the IgG level decreased below the protocol-defined discontinuation threshold of 3 g/L, and 2 of these 3 subjects developed pneumonia (Haemophilus influenza and Legionella pneumophila). Both of these pneumonias resolved with standard of care (SoC) treatment, including antibiotics.

In Trial 28113 (APRIL-LN), 3 of 4 subjects treated with atacicept 150 mg developed severe hypogammaglobulinemia (IgG < 3 g/L), and 2 of these 3 subjects developed serious pneumonias. However, decreases in serum IgG had started before atacicept treatment was initiated. In the 2 weeks after initiation of MMF and high dose prednisone (60 mg daily), serum IgG levels decreased by approximately 50%, and continued to decrease at approximately the same rate after initiation of atacicept. The decrease in serum IgG was more pronounced in subjects with proteinuria > 2 g/day, raising the possibility that significant urinary losses of Ig contributed to the severe hypogammaglobulinemia. More complete data regarding the PK, PD, and safety profile of atacicept in subjects with proteinuria > 1 g/day will be important to prescribers, subjects, and health authorities, irrespective of the underlying cause of the proteinuria.

Trial 27646, Clinical Trial 27646 in Systemic Lupus Erythematosus (APRIL-SLE)

Trial 27646 (APRIL-SLE) was a Phase II/III trial designed to evaluate the efficacy of atacicept compared to placebo in preventing new flares in subjects with SLE with relatively low disease activity at time of initiation of treatment with atacicept or placebo. A total of 461 subjects were enrolled to be treated for 52 weeks, followed by a 24-week Safety FU Period. During the trial, 2 subjects who were receiving atacicept 150 mg experienced fatal infections due to suspected leptospirosis and Streptococcus pneumoniae, respectively, for which a contributing role of atacicept could not be excluded. PPD

PPD

Following a recommendation by the responsible Independent Data Monitoring Committee, the atacicept 150 mg dose group was discontinued from the trial. The atacicept 75 mg and placebo groups remained blinded and trial conduct and assessments continued per protocol for subjects in these groups. Planned statistical analyses were modified accordingly; in particular the primary analysis was limited to the comparison of atacicept 75 mg vs placebo. While significant PD effects, in particular reductions in levels of serum Igs (IgG, IgA, and IgM) and mature naïve B cells, were demonstrated with the atacicept 75 mg dose, the primary clinical endpoint was not met, as subjects treated with atacicept 75 mg showed no benefit with respect to the prevention of new flares compared to placebo-treated subjects. However, a posthoc analysis of the primary endpoint, where subjects who discontinued treatment solely due to the Sponsor's termination of the atacicept 150 mg arm were not treated as flares, suggested efficacy of the atacicept 150 mg dose in reducing the proportion of subjects experiencing a flare compared to placebo.

Data from the APRIL-SLE trial and trials in other indications demonstrate that treatment with atacicept resulted in median decreases of 30% and 50% in IgG levels and IgA levels, respectively, from baseline to Week 52 of treatment. The APRIL-SLE study also demonstrated the significant PD effects of both the 75 mg and 150 mg doses (eg, decrease in Ig, anti-dsDNA and B cell counts).

Ongoing Trials

The Sponsor is continuing development of atacicept in SLE with the Phase IIb ADDRESS II core trial to show induction of clinical response in subjects with moderate to severe active SLE (EMR700461-023). Subjects who complete the core trial will be able to participate in the long-term extension trial (EMR700461-024).

3.5 Atacicept Mechanism of Action

Both BLyS and APRIL exert overlapping as well as distinct biological properties (Odendahl 2000, Hahne 1998). While both can trigger B cell proliferation and survival in vitro, BLyS (Schiemann 2001, Hahne 1998) but not APRIL (Varfolomeev 2004), is required for the generation and maintenance of a mature B cell compartment in vivo. APRIL-deficient mice display impaired IgA and IgA/IgM antibody responses to T cell-dependent and -independent mucosal antigens, respectively (Castigli 2004) and a pathogenic role of APRIL in a mouse model of IgAN has been shown (Kim 2015) suggesting that APRIL-dependent IgA production contributes to the pathogenesis of IgAN. In addition, APRIL, but not BLyS, can interact with heparin sulfate proteoglycans (Moreaux 2009, Huard 2008), which may act as a mechanism to increase the local concentration of APRIL on the cell surface for localized APRIL signaling. Adding to the

BLyS/APRIL signaling complexity, circulating heterotrimeric forms of BLyS and APRIL have been identified in serum samples taken from subjects with several different systemic rheumatic diseases (Roschke 2002). These heterotrimers have also been shown to induce B-cell proliferation in vitro.

Atacicept is capable of binding to all known conformations of BLyS and APRIL and is thus expected to interfere with 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, Moore 1999, Schneider 2005, Schneider 1999, Dillon 2010, Gross 2001).

3.5.1 Rationale for Efficacy in IgA Nephropathy

Data from a Phase II trial in SLE; the APRIL-SLE trial [NCT00624338]) and trials in other indications demonstrate that treatment with once-weekly atacicept 150 mg resulted in median decreases of 30% and 50% in IgG levels and IgA levels, respectively, from baseline to Week 52 of treatment. There are data correlating higher serum levels of Gd-IgA1 with greater severity of IgAN disease (Suzuki 2014), suggesting that reduction in serum levels of Gd-IgA1 may slow disease progression. Thus, it is anticipated that decreasing IgG and IgA levels in subjects with IgAN treated with atacicept would result in reduction in the deposition of Gd-IgA1 and immune complexes (both anti-IgG to Gd-IgA1 and anti-IgA to Gd-IgA1), and thus improve renal outcomes.

There are data showing that high serum APRIL correlates with increased expression of serum Gd-IgA1 (Zhai 2016) in IgAN patients and that high serum BLyS levels are associated with more severe clinical features as well as more severe histopathological features (Xin 2013). Moreover, data generated internally show positive BLyS and APRIL expression (and their receptors) in kidney tissues from IgAN patients, but absence in other kidney diseases (eg, minimal change disease) (Kumar 2016).

It is proposed that the administration of atacicept may have beneficial effects in subjects with IgAN, who do not have severe loss of kidney function or scarring on renal biopsy. A reduction in Gd-IgA1 through the blocking of BLyS and, more specifically, APRIL, given its importance in Ig isotype class switching, may decrease the formation, and therefore the deposition, of circulating immune complexes. This process may, in turn, slow or halt destructive inflammatory pathways leading to progressive damage of renal tissue.

This Phase II study will evaluate the efficacy and dose response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria ≥ 1 mg/mg by UPCR at Screening or within 12 months prior to the Screening Visit, or ≥ 0.75 mg/mg during Screening, while on a stable, dose of ACEi and/or ARB, considered optimal by the Investigator.

This clinical trial, MS700416-0035, will be conducted in compliance with the Clinical Trial Protocol (CTP), ICH GCP, the Japanese ministerial ordinance on GCP and any additional applicable regulatory requirements.

Refer to the current IB for detailed information on atacicept, including information about the nonclinical and clinical programs and Guidance for the Investigator.

3.6 Benefit-Risk Assessment

In Trial 27646 (APRIL-SLE) in SLE, both the atacicept 75 mg and 150 mg doses demonstrated significant PD effects (eg, decrease in Ig, anti-dsDNA and B cell counts). The 150 mg dose was associated with a reduction in SLE flare incidence. In Trial 27298 (AUGUST I) in RA, atacicept 25 mg dose was associated with approximately half of the reduction in serum immunoglobulins as compared to the 150 mg dose. Therefore, in the current study in IgAN, it is possible that all 3 doses of atacicept will be associated with significant PD effects, as well as clinical benefit in terms of reduction of disease activity.

Atacicept exerts multiple effects on the immune system which may lead to increased susceptibility to infection. An increased risk of serious infections (absolute increase < 2%) including 2 fatal respiratory infections, was observed after multiple dosing of 150 mg atacicept (see Section 3.4.3) in the APRIL-SLE study. The risk of infection associated with atacicept will be further evaluated in this IgAN study. Subjects in this IgAN study will not be taking background immunosuppressives or corticosteroids, and thus infection risks may be lower than what was observed in the studies of atacicept in SLE or RA.

The observation that atacicept exposure correlated with MS disease worsening led to discontinuation of the MS program. Thus, subjects with a history of any demyelinating or active central nervous system disease are excluded from this study.

IgAN with significant proteinuria may be associated with elevated urinary excretion of Ig (Matuosovic 2006), and possibly atacicept. These effects could alter the PD and PK profiles, respectively.

Study procedures include chest X-rays, electrocardiograms (ECGs), and regular blood sampling for measurement of safety parameters and biological markers; some minor risks are associated with these procedures.

The benefit-risk relationship has been carefully considered in the planning of this study. Based on the nonclinical and clinical data available to date, the conduct of the study is considered justifiable using multiple doses of 25 mg, 75 mg, and 150 mg of atacicept as specified in this CTP. The PK and PD profiles of the proposed atacicept doses are unknown in this IgAN population. In view of these unknown factors and the known infection risks of 150 mg atacicept in SLE, the Sponsor has taken a conservative approach to dosing. Namely, the safety, PK, and PD profiles will first be evaluated in the 2 lower atacicept doses (25 mg and 75 mg) before initiating dosing with the 150 mg atacicept dose. In addition, an IDMC is planned for the ongoing unblinded assessment of the safety and disease activity measurement in this study. The study shall be recommended to be discontinued in the event of new findings that would render continuation of the study unjustifiable.

Subjects may experience side effects or be at risk for symptoms, illnesses, or complications that could not be foreseen by the Sponsor. Given that this is the first clinical trial of atacicept in subjects

with IgAN, it is not clear whether subjects will experience significant clinical benefit from receiving treatment.

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

4 Study Objectives

4.1 Part A Objectives

Primary

- Evaluate the safety and tolerability profiles of atacicept in subjects with IgAN and persistent proteinuria (ie, UPCR ≥ 1 mg/mg) through Week 48, while on a stable dose of ACEi and/or ARB, considered optimal by the Investigator

Secondary

- Evaluate the PD effect of atacicept
- Evaluate the serum atacicept concentrations (PK)
- Evaluated the safety and tolerability of atacicept
- Evaluate the immunogenicity profile of atacicept

Other

- Evaluate the effect of atacicept compared to placebo in reducing proteinuria
- Evaluate the effect of atacicept compared to placebo on achieving complete clinical remission and other measures of renal response
- Evaluate the effect of atacicept compared to placebo on renal function (ie, eGRF)
- Evaluate the effect of atacicept compared to placebo on titers of antibodies to pneumococcal antigens, tetanus toxoid, and diphtheria toxoid

Exploratory

- Evaluate the association of baseline serum levels of BLyS and APRIL with clinical response and/or safety
- Evaluate the association of exploratory markers (eg, genetic variations, gene expression, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety

- Evaluate the association of renal histopathology at baseline (archival kidney biopsies if available) with clinical response and/or safety

- Evaluate the effect of atacicept compared to placebo on renal histopathology after treatment (optional repeat kidney biopsy)

4.2 Part B Objectives

Primary

- Evaluate the efficacy and dose-response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria (ie, UPCR ≥ 1 mg/mg) while on a stable, dose of ACEi and/or ARB, considered optimal by the Investigator, through Week 48

Secondary

- Evaluate the effect of atacicept compared to placebo on proteinuria (ie, UPCR < 1 mg/mg) at Week 48

- Evaluate the effect of atacicept compared to placebo on renal function (ie, eGFR) at Week 156

- Evaluate the safety and tolerability profiles of atacicept

Other

- Evaluate the effect of atacicept compared to placebo on proteinuria over 156 weeks

- Evaluate the effect of atacicept compared to placebo on achieving complete clinical remission and other measures of renal response

- Evaluate the effect of atacicept compared to placebo on renal function over 156 weeks

- Evaluate the serum atacicept concentrations (PK)

- Evaluate the PD effect of atacicept

- Evaluate the effect of atacicept compared to placebo on titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid

- Evaluate the immunogenicity profile of atacicept

Exploratory

- Evaluate the association of baseline serum levels of BLyS and APRIL with clinical response and/or safety

- Evaluate the association of exploratory markers (eg, genetic variations, gene expression, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety

- Evaluate the association of renal histopathology at baseline (archival kidney biopsies if available) with clinical response and/or safety

- Evaluate the effect of atacicept compared to placebo on renal histopathology after treatment (optional repeat kidney biopsy)

5 Investigational Plan

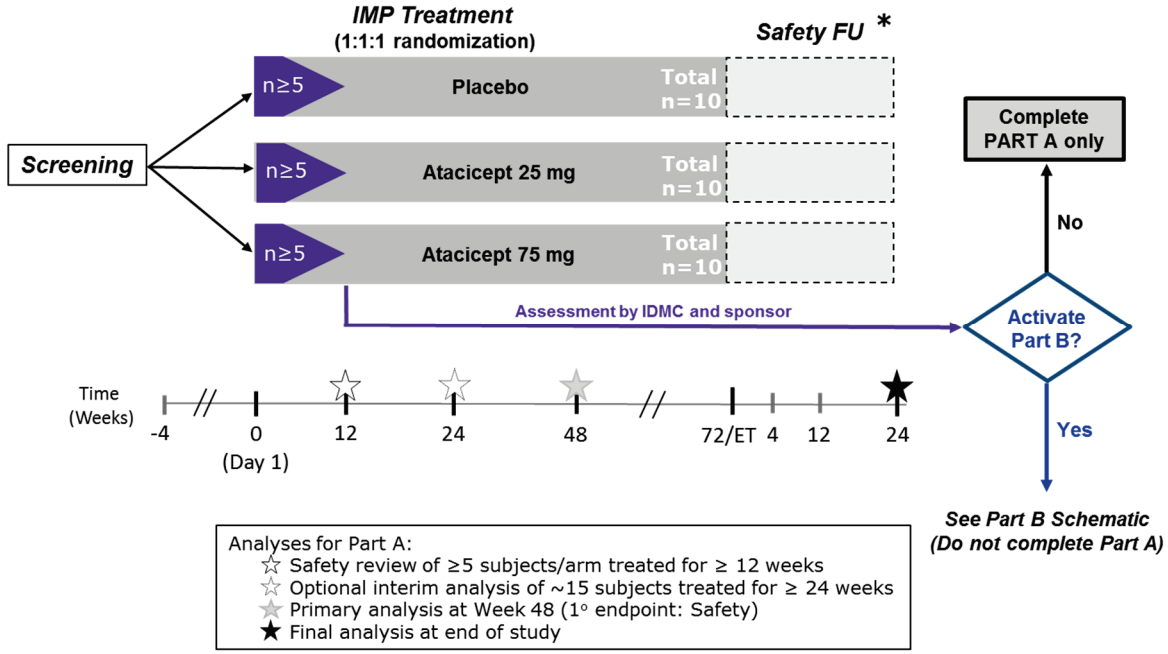
5.1 Overall Study Design and Plan

This Phase II, multicenter, DBPC, parallel arm trial has 2 parts. The primary analysis for this study will be after 48 weeks of IMP treatment.

A detailed schedule of study procedures/assessments is provided in Section 5.1.

The following Figure 1 illustrates the study design if only Part A is conducted. If Part B is activated, subjects from Part A will roll into that part of the study, as illustrated in Figure 2.

Figure 1 Schematic of Study Design for Part A (if Part B is not activated)

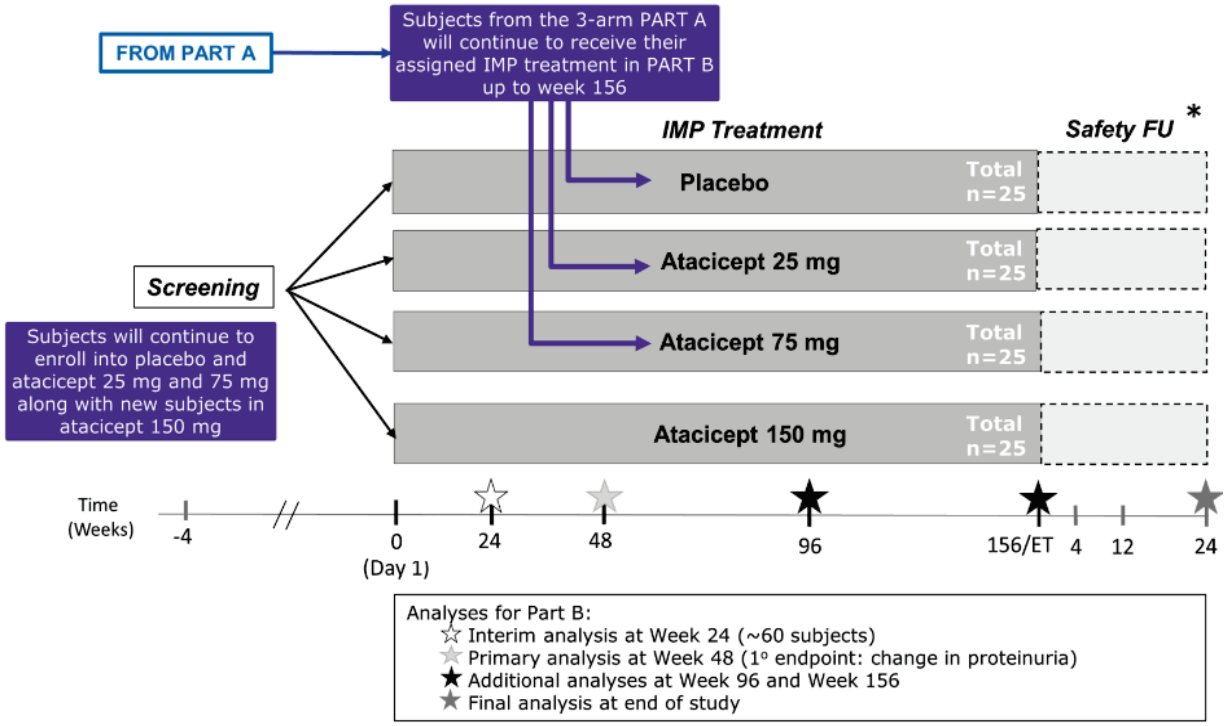


* Subjects who have early termination prior to Week 72 undergo an ET Visit and a Safety FU period with visits at Weeks 4, 12, 24, and every 12 weeks thereafter, until week 72.
ET=early termination visit, IMP=investigational medicinal product, Safety FU=24-week Safety follow-up period.

Part A: Approximately 30 subjects will be randomized in a 1:1:1 ratio to receiving placebo, atacicept 25 mg, or atacicept 75 mg; subcutaneously once a week. Part A will end IMP treatment at Week 72 if Part B is not activated; subjects will then enter a 24-week Safety FU period. Early terminating (ET) subjects who discontinue prior to Week 48 will undergo an ET Visit and a Safety FU period with visits at 4, 12, 24 weeks and every 12 weeks thereafter, until the end of the planned DBPC treatment period (Week 72). A review of cumulative safety data will be conducted after data from at least 5 subjects per arm have received at least 12 weeks of IMP treatment in Part A. After IDMC recommendation, an interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team. Following recommendation by the IDMC and decision by the Sponsor, enrollment may be opened for Part B. Primary analysis will be at week 48 if Part B is not activated.

Part B: Subjects already in Part A will roll into the DBPC treatment period of Part B. Enrollment will continue in the placebo, and atacicept 25 mg and 75 mg arms, and will begin in the newly-activated atacicept 150 mg arm (Figure 2). The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~ 15 subjects per arm, and that the final sample size will be ~ 25 subjects per arm. IDMC and the Sponsor's internal unblinded Firewall team will evaluate the results of futility analysis after ~ 60 subjects (~15 subjects/arm) have completed at least 24 weeks of IMP treatment. Primary analysis will be at week 48.

Figure 2 **Schematic of Study Design for Part B**



* Subjects who have early termination prior to Week 156 undergo an ET visit and a Safety FU period with visits at Weeks 4, 12, 24, and every 12 weeks thereafter, until week 156. ET=early termination visit, IMP=investigational medicinal product, Safety FU=24-week Safety follow-up period.

5.1.1 Study Periods

The first visit will be a Screening Visit and include review of the inclusion/exclusion criteria. The Day 1 Visit is the Baseline Visit. For all assessments except UPCR from 24-hour urine (see Section 8.3.1), the last non-missing value prior to randomization on Day 1 will be considered as the baseline value. Duration of the Screening Period will be up to 4 weeks, during which all screening assessments must be completed and reviewed to determine the subject's eligibility. Importantly, subjects should undergo the Day 1 Visit as soon as possible after all assessments for eligibility of the study have been confirmed. Archival renal tissues from previous kidney biopsies, if available, will be requested for central pathology review.

DBPC Treatment Period – 2-Part Design

Duration of the treatment period from randomization will be 72 weeks for Part A (if Part B is not activated) and 156 weeks for Part B (if activated). Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be reviewed again on Day 1 prior to randomization. The Day 1 procedures will be performed up to, at most, 4 weeks after the Screening Visit if the subject is found to be eligible. The first dose of the IMP (atacicept or placebo) will be given while the subject is still on site for the Day 1 visit. Subjects will be monitored at study visits at Weeks 1, 2 and 4, and every 4 weeks thereafter through Week 24, then every 8 weeks through Week 48, and then every 12 weeks.

Part A of the study will begin with 3 treatment arms. Subjects will be randomized in a ratio of 1:1:1 to receive placebo, atacicept 25 mg, or atacicept 75 mg, given by SC injection once weekly. If Part B is not activated, then only Part A will be conducted. An interim analysis may be performed, after ~ 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision (see Section 5.1 and Section 8.6).

Decision to Activate/Not to Activate Part B: After review of the cumulative safety data and recommendation by the IDMC, a decision will be made by the Sponsor to either initiate Part B or complete only the ongoing Part A study, without initiating Part B. The 2 possible scenarios are as follows:

- **Begin Part B**: If Part B is activated, the atacicept 150 mg arm will be opened for enrollment and the study will proceed with 4 treatment arms. All subjects will be scheduled to receive IMP treatment for 156 weeks. Subjects who are receiving IMP in Part A will continue on to the DBPC treatment period of Part B of the study and complete 156 weeks of IMP treatment. Additional subjects will be enrolled into all 4 treatment arms. The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment), and so that the final sample size is ~25 subjects per arm (total n = 100 subjects) to receive placebo, atacicept 25 mg, 75 mg

or 150 mg. If Part B is not activated, only Part A will be completed with ~10 subjects per arm treated up to 72 weeks; if Part B is activated, all subjects from Part A will roll into Part B and only Part B will be completed.

- **Complete only Part A**: If the decision is made not to proceed to Part B, then enrollment will continue into Part A until approximately 30 subjects have been enrolled (~ 10 subjects per arm). The study enrollment for the placebo and atacicept 25 mg and 75 mg arms will continue uninterrupted and subjects will receive IMP treatment until Week 72.

Complete Clinical Remission: After Week 48, subjects who are considered to have achieved complete clinical remission may have discontinuation of IMP dosing, at the discretion of the Investigator, after discussion with the medical monitor.

Complete clinical remission is defined as having at least 3 consecutive negative results (defined as urinary sediment red blood cell count of < 5/high-power field and UPCR of < 0.3 mg/mg from spot urine) over, at minimum, a 24-week period (adapted from Suzuki 2013).

Subjects meeting criteria for complete clinical remission and having discontinuation of IMP will complete an ET visit and Safety Follow-up (FU) visits until the end of the DBPC treatment period. IMP will not be restarted.

Safety FU Period

After the last dose of the IMP, all subjects are required to enter a Safety FU period. For subjects who completed the treatment (72 weeks for Part A only, or 156 weeks for Part B, if Part B is activated), the Safety FU period is 24 weeks, with visits at Weeks 4, 12 and 24.

For subjects who discontinue the IMP treatment prematurely, after an ET Visit, the length of the Safety FU period is either 24 weeks, or such that the sum of the IMP treatment period and the Safety FU period is 72 weeks for Part A only, or 156 weeks for Part B, if Part B is activated, whichever is longer, with visits at Weeks 4, 12, 24, and every 12 weeks thereafter.

Therefore, for each subject completing Part A only, the study is composed of an up-to-4 week Screening Period, a 72-week DBPC treatment Period, and a 24-week Safety FU period. Alternatively, if Part B is activated, the study is composed of an up-to-4 week Screening Period, a 156-week DBPC treatment Period, and a 24-week Safety FU period. If early discontinuation occurs, subjects will complete an ET Visit, and a Safety FU period, with visits at 4, 12, 24 weeks and every 12 weeks thereafter, until the end of the DBPC treatment period (Week 72 for Part A only, or Week 156 for Part B if Part B is activated) All visits will be conducted on an outpatient basis.

Further Analysis:

The PK will be evaluated in all subjects through measurement of serum atacicept concentrations at Day 1, and Week 1, 2, 4, 8, 12, 16, 24, 40, 48, 72, 96 (if Part B is activated) and 156 (if Part B is activated), and ET visits, in addition to Safety FU Week 4, 12, and 24 visits.

In addition, a subgroup of enrolled subjects (approximately 6 subjects per each treatment arm) will have additional PK sampling visits at Day 2 and/or 3 after the first dose in order to capture the drug's T_{max}. The PK analysis will be supported by population PK modeling.

The subjects who will be part of the subgroup will be registered by the study's central randomization system.

Subjects will be tested for formation of anti-drug antibodies (ADAs). Blood samples for assessment of binding and/or neutralizing anti-drug antibodies will be collected.

Circulating proteins (eg, cytokines, chemokines, and autoantibodies), analysis of immune cell subsets (B cell subset in particular), ribonucleic acid (RNA) gene expression and urinary biomarker analyses will be performed to support further development of atacicept. Baseline (predose) levels of BLyS and APRIL will be measured in all subjects. Post-randomization (postdose) samples of BLyS and APRIL will only be analyzed if the appropriate assays are available for additional assessments of serum BLyS and APRIL in the presence of atacicept.

5.2 Discussion of Study Design

5.2.1 Target Population

This study is designed to assess the effect of atacicept on proteinuria and renal function in subjects with IgAN with persistent proteinuria ≥ 1 mg/mg by UPCR at Screening or within 12 months prior to the Screening Visit, or ≥ 0.75 mg/mg during Screening. The study target population was chosen because this level of proteinuria has been associated with increased risk of significant renal outcomes such as end stage renal disease (up to 60-70% risk at 20 years).

At the Screening Visit, subjects will be required to be on a stable dose of ACEi and/or ARB considered optimal by the Investigator during the prior 8 weeks and have well-controlled blood pressure. The ACEi and ARB dose should represent the maximum labeled dose or the maximum tolerated dose that does not exceed the maximum labeled dose. Blood pressure lowering treatment should be optimized according to the local SoC.

The threshold of eGFR allowed for this study depends on the timing of the kidney biopsy. Specifically, subjects will be excluded with eGFR < 25 mL/min/1.73m^2 if the kidney biopsy was performed within 3 months from the Screening visit, or eGFR < 35 mL/min/1.73m^2 if kidney biopsy performed more than 3 months and within 12 months, or < 45 mL/min/1.73m^2 if kidney biopsy performed more than 12 months and within 60 months, or most recent kidney biopsy performed more than 60 months from the Screening Visit. These subjects are excluded since they are likely to have extensive renal scarring that will be less responsive to therapy, and are more susceptible to adverse outcomes.

Vaccination against pneumococcus and the influenza virus will be required as these are generally considered SoC treatment for patients receiving immunomodulating therapies and may reduce the risk of infection to enrolled subjects. Subjects with active or significant recent infection are excluded to avoid possible recurrence or worsening. Subjects with a history of, or current diagnosis

of, active or untreated latent TB, or positive hepatitis B or C serology are excluded to avoid the risk of reactivation (see exclusion criterion 23 and 24 in Section 5.3.2).

A number of abnormalities or interventions known to interfere with the immune system are excluded to avoid possible confounding of the atacicept safety profile.

Subjects treated with systemic CS within 4 months prior to the Screening Visit will be excluded so as to ensure that any potential effect is not carried forward into the study as a confounding factor. Additionally, the restriction of corticosteroid use will also limit the risk of untoward effects that CS are known to cause. For similar reasons, subjects treated with other immunosuppressants (eg MMF, azathioprine, calcineurin inhibitors) within 1 month prior to the Screening Visit will be excluded.

Cyclophosphamide administration is usually reserved for the treatment of very severe disease or disease that is unresponsive to other therapeutic interventions. However, evidence of long-term effects on renal function and immune system modulation in IgAN are inconclusive (Rauen 2015). For these reasons, only subjects with a previous history of cyclophosphamide use within 6 months prior to the Screening Visit will be excluded from the study.

In response to the finding of an increased rate of relapse of MS in atacicept-treated subjects in the ATAMS trial, subjects with a diagnosis of any demyelinating disease, such as but not restricted to, MS or optic neuritis (ON), are excluded from this study.

Atacicept reduces serum IgG levels, thus a minimum IgG level of 6 g/L is required at screening to decrease risk of reduction, in response to atacicept treatment, in IgG to < 3 g/L, a level that is associated with an increased risk of infection. For subjects whose IgG levels fall below 3 g/L during the study and who have already had dose frequency decreased to every other week, treatment will be discontinued. In ON, subjects at an increased risk of recurrent cardiovascular events (ie, those with a recent event) and/or significant arrhythmia (see exclusion criterion 17; see Section 5.3.2), will be excluded in order to decrease potential confounding of the study results (See Inclusion/Exclusion Criteria, Sections 5.3.1 and 5.3.2, respectively).

5.2.2 Rationale for the 2-part Study Design

Since atacicept has not been previously evaluated in subjects with IgAN, analysis of at least 5 subjects exposed to placebo, atacicept 25 mg and atacicept 75 mg weekly for at least 12 weeks will first be done in order to confirm that the PK, PD, and safety data are consistent with expectations based on data from other disease populations (including RA, MS, and SLE). After review of the cumulative safety data and recommendation by the IDMC, a decision will be made by the Sponsor to either initiate Part B or complete only Part A without continuing into Part B. If Part B is activated, the 150 mg arm will be included in the randomization of treatment arms. Conversely, if part B is not activated, the PK, PD, and safety profiles obtained from Part A may be used to inform the next study.

5.2.3 Rationale for Treatment Periods

A Screening Period of a maximum of 4 weeks is considered an acceptable duration during which subjects will complete screening activities and the disease activity will not vary to a large extent.

In RA, MS, and SLE clinical studies, atacicept reached approximately 80% of its maximum PD effects by 12 to 16 weeks of treatment. In other glomerular diseases, reduction in proteinuria has been demonstrated within 12 weeks of achieving therapeutic levels of the study drug (ie, rituximab) (Ruggenenti, 2012). This Phase II study will provide treatment for at least 72 weeks (Part A), and potentially up to a total of 156 weeks if part B is activated. Based on the PD effects of atacicept the proposed duration of treatment is likely to be sufficient to observe an effect of atacicept in reducing proteinuria and to assess longer term effects on eGFR. A 72-week treatment period should also be sufficient to allow uninterrupted IMP treatment in the event Part B is activated, minimizing the risk of subjects finishing Part A, before Part B can start (the decision to start Part B will be based on data from a minimum of 5 subjects per arm reaching at least 24 weeks of IMP treatment).

The design of the study is intended to first (during Part A) evaluate safety and tolerability of lower doses of atacicept (ie, 25 mg and 75 mg) in subjects with IgAN and to evaluate the effect of atacicept on relevant PD parameters (ie, IgG, IgA, IgM, Gd-IgA1, C3 and C4) across a 72-week IMP treatment duration. After the end of the 72-week treatment period, and if Part B is not activated, subjects will enter a 24-week Safety FU Period to explore if any treatment effect persists on PK, PD and clinical response (ie, proteinuria and eGFR) in the long-term. If subjects discontinue the IMP treatment prematurely, after an ET Visit, the length of the Safety FU period is either 24 weeks, or such that the sum of the IMP treatment period and the Safety FU period is 72 weeks for Part A only, or 156 weeks for Part B if Part B is activated, whichever is longer, with visits at Weeks 4, 12, 24, and every 12 weeks thereafter. In this case the potential clinical effects of atacicept on renal function, as measured by reduction of UPCR and prevention of eGFR decline from baseline, will be explored during the FU period without IMP treatment.

If only Part A will be conducted, a treatment period of 48 weeks for all randomized subjects is considered sufficiently long to assess the relationship between treatment and PK/PD effects.

If the second part of the study (Part B) is activated, the IMP treatment period continues for a total of 156 weeks. Part B aims to further evaluate the effects of atacicept treatment (including the 150 mg dose) compared to placebo on clinical response (ie, proteinuria and eGFR). If Part B is activated, a treatment period of 156 weeks for all randomized subjects is considered sufficiently long to observe a significant effect on proteinuria and a trend towards a change in eGFR trajectory.

The 24-week duration of the Safety FU Period (Part A or Part B) is based on the expected duration of measurable atacicept PD effects after IMP discontinuation.

5.2.4 Rationale for Renal Histopathology Assessments

Immunoglobulin A Nephropathy is diagnosed by the presence of IgA deposits in the mesangium. Moreover, individual renal histopathological lesions and immunofluorescent findings on kidney biopsies of patients with IgAN are predictors of clinical outcomes (ie, renal progression, disease

severity). The Oxford-MEST classification of IgAN (Coppo 2010, Roberts 2009) categorizes glomerular and tubulo-interstitial pathological lesions in kidney biopsies. Oxford-MEST classification has been shown to predict renal outcome (Barbour 2016, Shin 2016). Specifically, S1 (hazard ratio [HR] 2.70; 95% CI 1.45 to 5.01) and T2 (HR 14.94; 95% CI 5.99 to 37.25) by the Oxford-MEST were significant independent predictors of poor renal outcome (ie, ESRD or 50% reduction in eGFR) (Shin 2016). In the same study, moderate and marked glomerular IgA deposits significantly predicted renal outcome (ie, ESRD or 50% reduction in eGFR, HR 2.97; 95% CI 1.01 to 8.88, p = 0.04) independent of Oxford-MEST and clinical variables (ie, blood pressure, proteinuria, and eGFR). On the other hand, glomerular immunofluorescence patterns (not part of the Oxford-MEST score) reflect the pathophysiological mechanisms in IgAN (Shin 2016). Immunoglobulin A, IgG, Gd-IgA1, C3 and C4 glomerular deposition appear to be associated with poor renal outcome in subjects with IgAN (Berthoux 2012, Shin 2016), therefore reduction of these deposits is anticipated to be beneficial in subjects with IgAN.

Evaluations of renal histopathology in archival kidney biopsy specimens before treatment and in the optional kidney biopsy after 48 weeks of IMP treatment are included in this study in order to provide valuable information on the baseline characteristics that may correlate with clinical response to atacicept as well as histopathologic assessment of the effects of atacicept.

Archival Kidney Biopsy if Available before IMP Treatment

In addition to baseline proteinuria and eGFR, histological assessment of renal tissues by pre-treatment archival kidney biopsies (if available), will characterize IgAN subjects at baseline in terms of their risk of renal progression. The baseline histopathological features may be potential predictors for the treatment effect of atacicept compared with placebo (ie, clinical response and safety). Any kidney biopsy performed before randomization (Day 1) should be considered as SoC for IgAN since this procedure is not required by the protocol. Archival renal tissues/slides from previous kidney biopsies will be requested from all subjects for central pathology review.

Optional Post-treatment Kidney Biopsy

Post-treatment kidney biopsy in subjects with IgAN will evaluate the effect of atacicept at the tissue level. Specifically, reduction in the deposition of IgG, IgA, Gd-IgA1 (if assay is available), C3 and C4 will evaluate the effect of atacicept in modifying the pathogenesis and disease progression. Moreover, reduction in the deposition of these molecules and modification of the parameters of the Oxford-MEST classification of IgAN (Roberts 2009), will allow assessment of the subjects' renal status after 48 weeks of treatment, and re-assessment of the risk category for progression to end-stage renal disease. Finally, performing a post-treatment kidney biopsy will allow investigation of the association of pathologic findings with response to treatment; for example, non-response to atacicept may be associated with high fibrotic score (and thus unlikely to respond to immunomodulating therapy).

5.2.5 Scientific Rationale for Study Design

This Phase II study will evaluate the efficacy and dose-response of atacicept compared to placebo in reducing proteinuria in subjects with IgAN and persistent proteinuria ≥ 1 mg/mg by UPCR at

Screening or within 12 months prior to the Screening Visit, or ≥ 0.75 mg/mg during Screening, while on a stable dose of ACEi and/or ARB considered optimal by the Investigator.

Atacicept is capable of binding to all known conformations of BLyS and APRIL and is thus expected to interfere with 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, Moore 1999, Schneider 2005, Schneider 1999, Dillon 2010, Gross 2001), thereby potentially reducing the production and subsequent deposition of immunoglobulins in kidney parenchyma, and thus reducing the extent of kidney injury in IgAN patients.

Use of ACEis and ARBs:

The central component of supportive care in IgAN consists of appropriate blood pressure (BP) control and proteinuria management using ACEi and/or ARBs (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-Latascha 2004). Used in combination, ACEis and ARBs may have an additive effect in decreasing proteinuria. Therefore, in this study, subjects at the Screening Visit will be required to be on a stable and optimal dose (as determined by the Investigator) of ACEi and/or ARB, according to SoC. Stable and appropriate background medications for BP control are 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 continue to receive ACEi and/or ARB as stable background SoC during this trial.

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 recommended for subjects with preserved kidney function who have persistent proteinuria despite adequate BP 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 (Lv 2012). 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.

5.2.6 Justification for Dose

The doses selected for this study are based on PD effects on B cells and immunoglobulins observed in studies of atacicept in subjects with SLE, RA, or MS. Data from the APRIL-SLE trial and trials in other indications demonstrate that treatment with atacicept resulted in median reductions of 30% and 50% in serum IgG and IgA levels respectively, in subjects who received atacicept 150 mg once weekly SC from baseline to Week 52 of treatment.

In the AUGUST II study of subjects with RA, treatment with atacicept 150 mg weekly or 150 mg twice weekly for the first 4 weeks was associated with nearly identical PD effects and clinical responses. Therefore, atacicept 150 mg weekly was considered to provide a maximal PD response, and is likely to do so in IgAN subjects. The atacicept 75 mg dose in the APRIL-SLE study showed significant PD effects that were close (approximately 80%) to the PD effects observed with 150 mg dose. However, the 75 mg dose was not associated with significant reduction of SLE flare. It is difficult to predict, therefore, the extent to which efficacy may be observed with the 75 mg dose when administered to subjects with IgAN. The expectation is that the 75 mg dose will also have approximately 80% of the PD effect of the 150 mg dose in this population, and the relative level of clinical efficacy remains to be determined.

The atacicept 25 mg dose in the RA AUGUST I study demonstrated approximately 50% of the PD effects that were observed with the 150 mg dose. In other words, subjects who received the 25 mg dose had a median reductions of 15% and 25% from baseline in serum IgG and IgA levels. In a different B-cell targeting therapy, blisibimod, a peptibody which inhibits BLyS only, showed a trend after Week 48 for reduction in proteinuria by UPCR compared to placebo in subjects with IgAN (Anthera press release 2016). The reduction of approximately 8% in serum levels of IgG and IgA from baseline to Week 36 of treatment obtained with blisibimod, was observed in subjects with IgAN. Therefore, the 25 mg dose of atacicept, which previously showed a greater PD effect in reducing serum IgG and IgA levels, could potentially have clinical efficacy, although this remains to be determined in the present study.

Results of the APRIL-SLE study suggested that the 150 mg dose was associated with an absolute % increase in the risk of severe and serious infection of approximately 1.6% as compared to placebo. This is approximately the level of increased risk observed with effective immunomodulating therapies in other indications (Merrill 2010, Cohen 2006, Tahtinen 2015). The overall risk of severe and serious infections is expected to be lower in the proposed IgAN population given that they are not taking concomitant immunosuppressants and do not have extra-renal organ involvement. Specific infection risk mitigation measures will be implemented in this study. These measures include requiring a history of specific up-to-date vaccinations, vigilance on the part of the subject and Investigator for signs and symptoms of infection, dose frequency adjustment for subjects with large and rapid changes in serum IgG levels and implementation of a delayed start for the highest dose (150 mg). Based on previous safety analyses, neither the 25 mg nor the 75 mg dose has been associated with increased risk of infection and increased infection risk is not anticipated in IgAN subjects receiving these doses of atacicept.

5.2.7 Rationale for Endpoints

There is an extensive body of literature correlating proteinuria with renal survival in IgAN (Reich 2007, Moriyama 2014, Lv 2012, Bartosik 2001). A significant reduction in proteinuria is thus expected to lead to a slower rate of decline in kidney function (typically expressed in terms GFR) and a lower risk of progression to ESRD.

A potential effect of atacicept on the level of proteinuria is anticipated to be observable by the end of the 24-week treatment period. In other disease populations (RA, MS, and SLE), atacicept reached approximately 80% of its maximum PD effects by 12 to 16 weeks. In other glomerular

diseases, reduction in proteinuria has been demonstrated within 12 weeks of achieving therapeutic levels of the study drug (Ruggenentti, 2012). Thus, 48 weeks is a likely timeframe to ensure that atacicept treatment effect is significant.

In order to ensure that the possible effect of atacicept on proteinuria is not transient, and to assess longer term effects on eGFR, this Phase II study will provide treatment for a total of 156 weeks, if Part B is activated.

In order to ensure that the possible effect of atacicept on proteinuria is not transient, and to assess longer term effects on eGFR, this Phase II study will provide treatment for a total of 156 weeks.

Rationale for primary objectives and endpoints for Part A

Since atacicept has not been evaluated in patients with IgAN, Part A of the study will first evaluate the safety and tolerability profiles of lower doses of atacicept (ie, 25 mg and 75 mg) in subjects with IgAN through 48 weeks of treatment.

Rationale for secondary objectives and endpoints for Part A

The PK assessments will be important in this new indication for all the subjects participating in the study (Part A and Part B) in order to explore the exposure-response relationship with regard to correlation of atacicept exposure and clinical efficacy, renal function parameters (eGFR) and level of urinary protein excretion, as well as with other disease-relevant PD parameters including, but not limited to IgG, IgA, IgM, Gd-IgA1 (if assay is available), and B cell and plasma cell profiles.

In a PK subgroup, additional serum atacicept samples will be drawn to capture the expected time at maximum concentration (T_{max}). All concentration data will be incorporated into the integrated Population PK model to identify potential covariates and parameters relevant for the exposure and response predictions in an IgAN patient population.

Rationale for primary objectives and endpoints for Part B

Decreases in proteinuria by > 30 to 50% appear to predict improved renal survival (Praga 2003) and such reductions have been described in randomized controlled studies of IgAN with ACEi/ARBs and corticosteroids (Pozzi 1999, Descamps-Latascha 2004). A reduction in proteinuria by at least 25% would be considered clinically relevant because it is outside the intra-individual variability of proteinuria testing. The data obtained from this study are expected to further corroborate the association between levels of proteinuria and levels of renal function over time.

Rationale for secondary objectives and endpoints for Part B

As in Part A, the secondary efficacy endpoints will examine the effect of atacicept on various markers of kidney disease, including proteinuria and GFR. Both UPCR and UACR can provide an accurate estimation of the 24-hour urinary protein excretion (Ginsberg 1983). Several relevant thresholds will be examined for proteinuria, including UPCR < 1 mg/mg (a level which is less strongly associated with an adverse renal prognosis), < 0.2 mg/mg (considered disease remission),

and < 0.3 mg/mg (considered resolution of proteinuria), as well as > 50% reduction in proteinuria (correlated with lower rate of progression to ESRD in various kidney diseases). The effect on GFR will be assessed by comparing the slopes in the treatment groups as well as analysis of subjects with ≥ 40% decline in GFR, or ESRD. In order to evaluate the long-term effects of atacicept on proteinuria and GFR in this chronic disease, this Phase II study will provide treatment for a total of 156 weeks.

Levels of immunoglobulins (IgG, IgA, IgM) and B cells in response to atacicept will be evaluated as in Part A. The safety assessments are designed to characterize side effects and identify potential risks associated with the IMP and are standard for many studies. Other disease-specific parameters will be evaluated for clinical correlative or predictive changes. These include the IgG, IgA, and serum Gd-IgA1.

5.2.8 Inclusion of Special Populations

Not applicable.

5.3 Selection of Study Population

To be eligible for the study, subjects must meet all of the inclusion criteria specified in Section 5.3.1 and none of the exclusion criteria specified in Section 5.3.2. In addition, all subjects must continue to meet concomitant medication requirements for the Screening Period as specified in Section 6.5.1 and Section 6.5.2. All subjects will be reviewed for eligibility centrally by the Sponsor or designee prior to approval for randomization (see Section 5.4).

5.3.1 Inclusion Criteria

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

1. Male or female of ≥18 years of age, who provide written informed consent at or prior to the Screening Visit, and prior to the performance of any study activities
2. Renal biopsy report documenting IgAN within 60 months prior to the Screening Visit
3. UPCR ≥ 0.75 mg/mg by 24-hour urine collection during the Screening Period with at least one documented historical UPCR ≥ 1 mg/mg within 12 months prior to the Screening visit while on ACEi and/or ARB therapy, or UPCR ≥ 1 mg/mg by 24-hour urine collection during the Screening Period
4. Initiation of ACEi and/or ARB at least 12 weeks prior to the Screening Visit. The dose of ACEi and/or ARB must be stable for at least 8 weeks prior to the Screening Visit, throughout the Screening Period, and for the treatment period. The ACEi and ARB dose should represent the maximum tolerated or maximum labeled dose as determined by the investigator. BP lowering management should be optimized according to the local SoC.
5. History of vaccinations as follows: 1) vaccination against S. pneumoniae with PCV13 or PPSV23 with repeat administration as necessary to be up to date as per local SoC guidelines and 2) influenza virus (as seasonally required); or vaccination against these pathogens during the Screening Period. Subjects receiving one or more of these vaccinations during the Screening

Period must have at least 2 weeks between the vaccination(s) and the date of randomization. (Live or live-attenuated vaccines are not permitted per exclusion criterion 27)

6. A female participant is eligible to participate if she is not pregnant (Appendix III) not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix III.

   OR

   b. WOCBP must have both of the following:

   A WOCBP who agrees to use a highly effective contraception (ie, methods with a failure rate of less than 1 % per year) as detailed in in Appendix III of this protocol for at least the past 28 days before start of first dose of study treatment (as appropriate), during the treatment period and for at least 90 days after the last dose of study treatment.

   WOCBP must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day 1/randomization before dosing

5.3.2 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. Concomitant significant renal disease other than IgAN (eg, diabetic nephropathy, lupus nephritis, minimal change disease)

2. On kidney biopsy, more than 50% glomeruli with global glomerulosclerosis, or more than 50% of cortical area involved by tubular atrophy or interstitial fibrosis

3. Evidence of rapid progressive glomerulonephritis (loss of ≥ 50% of eGFR within 3 months and/or evidence of ≥ 50% glomeruli with crescent formations on kidney biopsy)

4. Diagnosis of Henoch-Schönlein purpura

5. Renal or other organ transplantation prior to, or expected during, the study

6. UPCR > 6 mg/mg during the Screening Period (as measured from a 24-hour urine collection)

7. Any of the following is exclusionary based on when the kidney biopsy was performed prior to the Screening Visit:

   - If kidney biopsy performed within 3 months, eGFR < 25 mL/min/1.73 m^2;
   - If kidney biopsy performed more than 3 months and within 12 months, eGFR < 35 mL/min/1.73 m^2;

- If kidney biopsy performed more than 12 months and within 60 months, eGFR < 45 mL/min/1.73 m^2;

- Most recent kidney biopsy performed more than 60 months

8. eGFR will be calculated as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for subjects in regions except in Japan, and as per the Japan Association of Chronic Kidney Disease formula 2008 for subjects in Japan (Matsuo 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)

   - Japan Association of Chronic Kidney Disease: eGFR = $194 \times Scr^{-1.094} \times age^{-0.287}$ (if male), or $194 \times Scr^{-1.094} \times age^{-0.287} \times 0.739$ (if female).

9. Serum IgG below 6 g/L at the Screening Visit

10. Serum albumin level < 25 g/L at the Screening Visit

11. Clinically significant or pre-defined abnormalities in laboratory tests (aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase level > 2.5 x upper limit of normal [ULN], total bilirubin > 1.5 x ULN, hemoglobin < 5.0 mmol/L [9 g/dL], white blood cells < 2.5 x 109/L, platelets < 75 x 109/L, or thyroid stimulating hormone [TSH] < 0.01 or ≥ 7.1 mIU/L per central laboratory results) (including serum chemistries), at screening

12. Clinically significant chest X-ray per Investigator or Sponsor opinion or evidence of active TB on chest X-ray. Chest X-ray must have been performed within 3 months prior to the Screening Visit or during the Screening Period.

13. Systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg after a period of 5 minutes rest, on 2 or more distinct visits during the Screening Period

14. Comorbidities requiring systemic CS therapy (such as asthma or inflammatory bowel disease). Systemic is defined as oral, rectal or any injectable route of administration (thus other routes are allowed, including inhaled, topical, ophthalmic, otic, and intranasal).

15. Use of cyclophosphamide within 6 months prior to the Screening Visit, or use of other immunosuppressants (eg, MMF, azathioprine, cyclosporine or other calcineurin inhibitors) within 1 month prior to the Screening Visit or expected use for the duration of the study

16. Use of systemic CS within 4 months from the Screening Visit or expected use for the duration of the study

17. Use of B-cell–directed biologic therapies such as blisibimod, belimumab, rituximab, ocrelizumab ever; use of other biologics (eg, anti-TNF, abatacept, anti-IL-6) within 6 months prior to or during Screening; or expected use of any of these agents for the duration of the study

18. Initiation or change in dose of statins, omega-3 fish oil, or dipyridimole, within 1 month prior to or during Screening or/and for the duration of the study

19. History or current diagnosis of any demyelinating disease such as, but not restricted to MS or ON

20. Active cardiac arrhythmia or clinically significant abnormality on ECG at the Screening Visit or on Day 1 (randomization) 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. This could include, but is not limited to, long QT syndrome, Wolff-Parkinson-White syndrome, or a malignant ventricular arrhythmia (eg, ventricular fibrillation or tachycardia) unless treated, as per central ECG reading at the Screening Visit and/or Investigator interpretation of the ECG at the Screening Visit or on Day 1 (randomization).

21. Presence of uncontrolled or New York Heart Association (NYHA 1994) Class 3 or 4 congestive heart failure at the Screening Visit:

    NYHA Class 3: Cardiac disease resulting in marked limitation of physical activity. Subjects are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.

    NYHA Class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

22. Major cardiovascular event(s) (eg, acute myocardial infarction, unstable angina or peripheral vascular disease symptoms, hospitalization for congestive heart failure, cardiac surgery, ischemic or hemorrhagic stroke, or transient ischemic attack) within 6 months prior to the Screening Visit

23. 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

24. 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 (ie, 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.

25. History, or current diagnosis, of active TB, or untreated latent TB infection (LTBI), 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. 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.

26. History of or positive human immunodeficiency virus, hepatitis C antibody and positive polymerase chain reaction, hepatitis B surface antigen (+), and/or hepatitis B core IgG and/or IgM antibody (+) at the Screening Visit

27. History of splenectomy

28. History of malignancy (hematologic or solid tumor) within 10 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

29. Immunization with live or live-attenuated vaccines (eg, measles-mumps-rubella, Herpes zoster, Yellow fever, and Influenza nasal mist) within 1 month prior to the Screening Visit or during the conduct of the study

30. Breastfeeding/lactating or pregnant women: any breastfeeding/lactation should have been discontinued at least 3 months prior to the Screening Visit

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

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

33. History of alcohol or drug abuse in the 1 year prior to the Screening Visit as per Investigator opinion or history of a urine drug screen positive for nonprescribed drugs

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

35. Treatment with other investigational agents within the last 3 months or 5 half-lives, or as per washout requirement from the previous protocol, whichever is longest, prior to the Screening Visit.

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 inclusion/exclusion 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.

Subjects who do not meet the above inclusion/exclusion criteria within the first screening episode and screen fail may undergo rescreening one time 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.

Chest X-ray and TB testing must be documented within 3 months of the rescreening visit or repeated during the Screening Visit. If immunizations for seasonal flu and for pneumococcal pneumonia with PPSV23 are up to date, then they do not need to be repeated. All other testing (including but not limited to ECG, hepatitis and HIV testing) is required to be redone at rescreening. Approval by the medical monitor is required prior to randomization.

5.4 Criteria for Initiation of Study Treatment

Eligible subjects will be randomized to treatment with atacicept or placebo through a central randomization process by an IWRS. This study will be double-blinded.

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.

5.4.1 Withdrawal from IMP or Discontinuation from Study Participation by the Subject

Subjects have the right to withdraw from treatment at any time. There are 2 types of withdrawal: (1) withdrawal from IMP (see Section 3.1.1); (2) complete withdrawal from the study.

1. Withdrawal from IMP

   If a subject withdraws from IMP, subject should undergo an ET Visit within 5 days of treatment withdrawal. After an ET Visit, subjects will complete the Safety FU visits at +4, +12, and +24 weeks from their ET Visit. After completion of the last Safety FU Visit, subjects will continue off-treatment FU visits every 12 weeks until they have completed either 72 weeks for Part A, or 156 weeks for if Part B is activated. Therefore, all subjects, regardless of IMP therapy, will be followed until the End of the planned DBPC treatment period.

2. Complete withdrawal from the study (see Section 5.4.3).

5.4.2 Withdrawal from IMP by Investigator or Sponsor

The subject must be withdrawn from IMP 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.
- 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 7.5.2).
- If disease activity is considered unacceptably high as per Section 6.4 and treatment escalation beyond permitted medication changes (Section 6.5.1) is warranted in the view of the Investigator. As per Section 6.5.2, discussion with the medical monitor should occur prior to discontinuing IMP for this reason.
- New onset MS or other demyelinating disease.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on Investigator judgement.
- Use of a nonpermitted medicine, as defined in Section 6.5.2. 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 6.5.3.
- Discontinuation of LTBI therapy before completion, if present at the Screening Visit.
- Serum IgG < 3 g/L, in those subjects taking every other week dosing.
- Surgery considered by the Investigator or Sponsor to be major.
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.

5.4.3 Withdrawal from the Study

Subjects are free to discontinue the study at any time without giving their reasons.

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

- Subject withdrew consent
- Death of the subject
- Subject lost to follow up
- Participation in another clinical trial

If a subject has failed to attend scheduled study assessments, the Investigator must determine and document the reasons and circumstances as completely and accurately as possible.

In case a subject has to be withdrawn from the study, the responsible designee medical monitor will be informed immediately, who will then inform the Sponsor's medically responsible individual (or Medical Responsible). All subjects who have received at least 1 dose of IMP and prematurely discontinue from treatment period (prior to Week 72 for Part A or Week 156 if Part B is activated), should be seen as soon as possible for an ET Visit, and undergo the assessments specified in the Safety FU period (see Schedule of Assessments, Table 1 or Table 2).

If there is a medical reason for withdrawal, 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 as agreed by the subject if the subject withdraws from the study, to ensure the subject receives the appropriate FU and care.

5.5 Premature Termination of the Study

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk-benefit judgment for any IMP. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP, or withdrawal of an IMP for safety reasons, or limitation of IMP supply.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.6 Definition of End of study

The end of study is defined as the last contact date with the last subject who participates in this study (ie, last subject's last visit).

6 Investigational Medicinal Product and Other Drugs Used in the Study

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

The atacicept protein is a soluble glycoprotein containing 313 amino acids, resulting from the fusion of human IgG1-Fc and the extracellular domain of the BLyS and APRIL receptor TACI, with a predicted mass of 35.4 kilodaltons. The product conformation is dimeric, and thus atacicept has a predicted mass of 73.4 kilodaltons. Atacicept is produced by Chinese hamster ovary cells. The molecular formula for atacicept is $C_{3104}H_{4788}N_{856}O_{950}S_{44}$. The human IgG1-Fc was modified

to reduce Fc binding to the C1q component of complement and the interaction with antibody receptors. Atacicept was tested and confirmed for reduction of these Fc effector functions.

Active IMP Product: dose/mode of administration/ dosing schedule: Atacicept is the active ingredient in the drug product. The IMP will be supplied by the Sponsor as a sterilized solution in a ready-to-use pre-filled type 1 glass syringe of atacicept prepared at a concentration of 25 mg/mL, 75 mg/mL or 150 mg/mL. The doses are supplied as single injections of 1.0 mL each. Dosing is intended as once weekly injections (also see Dose Frequency Reduction, Section 6.2).

Reference therapy: dose/mode of administration/dosing schedule: Placebo will be supplied as a sterilized solution for injection in pre-filled syringes matching the atacicept pre-filled syringes, each containing 1.0 mL.

Specific rules for treatment modifications: None

6.2 Dosage and Administration

Participants in this Phase II study will receive atacicept 25 mg, 75 mg or 150 mg (Part B only) or placebo as once weekly (QW) SC injections of 1 mL.

Table 3 summarizes the administration of IMP in the study for Part A and Part B.

Table 3 IMP Administration

Treatment Group	Estimated number of Subjects	Administration		
		SC Injection(s)	Frequency	Duration
Part A only				
Atacicept 25 mg	10	Single	QW	72 weeks
Atacicept 75 mg	10	Single	QW	72 weeks
Placebo	10	Single	QW	72 weeks
Part B (if activated, Part A subjects roll over to Part B)				
Atacicept 25 mg	25	Single	QW	156 weeks [a]
Atacicept 75 mg	25	Single	QW	156 weeks [a]
Atacicept 150 mg	25	Single	QW	156 weeks
Placebo	25	Single	QW	156 weeks [a]

SC=subcutaneously; QW=once weekly.
[a] Part B: 156 weeks includes the 72 weeks IMP administration from Part A.

The IMP must be injected SC into the abdomen (anterior abdominal wall) or thighs, using the pre-filled syringes and standard SC injection technique. Injection sites will be rotated for all doses and should be administered at least 5 centimeters away (approximately 2 inches) from the previous injection. The IMP should be administered in sites which do not have any existing skin pathology. The IMP should be administered at approximately the same time and day of each week.

Written instructions for administering the assigned dose will be provided at Day 1. In this occasion the first dose will be administered at the study site. The IMP kit will then be held at the clinic, to allow administration during Week 1 and Week 2 visits. At Week 2 visit, the first IMP kit will be dispensed to allow self-administration at home for Week 3. After Week 2 visit, IMP kits will be dispensed to subjects at each study visit up to Week 72 (for Part A) or Week 156 (if Part B is activated). After the first dose, subjects or caregivers will be permitted to administer the medication following instruction in injection technique and verification of satisfactory technique. Training of subjects (or a caregiver) on self-injection will be provided on Day 1/randomization and can be repeated at Week 1 (Day 8) or at additional visits as required per Investigator opinion (see Section 7).

When dosing during the week of a scheduled visit, and the dose is scheduled for the day of the study visit, it is expected the subject will not dose until after the scheduled visit assessments for that week are complete. The dose can otherwise be given up to ±2 days of the scheduled dosing day (except for the 1st and 2nd dose in the PK subgroup as the 24 hours post first and Day 8 predose PK time-points are important to be taken as scheduled). It is recommended that the weekly dose of IMP be taken on the same day of the week as the original dose. 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.

Dose Frequency Reduction

During the treatment period, subjects with large decreases in levels of serum IgG and who are at risk to develop severe hypogammaglobulinemia (serum IgG < 3g/L) will have DFRs or discontinuations according to the criteria specified below (ie, reduced from once weekly to once every other week [EOW]). The central lab will notify the IWRS that a subject will require DFR based on the criteria outlined in Table 4.

To maintain blinding of the treatment assignment, the IWRS will randomly select a predetermined number of subjects from the pool of placebo-treated subjects (enrolled globally in this study) to have DFR. Additionally, the dates of notification for these subjects will also be randomly selected from the 3-year treatment period (ie, a study week will be selected from among the scheduled study visits). The respective site(s) for these randomly-selected subjects will be notified on the randomly-assigned dates and instructed to reduce dose frequency for each selected subject.

The same notification text will be used to notify the sites for both subjects who meet DFR criteria and randomly-selected placebo-treated subjects. The subjects, sites, CRO and Sponsor will remain blinded.

The time from the serum IgG result at the Central lab to the site notification by the IWRS should be within ~3 days (before the subject is scheduled to receive the next weekly SC dosing of atacicept or placebo). All subjects whose dose frequency has been reduced will remain on EOW IMP administration throughout the remainder of the study.

Table 4 Dose Frequency Reduction for Subjects Taking Weekly Dosing

Week	Criteria	Reduction
Week 1	> 20% decrease in serum IgG from baseline (Day 1) and serum IgG < 5 g/L	Every other week
Week 2	> 25% decrease in serum IgG from baseline (Day 1) and serum IgG < 5 g/L	
Week 4	> 40% decrease in serum IgG from baseline (Day 1) or serum IgG < 4 g/L	
After Week 4	Serum IgG < 3.5 g/L	

For subjects taking EOW dosing, serum IgG will be retested after 4 weeks at a scheduled or unscheduled visit. If serum IgG is < 3 g/L, and this value represents the second consecutive finding of severe hypogammaglobuinemia (at least 4 weeks apart), the study drug will be discontinued. Criteria for IMP discontinuation are based on Suzuki 2013.

The central lab will notify the medical monitor that a subject meets the discontinuation criteria outlined in Table 4. The site will receive notification from the medical monitor to discontinue the subject and will follow the withdrawal instructions in Section 5.4.3.

Similarly, if serum IgG < 3 g/L results are observed during the Safety FU period, the site will be asked to confirm IMP discontinuation and retest serum IgG in 4 weeks (in case of first serum IgG < 3 g/L findings) and to strictly monitor for any signs or symptoms of infections (in case of a second consecutive serum IgG < 3 g/L at least 4 weeks apart).

Potential Adjustments in Dose Frequency Reduction Criteria

The DFR criteria have been designed based on medical knowledge and results from the APRIL-LN and other atacicept clinical studies. This criteria is expected to identify subjects at risk of developing severe hypogammaglobulinemia (serum IgG < 3 g/L). The number of subjects who will meet the criteria are expected to be low in this IgAN clinical trial since the subjects are required to have serum IgG levels ≥ 6 g/L at screening, and will not have background corticosteroids or immunosuppressants (neither newly initiated nor stable dosing is allowed).

However, should adjustment in the dose frequency criteria be required (eg, more subjects than expected meet the DFR criteria early in the study, or subjects develop IgG < 3 g/L without triggering the criteria for dose frequency reduction), a plan will be put into place wherein the IDMC will monitor the subjects and, should the need arise, will trigger a discussion and decision about adjusting the DFR criteria. Guidance for criteria adjustments will be included in the IDMC charter so that an independent decision can be made.

6.3 Assignment to Treatment Groups

In the beginning of the study (Part A), eligible subjects will be randomized in a ratio of 1:1:1 to receive placebo, atacicept 25 mg, or atacicept 75 mg by the IWRS. After at least 5 subjects per arm have had at least 12 weeks of study drug, the IDMC will convene to review the cumulative safety data. Taking into account IDMC approval, the Sponsor will determine whether or not the study may then proceed with 4 treatment arms, ie, placebo or atacicept 25 mg, 75 mg, or 150 mg by the IWRS (also see Section 5.1). The randomization ratio will be adjusted such that the

4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of futility analysis, and that the final sample size will be approximately 25 subjects per arm.

Treatment kits will contain enough medication for 4 administrations. At each visit when study medication is dispensed, the study staff will contact the IWRS to obtain appropriate kit numbers and the specified kits will then be dispensed. All other Sponsor and CRO study staff will be blinded to the study group assignment; refer to Section 6.10 for details on this aspect.

6.4 Non-investigational Medicinal Products to be Used

Rescue medications are medicines identified in the CTP as those that may be administered to the subject when the efficacy of the IMP is not satisfactory, in case of adverse reactions, or to manage an emergency situation. The Sponsor will not provide any rescue, permitted, or concomitant medications during the study.

Rescue medications to mitigate local effects of IMP which have occurred at the administration site (eg, Injection site reaction [ISRs]) are allowed as treatment. These may include topical or systemic antihistamines, topical CS, paracetamol, or nonsteroidal anti-inflammatory drugs. Subjects with concomitant severe hypogammaglobulinemia (serum IgG < 3 g/L) and severe infection can be considered for treatment with Ig supplementation. Any medications used should be recorded in the Electronic Case Report Form (eCRF).

If during the course of the study, IgAN disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes (Section 6.5.1) is warranted in the opinion of the Investigator, then IMP should be discontinued when a prohibited medicine is initiated. As there are no proven disease-modifying therapies for IgAN, the benefit of rescue therapy is not established.

If additional treatment is given due to unacceptable disease activity, and thus IMP discontinued, initiation of corticosteroid therapy may be considered, starting at up to a maximum dose of 0.8 mg/kg (and no higher than 60 mg/day of prednisone equivalent). In contrast, the initiation of immunosuppressants and/or biologics should be avoided for 12 weeks (approximately 5 half-lives of atacicept) after IMP discontinuation (according to the discretion of the Investigator).

Protocol-defined IgAN disease activity that may be considered unacceptably high as determined by the Investigator or Sponsor includes the following:

1. eGFR has decreased > 30% from baseline

2. Symptomatic nephrotic range proteinuria or UPCR (defined as > 3.5 g/day or mg/mg respectively), at any point during the study.

6.5 Concomitant Medications and Therapies

A prior medication is any drug or substance taken prior to the time the subject enters the Screening Visit, ie, up until the time at which they provide informed consent. All prior medications will be recorded on the eCRF, noting the name, dose, duration and indication of each drug.

Concomitant medication is defined as any medication, other than the study medication, which is taken during the study from the date of signature of informed consent until the end of study visit (Safety FU Week 24) or end of treatment visit (Week 72/ET for Part A and Week 156/ET for Part B), ie, the last visit for the subject, including prescription and over-the-counter medicines.

All concomitant medications taken by the subject during the study, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

See Section for rescue medications (Section 6.4).

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

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

Permitted medications (including rescue medications) are any medications that are required by the subject during the course of the study and which are not specifically prohibited by the CTP (see Section 6.5.2). Any such medications prescribed or used should be recorded in the eCRF.

Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers

All subjects will have begun treatment with ACEi and/or ARB at least 12 weeks prior to the Screening Visit, and will have been on a stable dose for at least 8 weeks prior to the Screening Visit and for the duration of Screening Period. The dose of ACEi and/or ARB should remain stable for the duration of the study.

All other antihypertensive medications, including diuretics, aldosterone antagonists, calcium-channel blockers and ß-blockers can be used at any time-point during the study per the Investigator and following current guidelines.

Statins, omega-3 fish oil, or dipyridamole are permitted, but it is recommended to keep doses stable.

Use of these additional treatments commonly given to subjects with IgA outside of above dose recommendations will incur protocol deviations but does not require IMP discontinuation. Any medications (other than those excluded by the CTP) that are considered necessary for the subjects'

welfare and will not interfere with the study medication may be given at the Investigator's discretion.

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.

Vaccinations

Subjects will be required to have up-to-date vaccinations against S. pneumonia (PCV13 or PPSV23) and influenza virus (as seasonally required) or to receive vaccinations against these pathogens during the Screening Period and at least 2 weeks prior to randomization. In addition, it is strongly recommended that Investigators review the subject's vaccine status, and ensure they remain up to date with pneumococcal vaccinations as per local guidelines during the study. Both the US Centers for Disease Control and World Health Organization recommend a single re-vaccination with PPSV23 > 5 years after a first vaccination. Influenza vaccinations should be kept up to date during the study, and administration documented at the start of each new season while subjects are enrolled in the study. Live and live-attenuated vaccinations will not be permitted during the study period (See Section 6.5.2).

6.5.2 Prohibited Medicines

The following treatments are not permitted during the study:

- Systemic CS (eg, oral, iv, or intramuscular)

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

- Cyclophosphamide or other immunosuppressants (eg, MMF, azathioprine, cyclosporine, or other calcineurin inhibitors)
- Biologic therapies other than IMP
- B-cell-directed therapies such as blisibimod, belimumab, or rituximab, or other biologics (eg, TNF inhibitors, abatacept, or tocilizumab)
- Vaccines: Live and live-attenuated vaccines (eg, measles-mumps-rubella, Yellow fever, and influenza nasal mist) are prohibited during the study. The effect of atacicept on the ability of the immune system to clear an infection which might be introduced with a live vaccine has not been evaluated in humans.

Use of any of the above nonpermitted medicines and therapies require IMP discontinuation (see Section 5.4.1) and results in treatment failure (see Section 8.3.2).

Refer to the inclusion and exclusion criteria (Section 5.3) for prohibited medications before and during the study. See also Section 5.4.1.

6.5.3 Other Interventions

Subjects must adhere to the following restrictions:

Women of Childbearing Potential

WOCBP must be willing to use a highly effective method of contraception for at least the past 28 days prior to randomization, throughout the study, and for at least 90 days after the last dose of IMP. See Section 5.3.1.

Other Therapies

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.

6.5.4 Special Precautions

Hypersensitivity

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, occurs, 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 7.5.4.4.

Cardiac disease/disorders

Patients with renal disease are at increased risk for cardiac disease, such as cardiac arrhythmias, cardiac failure, and coronary heart disease. Treatment with IMP must be temporarily discontinued in subjects who develop new onset or worsening of clinically significant symptomatic arrhythmias that require medical intervention (such as, but not limited to, paroxysmal atrial tachycardia, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome, or a malignant ventricular arrhythmia [eg, ventricular fibrillation or tachycardia]), or cardiac failure, cardiomyopathy, or cardiac ischemic symptoms. Once appropriately treated and controlled, the subject should be discussed with the Medical Monitor and evaluated for resumption of IMP or permanent discontinuation.

Infection

As atacicept has the potential risk of impairing the response to infection, subjects must be carefully examined for signs of infection and questioned about recent infective illnesses and recent vaccination(s). If, in the opinion of the Investigator, laboratory findings raise concern that there

may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section 5.3.

Caution should be exercised when administering atacicept to subjects with underlying conditions that may predispose them to infections. To further mitigate the risk of infection that may be associated with a possible large drop in IgG, serum IgG assessments are performed at each visit in a blinded fashion (with Medical Surveillance Team being unblinded) and a mechanism is in place for subjects who are at risk to develop severe hypogammaglobulinemia (serum IgG < 3g/L) (see Table 4 for DFR criteria), the study drug administration frequency will switch to EOW. This will allow early detection of such a potential drop and implementation of DFR. In addition, subjects will be discontinued at any point during the study, if serum IgG decreases below 3 g/L at two consecutive measurements performed at least 4 weeks apart (Suzuki 2013).

Subjects should be reminded of the importance of good hygiene practices, such as hand washing for their care providers and/or social contacts, especially those suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. Subjects should be advised to promptly report to the Investigator any signs or symptoms suggestive of an infection.

The Investigator will examine subjects for possible infections at scheduled visits, and unscheduled visits as appropriate. Any subject who experiences a serious, severe, or significant infection or who has experienced chronic or recurrent significant infections should be discussed with the Medical Monitor and evaluated with respect to continuation of IMP.

The risk of serious infection associated with atacicept 25 mg, 75 mg or 150 mg has been evaluated in RA and MS subjects, and the risk of 75 mg and 150 mg has been evaluated in the APRIL-SLE study (see Section 3.4.2). A greater proportion of subjects experienced infection and infestation-related SAEs in the atacicept 150 mg treatment groups compared with placebo (approximately 2% absolute increase). The 150 mg arm was discontinued prematurely following fatal infections in 2 subjects in the APRIL-SLE study.

Targeted B cell therapies, other than atacicept, investigated to date have demonstrated a greater tendency toward serious infectious risk in Asian populations compared with non-Asians. Of note, approximately 19% (89/455) of the study population in the APRIL-SLE study was Asian. In APRIL-SLE, there was no increased risk for serious infections with 150 mg atacicept compared to placebo in the Asian subjects, although serious infection risk was 10.3% higher in the subjects treated with atacicept 75 mg compared to placebo (75 mg 24.1% [7/29], 150 mg 9.7% [3/31], and placebo 13.8% [4/29]). Comparison of the proportions of subjects with serious infections in non-Asian subjects (75 mg 4.7% [6/128], 150 mg 7.1% [8/113], and placebo 5.6% [7/125]) demonstrated 1.5% more subjects with serious infections in the group treated with atacicept 150 mg but no increased risk for atacicept 75 mg compared to subjects who received placebo. Ongoing evaluation of serious infection risk associated with atacicept dosing regimens in the overall population and also in specific population subsets is an important component of risk management that will continue in current and future atacicept studies.

Other Withdrawal Criteria

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.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Subjects will be instructed by study site personnel to monitor for early signs of infection, such as upper respiratory symptoms, fever, painful urination, 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.

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in accordance with all applicable local regulatory requirements and GMP Guidelines.

Atacicept and placebo will be supplied to the investigational site in prefilled 1 mL glass syringes.

Atacicept and placebo will be packed in boxes containing 4 prefilled syringes each (enough for 4 administrations).

From the unique medication number on the labels together with the packaging documentation, full re-traceability is given according to the current GMP guidelines.

The information on the syringe and box labels will be in accordance with all applicable regulatory requirements.

All IMPs will be shipped to sites in cool transport containers that are monitored with temperature control devices.

All subjects will be provided with injection instructions and subject cards at the time of study entry. The cards will include at least the following information:

- Study title or short title and study number
- Contact details of the Investigator
- Subject ID (to be entered by the Investigator)
- Further information in case of emergency, including a point of contact for breaking the blind.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

All IMP is provided in prefilled syringes to the investigational site via cooled transport. No additional preparation is required at the site.

All IMP supplied to the site must be stored carefully, safely, in the original containers, and separately from other drugs. The storage facility at the study site should be locked and temperature-controlled. The IMP **must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light**. The IMP temperature will be monitored per the standard process for refrigerated medication and documented.

The IMP syringes should be removed from the refrigerator and maintained at room temperature for approximately 30 to 60 minutes prior to SC injection. Shaking of the syringes should be avoided. Additional details on the instructions for handling and storage will be provided in the drug administration instructions and provided to subjects as required for home injection.

Subjects or family members/caregivers who receive appropriate training will be permitted to administer IMP in this study. To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the IMP. Subjects will be provided with instructions on proper storage including instructions to store their IMP under refrigeration at 2°C to 8°C (36°F to 46°F) and not to leave their medicine unattended or in a place that might get too hot, eg, inside a car. Subjects should have access to refrigeration to store the IMP.

The IMP should NOT be frozen.

In the event of a temperature deviation at the investigational site, the site must contact the Clinical Research Associate/Monitor without delay for further evaluation and assessment by the designated QA personnel at Merck KGaA or delegated Contract Manufacturing Organization. The IMP with the temperature excursion should still be stored at the required temperature, but quarantined during the investigations and must be appropriately labeled as “quarantine storage”.

No IMP should be administered after the date of expiration indicated on the product packaging.

6.8 Investigational Medicinal Product Accountability

The Investigator (or designee) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.

- The inventory of IMP provided for the clinical trial and prepared at the site.
- The use of each dose by each subject.
- The disposition (including return, if applicable) of any unused IMP.
- Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject study numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present study. No IMP that is dispensed to a subject may be redispensed to a different subject.

Subjects will be required to return all unused syringes and used syringe boxes. Sharps containers will be provided to dispose of used syringes.

A Study Monitor will periodically collect the IMP accountability forms and will count all unused syringes. Thus, IMP accountability will only be based on the count of unused syringes. Used syringe boxes and sharps containers will be checked by a study monitor before authorizing their destruction by the study site. Sites should destroy syringes used for in-clinic dosing per institutional procedure after approval by the responsible monitor. This activity will be done if the standard procedure at the study site allows it, otherwise the study team will be authorized to destroy sharps containers with used syringes before the monitoring visit.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on visits defined in Section 7.1. All other dosing will be done by the subject or subject's caregiver at home throughout the rest of the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient IMP for at-home dosing until the next scheduled visit. Subjects will be instructed to return all unused IMP including the boxes at each clinic visit, in order to allow the assessment of compliance with study treatment.

6.10 Blinding

This study will be double-blinded. The double-blind will be strictly enforced during treatment and Safety FU periods for all subjects in Part A and Part B (if activated). The planned primary analysis will be performed by the Sponsor/CRO staff. After the primary analysis, the sites and subjects remain blinded until the end of the trial. A list of the restricted Sponsor/CRO staff who are required to be unblinded to the treatment code before, during, and after primary analysis will be pre-specified and documented in the study unblinding plan. Sponsor and CRO staff who are directly involved in the conduct of the study will remain blinded to individual subject data. The trial team will follow adequate standard operating procedures (SOPs) to guard against inappropriate dissemination of treatment codes outside of the approved list. Additionally, blinded pathologists will centrally review all kidney biopsies during the study.

Members of the IDMC will be unblinded for periodic safety review, and analysis after at least 5 subjects in each arm have completed at least 12 weeks of treatment prior to initiating the 150 mg

dose arm, and the planned interim futility review. The IDMC will review available data in a blinded fashion with the capability to review unblinded data as needed.

An Unblinded Firewall Team, composed of senior members from the Sponsor's departments in Clinical, Safety, Quantitative Pharmacology, and Biostatistics, will be unblinded for planned interim analyses, including one performed after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision, and the interim futility analysis (if Part B is activated) which will be performed after at least 60 subjects have completed the treatment period through Week 24. In order to preserve the integrity of the primary analysis, members of the Unblinded Firewall Team will not be further involved in the conduct and analysis of the study until unblinding of the study for the primary analysis. Bioanalytical scientist(s) as well as independent PK/PD modeler(s) will be unblinded to allow for sample analysis decision and preliminary PK/PD modeling activities, respectively. A Firewall Charter and unblinding plan will be established prior to access to any unblinded data can be granted.

Packaging and labeling will be prepared to protect the blinded nature of the study. Study medications will be provided in treatment kits containing 4 pre-filled syringes of IMP per kit. Pre-filled syringes of IMP (atacicept or placebo) will not be distinguishable from each other and will be covered by suitable labels to maintain blinding. 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.

After Day 1, results of analyses that can reveal the PD effects of atacicept in an individual subject will be blinded to the study site, the Sponsor, and the CRO. These analyses will include: immunoglobulins (IgA, IgM, and IgG), Gd-IgA1 (if corresponding assay is available), complements (C3 and C4), and flow cytometry of immune cells (including B cell and plasma cell levels). However, as detailed above (Table 4), a dose frequency adjustment or discontinuation of IMP may be necessary if decreases in serum IgG observed by the central lab meet pre-specified criteria. This dose adjustment can introduce bias as to the subject receiving atacicept and not placebo. To maintain blinding of the treatment assignment, the IWRS will randomly select a predetermined number of subjects from the pool of placebo-treated subjects to have dose frequency reductions at randomly selected time points during the 72-week or 156-week treatment period in Part A or Part B, respectively, of the trial.

The efficacy assessments of this study are based on objective criteria including serum creatinine and urinalyses. If the Investigator considers it necessary to review any of the above results for acute medical management of the subject after Day 1, then this should be discussed with the medical monitor.

6.11 Emergency Unblinding

There is no known antidote to atacicept, so symptomatic and supportive treatment of any suspected and related AE, if necessary, is clinically indicated. Treatment with intravenous Ig can be considered in situations of severe hypogammaglobulinemia (eg, serum IgG < 3 g/L) associated with infection.

The study blinding may be broken for an individual subject only in the case of an emergency when knowledge of the IMP is essential for the clinical management of the subject. Contact information for breaking the blind in an emergency will be provided on the subject emergency card handed out to each subject (see Section 9.4).

The Investigator will have the ability to break the blind with regard to IMP for any subject through the IWRS. However, the Investigator should make every effort to contact by telephone the responsible Medical Monitor or their designee to discuss the subject's emergency situation and the need to unblind prior to unblinding any subject, and must contact the Sponsor or designee by telephone within 1 working day after the event occurs without revealing to the Sponsor personnel the result of the code break. The Investigator will be able to access the subject's treatment assignment 24 hours a day through the IWRS, using a unique access code and user number (different from those used to assign subjects to treatment through the IWRS). Causality assessments if emergency unblinding is for an AE/SAE should be documented for the AE/SAE prior to unblinding. If the blind is broken, the Investigator must inform the responsible medical monitor or their designee immediately without revealing the result of the code break by telephone. The Investigator must record in the subject's eCRF and source documents the date of unblinding and the reason.

If emergency unblinding is required, the affected subject must be terminated early from the study and go into Safety FU. These subjects will also complete all assessments and procedures specified for the ET Visit before entering the Safety FU Period.

The blind may also be broken in the case of a pregnancy should the subject desire this information.

If an SAE is reported, the Sponsor's Global Drug Safety department or designee may unblind the treatment assignment for the individual subject. If an expedited regulatory report is required, this report will usually identify the subject's treatment assignment according to regulations. When applicable, an expedited blinded report will be sent to all Investigators in accordance with regulations.

The IDMC will have access to unblinded study data as defined by the charter.

6.11.1 Unblinding for Regulatory Authorities

In cases where unblinding is required for the purposes of reporting expedited safety events to country-specific regulatory agencies or IECs, the unblinding will be performed by an authorized person(s). A blinded version of any documents to be submitted to the authorities will be shared as appropriate with study staff and site personnel. Only the authorized person(s) within the CRO and regulatory affairs will have access to the unblinded version of any documents. The procedures for requesting and obtaining unblinded information and for maintaining the integrity of the data and clinical trial are outlined in the pharmacovigilance plan for this study.

6.12 Treatment of Overdose

An overdose is defined as a subject receiving more than 1 dose equivalent within ≤ 4 days.

Even if it does not meet other criteria for an SAE, any overdose must be recorded in the study medication section of the eCRF.

In addition, for monitoring purposes, any case of overdose – whether or not associated with an AE (serious or nonserious) – must be reported to the Sponsor's Global Drug Safety department or designee in an expedited manner using the appropriate reporting form (see Section 7.5.1.4).

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 opinion.

6.13 Medical Care of Subjects after End of Study

After a subject has completed the study including the Safety FU 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 Study Procedures and Assessments

Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

Upon subject's agreement, the subject's primary health care provider can be informed about the subject's enrollment in the study.

Vital signs should be done before any scheduled ECG (ECG should be performed before any PK, PD and laboratory samples are collected). Laboratory samples should be collected after PK sampling (if scheduled).

For subjects in the optional PK subgroup, the PK sample is to be taken before the study medication is administered. All PK samples, except at Day 2 and/or Day 3, must be taken within 25 hours prior to dosing, ie, the sample must be taken on the same day as, or the day before (but no more than 25 hours before), the subject is due to receive the next injection of the IMP. The PK samples at Day 2 and Day 3 are collected 24 hours following atacicept administration (ie, 24 hours post-first dose on Day 2 and 48 hours post-first dose on Day 3). In exceptional cases, on Day 2, and Day 3, the visits and blood sampling can be omitted if there are major logistical hurdles for the subject to attend this visit.

Unscheduled visits may occur at any time during the study in case of AEs (assessments to be performed according to the Investigator's judgement).

7.1 Schedule of Assessments

7.1.1 Screening Period

The subjects' 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 such as date of birth, self-reported race, ethnic origin, gender, weight, height, and body mass index (calculated by the CRO/Sponsor) will be collected at screening. Please refer to the Schedule of Assessments (Table 1 for Part A, or Table 2 for Part B).

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
- Obtain written release form for requesting archival renal tissue
- Obtain written informed consent for optional pre-treatment kidney biopsy prior to Screening procedures. The examination will be performed at the discretion of the site PI if deemed necessary as per SoC.
- Obtain additional written informed consent if participating in the pharmacogenetics (PGx) sampling, PK subgroup, as necessary
- Review inclusion and exclusion criteria
- Collect demographic data
- Complete medical and disease history (including 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)
- Document the criteria for IgAN diagnosis for eligibility
- Obtain history and status of medications, surgeries and other procedures, with particular attention to current and previous treatments for IgAN
- Assess vital signs: seated systolic and diastolic BP, pulse rate, oral temperature, height and weight measurements (see Section 7.5.4.1 for details)
- Perform standard, single, 12-lead ECG (see Section 7.5.4.3)
- Complete physical examination
- Obtain chest X-ray. The results of a chest X-ray within 3 months before the Screening Visit are acceptable if there are no clinical changes.
- Collect blood and fresh clean catch urine samples for routine laboratory tests (see Table 6). The laboratory tests will include:

  - Clinical chemistry and hematology
  - TSH
  - 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 for 24-hour urine total protein and UPCR (one for Screening and one for the Day 1 Visit)
  - Two spot urine specimen cups for home urine collection from clean-catch, midstream specimen of first morning void for spot UPCR and UACR, to be completed as soon as possible during the Screening Period and brought back to the next clinic visit (one for Screening and one for 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]
- Optional pre-treatment kidney biopsy is to be performed after collection of the above-mentioned urine samples during the Screening period, when subjects return the 24-hour urine collection and midstream clean-catch spot urine from the first morning void (collected at home), as per the Screening visit requirements.

PD analyses (see Section 7.7.3)

- Serum BLyS and APRIL levels
- Immunoglobulins: IgG

Other exploratory assessments

- Circulating proteins (see Section 7.7.4.1)

Safety

- Record AEs beginning after the informed consent form (ICF) has been signed.
- Review/record prior and concomitant medications
- Review/record vaccinations. Administer pneumococcal and seasonal injectable influenza virus vaccine, if needed (at least 2 weeks prior to randomization).

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 one additional time upon approval of the medical monitor (see Sections 5.4 and 5.3.2).

7.1.2 Double-blind, Placebo-controlled Treatment Period

At all site visits, the scheduled assessments must be performed before administration of the study medication.

Subjects will remain on site for at least 2 hours after the first and second injections of atacicept (Day 1 and Week 1) to monitor for any hypersensitivity reactions.

Non-fasting blood samples will be collected for all subjects.

Scheduled site visits after Day 1 may take place within ±3 days (Weeks 1 to 4), ±5 days (Weeks 8 to 48) and ±7 days (Weeks 60 to 156) of the protocol-specified day. PK samples taken as part of the PK subgroup must be taken on the scheduled day and time.

7.1.2.1 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 1 Visit as required.

Administration instructions will be provided, but may vary slightly per IRB approval. These dosing instructions will be reviewed with the subject/caregiver before leaving the site. Treatment kits will contain enough medication for 4 administrations. 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

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)
- Optional post-treatment kidney biopsy consent form
- Vital signs (BP, pulse rate, oral temperature) (see Section 7.5.4.1 for details)
- Standard, single, 12-lead ECG (see Section 7.5.4.3)
- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Section 7.5.3).
- Urine:

  - Urine sample from clean-catch mid-stream specimen of first morning void for UPCR, UACR, and urine protein electrophoresis (UPEP).
    - Subject will need the specimen cup before the morning of collection. Subject will collect the sample the morning of the clinic visit, and bring the sample to the visit.
  - 24-hour urine collected to measure proteinuria by total protein and
  - Urine sample from clean-catch mid-stream specimen collected during the clinic visit for urinalysis and urine sediments.
  - Urine pregnancy test for all WOCBP. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP.
- Dispense: One spot urine specimen cup for home urine collection from clean-catch, midstream specimen of first morning void for spot UPCR and UACR, to be brought to the next clinic visit.

PK (see Section 7.6)

- Blood samples will be collected **within 25 hours prior to the first dose** of IMP (predose) to assess levels of serum atacicept. The exact time and date of blood sampling should be recorded.
- Anti-drug antibodies (binding and neutralizing) (see Section 7.6.2).

PD analyses (see Section 7.7.3)

- Blood samples will be collected to assess serum BLyS and APRIL **prior to the first dose** of IMP (predose).
- Vaccine immunization titers: antibody titers to tetanus toxoid, diphtheria toxoid, and selected pneumococcal antigens (see Section 7.7.2)
- Serum immunoglobulins: IgG, IgA, and IgM
- Serum Gd-IgA1 if assay is available
- Serum complement C3 and C4

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Exploratory assessments

- Sampling for genotyping (PGx) (optional): At Day 1, a sample of blood will be collected from the subject. However, the blood sample may be collected any time after a subject has provided PGx consent to participate, and the subject is found to be eligible for the study.
- Gene expression profiling (see Section 7.7.4.2)

- Circulating proteins (see Section 7.7.4.1)
- Flow cytometry analyses in peripheral blood (see Section 7.7.3) (at selected sites only)
- Urine sample for exploratory markers (eg, cytokine proteins, RNA) (see Section 7.7)

Randomization

Part A only:

Eligible subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups by the IWRS. Subjects will receive 72 weeks of IMP treatment and will be treated as outpatients during the study.

Part B if activated:

Eligible subjects will be randomized to 1 of 4 treatment groups by the IWRS. The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment), and so that the final sample size is ~25 subjects per arm (total n = 100 subjects) to receive placebo, atacicept 25 mg, 75 mg or 150 mg.

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. This can be repeated at Week 1 or at additional visits as required per Investigator's opinion. If subjects and caregivers choose not to administer the IMP, injections will continue to be given at the site by a qualified member of the site staff (or by other healthcare personnel as the site staff deems appropriate).
- The first dose (on Day 1) 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.
- The study staff will record the exact time and location of dosing and monitor the following:
    - ISRs (local tolerability) (see Section 7.5.4.4).
    - Pulse and BP for 2 hours at approximately the following time points 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 7.5.4.5).
- During the week of a scheduled visit, the subject is expected not to dose until after the completion of the study visit for that week. It is recommended to administer the weekly dose of IMP on the same day of the week as the original dose. The IMP dose can otherwise be administered up to ±2 days from the scheduled dosing day. Exceptionally, a dose can be given up to ±3 days from the scheduled dosing day, as long as 4 days have passed from the

previous injection. In this case subsequent doses should be resumed on the same day of the week as the original dose.

PK sampling (post-first dose)

- If participating in the PK subgroup (see Section 7.6), additional blood samples will be collected only for PK analysis at the following time points 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.

7.1.2.2 Weeks 0 (Day 2) to Week 72

After completion of the Day 1/Randomization visit, the following visits will take place as follows:

Day 2 and/or Day 3 (only for subjects participating in the PK subgroup)

- A blood sample will be collected only for PK analysis at the following visits: **Day 2 (24 hours post-first dose), and/or Day 3**. The subject can be registered to this subgroup analysis through the IWRS (this will be done during the randomization process).
- Record concomitant medications, AEs, and local injection tolerability.

Week 1 (Day 8±3)

Predose Assessments

- Record vital signs (BP, pulse rate, and oral temperature) (see Section 7.5.4.1 for details)
- Disease-focused physical examination
- Dispense spot urine specimen cup, prior to the Day 15 Visit.

PK blood sampling (see Section 7.6)

- Blood sample for PK analysis at all scheduled visits will be collected **within 25 hours before the next scheduled dose of IMP** to assess trough levels of serum atacicept. The exact time and date of blood sampling should be recorded.

PD analyses

- Immunoglobulins: IgG, IgA and IgM

Exploratory assessments

- Gene expression profiling (see Section 7.7.4.2)

Safety

- Review prior and concomitant medications and therapies
- Record AEs

Treatment with IMP

- Instruct/review with subject (or caregiver) how to self-administer SC injection (**as needed**).
- The subject (or caregiver) will administer the IMP via SC injection under the close supervision of the study staff.
- The study staff will record the exact time and location of dosing and monitor the following:
- The study staff will monitor and record ISRs (local tolerability) (see Section 7.5.4.4). This will be monitored continuously throughout the treatment period.
- If hypersensitivity reaction occurs at any time, treat subject symptomatically (see Section 7.5.4.5).

Completion of Site Visit

- Administration instructions will be provided, but may vary slightly per IRB approval. These dosing instructions will be reviewed with the subject/caregiver before leaving the site.

Week 2 (Day 15±3)

Predose Assessments

- Record vital signs (BP, pulse rate, and oral temperature) (see Section 7.5.4.1 for details)
- Disease-focused physical examination
- Blood and urine samples will be collected for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Section 7.5.3).

Urine:

- Urine sample from clean-catch mid-stream specimen of first morning void for urine protein, urine creatinine, and urine albumin.
    - Subject will need the specimen cup before the morning of collection. Subject will collect the sample the morning of the clinic visit, and bring the sample to the visit.
- Urine sample from clean-catch mid-stream specimen collected during the clinic visit for urinalysis and urine sediments.
- Dispense spot urine specimen cup, prior to Week 4 (Day 29) visit

PK blood sampling (see Section 7.6)

- Blood sample for PK analysis at all scheduled visits will be collected **within 25 hours before the next scheduled dose of IMP** to assess trough levels of serum atacicept. The exact time and date of blood sampling should be recorded.

PD analyses

- Immunoglobulins: IgG, IgA and IgM

Safety

- Review prior and concomitant medications and therapies
- Record AEs.

Treatment with IMP

- Instruct/review with subject (or caregiver) how to self-administer SC injection (**as needed**)
- The subject (or caregiver) will administer the IMP via SC injection under the close supervision of the study staff.
- The study staff will record the exact time and location of dosing and monitor the following:
    - ISRs (local tolerability) (see Section 7.5.4.4). This will be monitored continuously throughout the treatment period.
    - If hypersensitivity reaction occurs at any time, treat subject symptomatically (see Section 7.5.4.5).

Week 4 (Day 29±3)

Predose Assessments

- Record vital signs (BP, pulse rate, and oral temperature) (see Section 7.5.4.1 for details)
- Standard, single, 12-lead ECG (see Section 7.5.4.3)
- Disease-focused physical examination
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Section 7.5.3) and PD analyses.

Urine:

- Urine sample from clean-catch mid-stream specimen of first morning void for urine protein, urine creatinine, and urine albumin.
    - Subject will need the specimen cup before the morning of collection. Subject will collect the sample the morning of the clinic visit, and bring the sample to the visit.
- Urine sample from clean-catch mid-stream specimen collected during the clinic visit for urinalysis and urine sediments.
- Urine pregnancy test for all WOCBP. A serum pregnancy will be done if the urine test is positive.
- Dispense spot urine specimen cup, prior to Week 8 (Day 57) Visit

PK blood sampling (see Section 7.6)

- Blood sample for PK analysis at all scheduled visits will be collected **within 25 hours before the next scheduled dose of IMP** to assess trough levels of serum atacicept. The exact time and date of blood sampling should be recorded.

PD analyses

- Blood samples will be collected to assess serum BLyS and APRIL
- Immunoglobulins: IgG, IgA and IgM
- Serum and urine Gd-IgA1 if assay is available

Exploratory endpoints

- Gene expression profiling (see Section 7.7.4.2)
- Circulating proteins (see Section 7.7.4.1)
- Flow cytometry at selected sites only
- Urine sample for exploratory markers (eg, cytokine proteins, RNA) (see Section 7.7)

Safety

- Review prior and concomitant medications and therapies
- Record AEs.

Treatment with IMP

- Instruct/review with subject (or caregiver) how to self-administer SC injection (**as needed**)
- The subject (or caregiver) will administer the IMP via SC injection under the close supervision of the study staff.
- The study staff will record the exact time and location of dosing and monitor the following:
    - ISRs (local tolerability) (see Section 7.5.4.4). This will be monitored continuously throughout the treatment period.
    - If hypersensitivity reaction occurs at any time, treat subject symptomatically (see Section 7.5.4.5).
- Site personnel should instruct subjects to return kits to the pharmacy before their expiry date and should ensure that new kits are dispensed when necessary

Completion of Site Visit

Following completion of all visit procedures described above, the subject may leave the site once the following procedures have been completed:

- Collect IMP and assess compliance

- Dispense IMP and instruct subject (or caregivers) to store IMP in accordance with the instructions on the label.
- Administration instructions will be provided, but may vary slightly per IRB approval. These dosing instructions will be reviewed with the subject/caregiver before leaving the site. Treatment kits will contain enough medication for 4 administrations. At each of these visits, site staff will contact the IWRS to obtain appropriate kit numbers and the specified kit will be dispensed.
- Instruct subjects (or caregivers) to take their IMP at approximately the same time and day each week. They should not take IMP for the weeks of a scheduled visit until the visit.

Site personnel should instruct subjects to return kits to the pharmacy before their expiry date and should ensure that new "extra" kits are dispensed when necessary.

Week 8 (Day 57±5); Week 16 (Day 113±5); Week 20 (Day 141±5); Week 32 (Day 225±5); Week 40 (Day 281±5); Week 60 (Day 421±7)

The same schedule of assessments as **Week 2** should be followed.

In addition:

- Urine pregnancy test for all WOCBP at every visit. A serum pregnancy test will be done if the urine pregnancy test is positive.
- Blood for **PK samples** should only be obtained **at Weeks 8, 16 and 40**.
- Collect IMP and assess compliance
- Dispense IMP and instruct subject (or caregivers) to store IMP in accordance with the instructions on the label.
- **At Week 20**, dispense 24-hour urine collection container prior to Week 24 (Day 169 ± 5)
- **At Week 40**, dispense 24-hour urine collection container prior to Week 48 (Day 337 ± 5)
- **At Week 60,** dispense 24-hour urine collection container prior to Week 72 (Day 505 ± 7)

Week 12 (Day 85±5).

The same schedule of assessments as **Week 4** should be followed, along with:

- Serum complement C3 and C4 for PD analyses.

Week 24 (Day 169±5)

The same schedule of assessments as **Week 4** should be followed along with:

- 24-hour urine collected to measure proteinuria by total protein and UPCR
- Spot urine for UPEP
- Serum Complement C3 and C4 for PD analyses
- Anti-drug antibodies

Week 48 (Day 337±5)

The same schedule of assessments as **Week 24** should be followed. In addition,

- Weight measurements
- Complete physical examination
- Optional post-treatment kidney biopsy
- Vaccine immunization titers: antibody titers to tetanus toxoid, diphtheria toxoid, and selected pneumococcal antigens (see Section 7.7.2).

Week 72 (Day 505 ±7)

The same schedule of assessments as **Week 48** should be followed. However, UPEP and optional post-treatment kidney biopsy will not be collected at this visit.

Additionally, if Part B is not activated, IMP administration and IMP distribution dispensing to subject will not take place.

All visits should occur within the timeframe as stated above.

Additional Visits if Part B is activated:

Week 84 (Day 589±7); Week 108 (Day 757±7); Week 120 (Day 841±7); Week 132 (Day 925±7); Week 144 (Day 1009±7)

The same schedule of assessments as **Week 8** should be followed. However, blood samples for PK to assess levels of serum atacicept will not be collected at these visits. At Week 84 (Day 589±7) and Week 144 (Day 1009±7), dispensed 24-hour urine collection container prior to Week 96 (Day 673±7) and Week 156 (Day 1093±7), respectively.

Week 96 (Day 673±7)

The same schedule of assessments as **Week 24** should be followed. In addition,

- Weight measurements
- Complete physical examination

Week 156 (Day 1093±7)

The same schedule of assessments as **Week 48** should be followed. However, optional post-treatment kidney biopsy will not be performed at this visit. IMP administration and IMP distribution dispensing to subject will not take place.

All visits should occur within the timeframe as stated above.

7.1.3 End of Treatment Visit (Early Termination)

Criteria for discontinuation are provided in Section 5.4.

Subjects who are discontinued from IMP will complete the ET Visit as soon as possible (within 5 days) after IMP discontinuation. These subjects should receive a 24-hour urine collection container no later than 1 day before the scheduled ET visit.

The same schedule of assessments as **Week 72** (if Part A only) or **Week 156** (if Part B activated) should be followed.

7.1.4 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 treatment (72 weeks for Part A only, or 156 weeks for Part B, if Part B is activated), the Safety FU period is 24 weeks, with visits at Weeks 4, 12 and 24.

For subjects who discontinue the IMP treatment prematurely, after an ET Visit, the length of the Safety FU period is either 24 weeks, or such that the sum of the IMP treatment period and the Safety FU period is 72 weeks for Part A only, or 156 weeks for Part B, if Part B is activated, whichever is longer, with visits at Weeks 4, 12, 24, and every 12 weeks thereafter.

Therefore, for each subject completing Part A only, the study is composed of an up-to-4 week Screening Period, a 72-week DBPC treatment Period, and a 24-week Safety FU period. Alternatively, if Part B is activated, the study is composed of an up-to-4 week Screening Period, a 156-week DBPC treatment Period, and a 24-week Safety FU period. If early discontinuation occurs, subjects will complete an ET Visit, and a Safety FU period, with visits at 4, 12, 24 weeks and every 12 weeks thereafter, until the end of the DBPC treatment period (Week 72 for Part A only, or Week 156 for Part B if Part B is activated) All visits will be conducted on an outpatient basis.

At the FU visits, the following assessments will be performed (see Table 1 for Part A or Table 2 for Part B), except where indicated otherwise. Where possible, the Investigator should schedule these visits to take place in the morning.

- Record Vital signs (BP, pulse rate, oral temperature) (see Section 7.5.4.1 for details)
- Disease-focused physical examination (see Section 7.5.4.2 for details)
- Blood and urine samples will be collected for routine laboratory tests (clinical chemistry, hematology, and urinalysis) as detailed in Section 7.5.3.

Urine:

- Urine sample from clean-catch mid-stream specimen of first morning void for UPCR and UACR
    - Subject will need the specimen cup before the morning of collection. Subject will collect the sample the morning of the clinic visit, and bring the sample to the visit.

- Urine sample from clean-catch mid-stream specimen collected during the clinic visit for urinalysis and urine sediments.
- Urine pregnancy test for all WOCBP (**Safety FU Weeks 4, 12, and 24; FU last visit**)

PK analyses: Blood samples will be collected for:

- PK analysis of serum atacicept (**Safety FU Weeks 4, 12 and 24 only**)
- Anti-drug antibodies (binding and neutralizing) (**Safety FU Weeks 12 and 24 only**) (see Section 7.6.2)

PD analyses: Blood samples will be collected for:

- Measurement of serum BLyS and APRIL (**Safety FU Week 24 only**)
- Immunoglobulins: IgG, IgA, IgM
- Serum Gd-IgA1 if assay is available (**Safety FU Week 12 and 24; every 12 weeks FU**)
- Serum Complement C3 and C4 (**Safety FU Week 12 and 24; every 12 weeks FU**)

Exploratory analyses

- Gene expression profiling (see Section 7.7.4.2) (**Safety FU Week 24 and FU last visit only**)
- Circulating proteins (see Section 7.7.4.1) (**Safety FU Week 24 and FU last visit only**)
- Urine for exploratory markers (see Section 7.7) (**Safety FU Week 24 and FU last visit only**)
- Flow cytometry analysis (see Section 7.7.3) (**FU Week 24 only**)

Safety

- Review prior and concomitant medications and therapies
- Record AEs.

7.2 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.

Medical history data (including previous illnesses) and physical examination will be performed.

All other baseline measurements such as safety laboratory parameters, ECG, and vital signs will be assessed.

7.3 Efficacy Assessments

Assessments for the endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B).

Clinical renal disease assessments:

- Proteinuria by spot UPCR, spot UACR, total protein and UPCR by 24-hour urine collection.
- Active urinary sediments by urinalysis with microscopic examination.
- Renal function by eGFR will be calculated as follows:
- 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 (ie, IgG, IgA, and IgM), Gd-IgA1 (if assay available), serum complement C3 and C4 levels, BLyS, and APRIL will be assessed.

Baseline (predose) levels of free BLyS and free APRIL will be measured in all subjects. Post-randomization (postdose) samples of BLyS and APRIL will only be analyzed if the appropriate assays are available for additional assessments of BLyS and APRIL in the presence of atacicept.

Circulating proteins (eg, cytokines, chemokines, and additional autoantibodies) and pharmacogenetics or gene expression (RNA) analyses may be performed.

Urine assessments:

Urinary exploratory markers (eg, IgG, IgA, IgM, Gd-IgA1 [if assay is available]), cytokine proteins (eg, BLyS, APRIL [if assay available]; cell pellet for cytospin and/or gene expression [RNA]) analyses from spot urine may be performed.

Renal tissues by archival and optional kidney biopsies:

Assessment of glomerular IgG, IgA, Gd-IgA1 (if assay is available), C3 and C4 deposition by immunofluorescence, and classification of IgAN parameters will be performed on: 1) archival kidney biopsy (if available) to evaluate the prognostic risk of renal progression (ie, loss of function), and 2) optional post-treatment kidney biopsy to evaluate the renal status at Week 48 and categorize the risk for progression to end-stage renal disease. Parenchymal expression analysis of BLyS and APRIL will be performed on archival kidney biopsy (if available) to evaluate the prognostic risk of renal progression (ie, loss of function). The degree of deposits (IgG, IgA, Gd-IgA1 [if assay is available], C3, C4) and BLyS and APRIL expression will be represented semiquantitatively (grade 0, no or trace; grade 1, mild; grade 2, moderate; grade 3, marked) in the mesangium and along the glomerular capillary loops, respectively. Tubular expression of BLyS and APRIL will be graded as follows: grade 1, mild; grade 2, moderate; grade 3, marked.

Scoring of renal tissues by immunohistochemistry will be performed using the Oxford-MEST classification of IgAN: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). The mesangial cellularity will be scored 0 (< 4 mesangial cells/mesangial area), 1 (4–5 cells), 2 (6–7 cells), and 3 (> 8 cells) for each glomerulus. The mean score of all glomeruli will be classified as M0 (≤ 0.5) and M1 (> 0.5). When more than half of glomeruli show score ≥ 1, the case will be classified as M1 without scoring each glomerulus. Segmental glomerulosclerosis and endocapillary hypercellularity will be categorized as either present (S1 and E1) or absent (S0 and E0). Tubular atrophy/interstitial fibrosis will be classified as T0 (0–25% of cortical area), T1 (26–50% of cortical area), or T2 (> 50% of cortical area).

7.4 Assessment of Safety

- **General assessments:** Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, and evaluation of AE/SAEs, with particular attention given to infections (serious), cardiovascular events, local tolerability (ISRs) and hypersensitivity reactions. The IDMC will meet at appropriate time(s) during the study. The IDMC will review available data in a blinded fashion with the capability to review unblinded data as needed. In the case of a safety concern arising, the IDMC members are allowed to request immediate unblinding of the partial or complete dataset.

  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.

- **Specific planned assessments or Adverse Events of Special Interest:** AEs of special interest (AESI) include: cardiac failure, ischemic heart disease, cardiac arrhythmia, infections, hypersensitivity reactions (including anaphylactic/anaphylactoid shock conditions, asthma/bronchospasm, and angioedema), and ISRs.

  A comprehensive safety review (AEs, SAEs, physical examinations, vital signs, ECGs, clinical laboratory tests) will be performed by the IDMC after at least 5 subjects in each arm have received at least 12 weeks of treatment. Based on this analysis, the IDMC will provide recommendation on whether or not to begin Part B.

7.5 Adverse Events

7.5.1.1 Adverse Event Definitions

Adverse Event

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/intensity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

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 usual activities.

Investigators must also systematically assess the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not suspected to be reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this CTP. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this CTP.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (eg, anemia, increased alanine aminotransferase) must be reported as the AE rather than just the abnormal value itself.

Serious Adverse Event

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening.

NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death given the degree or prognosis of illness that is present; it does not refer to an event that hypothetically might cause death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based on 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 an IMP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner as described in Section 7.5.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (eg, 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 (eg, 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 defined as baseline medical conditions, and are NOT to be considered AEs.

Worsening of underlying disease is not an AE and therefore not an SAE per se, rather an efficacy end-point, unless deemed to be causally related to IMP administration.

Data on outpatient emergency room visits and possible AEs leading to emergency room visits that do not lead to hospitalization will be recorded on the eCRF.

Pre-defined AEs of Special Interest for Safety Monitoring

Adverse events of special interest (AESIs) include infections, cardiac failure, cardiomyopathy or ischemic heart disease, hypersensitivity reactions (including anaphylactic reactions/shock and angioedema), and ISRs and should be reported as such in the eCRF. Additionally, infection and

cardiac event AESIs are to be reported using SAE forms within 7 days of knowledge of the event by the Investigator but otherwise as per procedures outlined in Section 7.5.1.4.

7.5.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be asked about changes in his/her condition. During the reporting period of the study (defined below) any unfavorable changes in the subject's condition will be recorded as AEs, whether 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 will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be reported using an AE Form in the eCRF as described in Section 7.5.1.4. All AEs should be followed until resolved, stabilized, the patient is lost to follow-up or reach the end of the reporting period.

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

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor or designee.

7.5.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is screened (date of first signature of informed consent) and continues through the study's post treatment follow-up period, defined as the Safety FU Period (Safety FU Week 4 through FU Week 24 and/or additional every 12-week FU when applicable until week 72 for Part A, or week 156 for Part B, if Part B is activated). SAEs occurring after a subject has taken the last dose of IMP will be collected throughout the subject's participation until the end of the study for the subject, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator feels the SAE was related to IMP, drug delivery system, or protocol procedure.

7.5.1.4 Procedure for Reporting Serious Adverse Events

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 designee. All reports should be transmitted using the SAESI Report Form, in the eCRF which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names,

addresses, and telephone and fax numbers for SAE reporting will be included in the study-specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form (if sent during eCRF unavailability) must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, 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. 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.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.5.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

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

The Investigator must report SAEs (particularly deaths) in accordance with applicable site-specific requirements to the IRB that approved the study.

In accordance with ICH GCP and the Japanese ministerial ordinance on GCP, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study." In particular and in line with respective applicable regulations, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). In addition, according to applicable regulations, the Sponsor/designee will inform the study Investigators and the Heads of the study sites of all SAEs which were reported to the health authorities. In accordance with the Japanese regulatory requirements concerning safety reporting the Investigator should place copies of the Safety Reports in the Investigator Site File. The Head of the study site should also maintain copies of safety reports appropriately.

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.

7.5.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the study (see Section 7.5.1.3) and are assessed for final outcome at the last FU Visit. All SAEs ongoing at the last 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 FU procedures are performed.

7.5.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.5.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to 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 according to the same process as described for SAE reporting in Section 7.5.1.4.

Investigators must actively follow up, document and report on the outcome of all these 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 Report 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 must be reported in an expedited manner as described in Section 7.5.1.4, while normal outcomes must be reported within 45 days after delivery.

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

7.5.3 Clinical Laboratory Assessments

The list of laboratory normal ranges will be supplied to Merck KGaA or its designee by the central laboratory prior to shipment of study IMP. Any change in laboratory normal ranges during the

study will additionally be forwarded to Merck KGaA/EMD Serono. Nonfasting blood samples will be collected. Laboratory data will be reported as Système International (SI) units.

Samples for the following laboratory tests will be collected at the visits specified in Table 1 for Part A or Table 2 for Part B. Sample collection, preparation and handling/shipment procedures are described in the Manual of Procedures.

Urine sampling and testing

Urine samples need to be collected in different ways for different tests (also see Table 5):

For the quantitative proteinuria assessments at the Screening Visit, Day 1, Weeks 24, 48, 72, 96, and 156, ET visit, a urine total protein and UPCR will be determined in an aliquot of a 24-hour urine collection. Subjects will be provided with the materials for conducting their 24-hour urine collections and will have to bring the collection to the clinic. 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, and within 5 days after the Screening Visit. 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 instructions: The 24-hour urine collection should begin 2 days 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.

Spot urine collection instructions: For all study visits except study Day 2, Day 3 and Week 1, there will be 2 spot urine samples collected.

- Spot urine sample from the first morning void of the day of the clinic visit (for UPCR, UACR and UPEP, as indicated per the schedule of assessments)
    - Obtained at home: Subjects will be provided with a urine cup and instructions for cleaning and midstream collection to provide a clean catch specimen, to capture this sample at home, the morning of their clinic visit, and bring it with them to the clinic.
- Spot urine sample from "fresh" urine collected during the scheduled clinic visit (dipstick and urine microscopy, including sediment).
    - Obtained at the clinic visit: Subjects will be provided a urine cup and instructions for cleaning and midstream collection to provide a clean catch specimen.

Urine pregnancy tests will be conducted using the random sample taken at the clinic visit.

All spot urine samples will be collected using a clean-catch, midstream method.

Table 5 Urine Sample Collection

Test	Specimen Collection	Metric or method
Quantitative proteinuria at the Screening Visit, Study Day 1, Weeks 24, 48, 72, 96, 156, and ET	24-hour urine collection	UPCR, Total protein
Quantitative proteinuria at all visits except Study Day 2, Day 3, and Week 1	Spot urine first morning void at home (clean-catch, midstream method)	UPCR, UACR
Urinalysis and microscopy at all visits except Study Day 2, Day 3, and Week 1	Random urine freshly collected during clinic visit (clean-catch, midstream method)	Dipstick tests and urine microscopy (including urine sediment)
Urine pregnancy test at all visits except at the Screening Visit, Study Day 2, Day 3, Day 8 and Day 15	Spot urine (from the random urine freshly collected during clinic visit above)	Urine pregnancy test
Urine electrophoresis at Study Day 1, Weeks 24, 48, 96, 156, and ET	Spot urine (from either type of random urine sample above)	UPEP

UACR=albumin to creatinine ratio; UPCR=protein to creatinine ratio; UPEP=urine protein electrophoresis.

If the female subject is actively menstruating at a visit where urine sampling is to be performed, urine sampling should be delayed by up to 2 weeks to be collected after menses is complete.

For WOCBP including those who are postmenopausal for less than 12 months, serum pregnancy tests will be performed at initial screening and urine pregnancy tests will be performed at the visits specified in Table 1 for Part A or Table 2 for Part B. It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 12 months or who are surgically sterile. Urine pregnancy tests will be performed locally.

Anti-drug antibody titers (binding and neutralizing) will be analyzed by the Sponsor's bioanalytical laboratory.

All other parameters will be analyzed at the central laboratory. Repeat laboratory testing may be required during the study for various reasons, eg, loss of sample en route to the central laboratory.

Table 6 Clinical Laboratory Evaluations

Chemistry Panel	Hematology (CBC)	Complete Urinalysis [a]	Other Tests
Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range) Calcium Serum creatinine	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	pH Leukocytes Nitrite Glucose Ketones Protein Blood **Urine sediment analysis**	Vaccine immunization titers (antibody titers to tetanus toxoid, diphtheria, and pneumococcal antigens) Serum IgG, IgA, IgM Serum C3 and C4 Flow cytometry analysis of total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and plasma cells, plasma

Chemistry Panel	Hematology (CBC)	Complete Urinalysis [a]	Other Tests
(eGFR will be calculated from serum creatinine using the CKD-EPI equation) Glucose Potassium Sodium Total protein Uric acid	Red blood cells White blood cells and differential	Urine red blood cells and white blood cells/high powered field Casts Organisms Crystals	blasts, and NK cells (at selected sites only) HBsAg, anti-HBc [total and IgM] (hepatitis B) 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 TSH Serum pregnancy test (β-hCG) required only for WOCBP Quantiferon test for TB
	Additional urinalysis [b]		
	Total protein from 24-hour urine collection UPCR from 24-hour urine collection UPCR from spot urine UACR from spot urine UPEP from spot urine Urine pregnancy test (performed in local laboratory)		

anti-HCV= antibodies to hepatitis C virus; anti-HIV 1 and 2= antibodies to human immunodeficiency virus 1 and 2; APRIL= a proliferation-inducing ligand; BLyS= B lymphocyte stimulator; CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; GFR= glomerular filtration rate; anti-HBc= antibodies to hepatitis B core antigen; HBsAg= Hepatitis B surface antigen; Ig (A, G, M)= immunoglobulin (A, G, M); NK= natural killer cells; PCR= polymerase chain reaction; PK= pharmacokinetics; TSH= thyroid stimulating hormone; UACR= urine albumin to creatinine ratio; UPCR= urine protein to creatinine ratio; UPEP= urine protein electrophoresis; WOCBP= women of childbearing potential.

a Spot urine samples for urinalysis will be collected during the site visit using a fresh, clean-catch, mid-stream method for urinalysis (microscopy).

b Spot urine samples will be collected from the FIRST MORNING VOID, using a clean catch, mid-stream method (for UPCR, UACR and UPEP). If the female subject is actively menstruating at a visit where urine sampling is to be performed, urine sampling should be delayed by up to 2 weeks to be collected after menses is complete.

7.5.4 Vital Signs, Physical Examinations, and Other Assessments

7.5.4.1 Vital Signs

Vital sign measurements (BP, pulse rate, oral temperature), weight and height will be measured prior to any other study-related procedures, at the visits specified in Table 1 for Part A or Table 2 for Part B. Height will be measured at the Screening Visit only. Weight will be measured at Screening, and yearly at Weeks 48, 72, 96 and 156.

- BP (systolic and diastolic) and pulse rate must be measured with the subject in a seated position, after at least 3 minutes resting.
- Oral body temperature
- Weight and height

Weight will be measured in kilograms and height will be measured in centimeters. Body weight will be measured with a balance beam scale if possible.

7.5.4.2 Physical Examination

A physical examination will be performed at the visits specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B). A complete physical examination will be performed at

the Screening Visit, Weeks 48, 72, 96 and 156/ET. All other physical examinations will be disease-focused.

Physical examinations driven by the subject's complaints upon questioning will be performed during the study as deemed necessary for routine medical care.

A complete physical examination will include the following body systems: General Appearance, Skin, Lymph Nodes (Cervical), Head, Ears, Eyes, Nose, Throat (HEENT), Neck, Thorax/Lungs, Cardiovascular, Abdomen, Musculoskeletal, and Neurological.

Disease-focused physical examinations will target the cardiovascular system (including peripheral edema), the Respiratory system, and the General Appearance of the subject.

At other visits, assessments should be performed as needed to fully obtain information needed to fully evaluate any subject complaints or AEs.

7.5.4.3 Resting 12-lead ECG

Digital ECGs for all subjects will be recorded at the site using an ECG machine provided by the central ECG vendor.

A standard, single, digital 12-lead ECG will be obtained after the subject has been resting quietly in supine position for 15 minutes. ECG recordings will be performed predose at the Screening Visit, predose Day 1, Weeks 4, 12, 24, 48, 72, 96, 156 and ET Visit (see Table 1 for Part A or Table 2 for Part B).

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 digital ECGs will also be electronically transferred to the central ECG laboratory to be read by a cardiologist. The result of the central read will be used for statistical evaluation of ECG data and for eligibility determination at the Screening Visit. The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values will not be recorded as AEs unless they are the reason for discontinuation of the study IMP due to AEs or are SAEs.

7.5.4.4 Local Tolerability (Injection Site Assessment)

Any local ISRs will be recorded as AEs and identified as AESIs in the eCRF, starting after first IMP administration and continuing through the treatment period (Weeks 0 to 156).

The most common ISR AEs form the basis for the definition of ISR in this study and are described below:

Redness

Grade	Description
0	NONE: No visible redness
1	MILD: ≤ 2 cm redness
2	MODERATE: > 2 to ≤ 5 cm redness
3	SEVERE: > 5 cm redness

Redness will be assessed by the Investigator or his/her designee. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe and photo-documentation, including a caliber, will be done and filed in the source documents.

Bruising

Grade	Description
0	NONE: No visible bruising
1	MILD: ≤ 2 cm bruising
2	MODERATE: > 2 to ≤ 5 cm bruising
3	SEVERE: > 5 cm bruising

Bruising will be assessed by the Investigator or his/her designee. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe and photo-documentation, including a caliber, will be done and filed in the source documents.

Swelling

Grade	Description
0	NONE: No swelling detected
1	MILD: Palpable 'firmness' only
2	MODERATE: ≤ 4 cm swelling
3	SEVERE: > 4 cm swelling

Swelling will be assessed by the Investigator or his/her designee. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe and photo-documentation, including a caliber, will be done and filed in the source documents.

Induration

Grade	Description
0	NONE: No induration
1	MILD: Able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
2	MODERATE: Able to slide skin, unable to pinch skin
3	SEVERE: Unable to slide or pinch skin

Induration will be assessed by the Investigator or his/her designee. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe and photo-documentation, including a caliber, will be done and filed in the source documents.

Itching

Grade	Description
0	NONE
1	MILD
2	MODERATE
3	SEVERE

The subject will be asked the degree of itching they are experiencing. An additional assessment by a physician will be made in case a local reaction has been evaluated as moderate or severe and photo-documentation, including a caliber, will be done and filed in the source documents.

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 (eg, injection site necrosis, injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (eg, injection site necrosis, injection site abscess, injection site cellulitis) rather than the term "injection site reaction".

Subjects who complete Week 72 for Part A or Week 156 for Part B with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required. All ISRs will be recorded as AEs using standardized criteria and pre-specified descriptive terms as provided by the Sponsor and according to Common Terminology Criteria for Adverse Events (CTCAE).

7.5.4.5 Suspected Hypersensitivity Reaction

In the event of a suspected hypersensitivity reaction to the IMP, the subject should be treated symptomatically (see Section 6.5.5).

7.5.4.6 Review of Concomitant Medications and Procedures

Data concerning concomitant medications and procedures will be collected throughout the study. These data will be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and through questioning of the subject. The information thus collected must be reviewed and assessed medically before it is transcribed to the eCRF.

7.5.4.7 Unscheduled Visits

Unscheduled visits may occur at any time during the study in case of AEs (assessments to be performed according to the Investigator's judgement).

7.6 Pharmacokinetics

PK assessments will be performed for atacicept in serum. Instructions for the collection, preparation, and handling/shipment of PK blood samples will be specified in the Laboratory Manual. Sample analysis will be performed under the supervision of the Sponsor.

Blood samples for PK analysis at all scheduled visits will be collected **within 25 hours before the next scheduled dose of IMP** to assess trough levels of serum atacicept. The exact time and date of blood sampling should be recorded.

Serum atacicept samples will be drawn at study visits according to the Schedule of Assessments in Table 1 for Part A or Table 2 for Part B. In a subgroup, additional serum atacicept samples will be drawn (PK subgroup) to capture the expected T_{max}. All concentration data will be incorporated into the integrated Population PK model to identify potential covariates and parameters relevant for the exposure and response predictions in this particular patient population with IgAN.

The data cut-off point for the futility analysis (Part B) (after at least 60 subjects have completed week 24 treatment period will also be used to start PK/PD modeling and simulation activities by an independent modeler in preparation of the final PK/PD modeling and simulation analyses, which will occur once the study is completed after database lock. Responsibilities and names of unblinded personnel will be specified in, and governed by, the unblinding plan.

Pharmacokinetics assessments for Part A

Blood samples for PK analysis will be collected pre-dose at Day 1 and then according to the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B) for the treatment and FU periods.

In addition, a subgroup of subjects (approximately 18 subjects with 6 subjects per each treatment arm) enrolled will have additional PK sampling visits that will be done at Day 2 and/or 3 after the first dose in order to capture the drug's T_{max}. The exact time and date of blood sampling should be recorded.

Pharmacokinetics assessments for Part B

Blood samples for PK analysis will be collected pre-dose at Day 1 and then according to the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B) for the treatment and FU periods.

When Part B is activated, approximately 6 subjects from the 150 mg arm will have additional PK sampling visits that will be performed at Day 2 and/or 3 after the first dose, to complement the PK sub-study group. The exact time and date of blood sampling should be recorded.

In total, approximately 24 subjects with approximately 6 subjects per each treatment arm will have additional PK sampling visits at the specified time points through Week 156.

7.6.1 Pharmacokinetics Calculations

The PK analysis of atacicept will be performed under the responsibility of the Sponsor according to the Sponsor's SOPs. Atacicept serum concentrations will be summarized for the time points presented in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B). The pre-dose sample will be considered as if it had been taken simultaneously with the administration.

Individual atacicept concentration data will be incorporated into the existing population PK model for atacicept in order to estimate typical population parameters and magnitude of the inter- and intra-individual variability in the studied indication as well as to identify covariate (eg, demography and renal function) factors that are significant predictors of variability. Exposure metrics of interest, eg, C_{max} and AUC will also be calculated based on this model, including eGFR as a potential covariate. In addition, PK and PD exposure-response relationships for selected endpoints of interest (eg, Igs) in this study population will also be investigated.

Details of the planned modeling work will be provided in an analysis plan.

7.6.2 Anti-Drug Antibodies

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 for Part A or Table 2 for Part B). 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. Instructions for the collection, preparation and handling/shipment of blood samples are provided in a manual of procedures. The samples will be analyzed under the supervision of Sponsor.

7.7 Other Assessments

7.7.1 Biomarkers

Instructions for the collection, preparation and handling/shipment of all biomarker samples are provided in a Manual of Procedures. Storage and analyses of samples will be handled according to the specifications as described in the Informed Consent Form

Serum biomarkers

The following markers may be evaluated: pre-dose serum BLyS and serum APRIL (post-dose only if assay available), serum IgG, IgA, and IgM, serum Gd-IgA1 (if assay is available), and serum C3 and C4, and/or other biomarkers of interest. Changes in serum IgG, IgA, IgM, Gd-IgA1, C3 and C4 may be predictive of disease development and severity and reflective of response to therapy in IgAN.

Urinary biomarkers

Urinary exploratory markers including but not limited to IgG, IgA, IgM, Gd-IgA1 (if assay available), cytokine proteins (eg, BLyS, APRIL if assay available); cell pellet for cytospin and/or gene expression (RNA) may be analyzed.

Renal Tissue by Histopathologic Assessments

Archival kidney biopsy specimens, if available before IMP treatment, will be assessed for baseline risk of renal progression in addition to the potential predictor of treatment response. The optional post-treatment kidney biopsy obtained at (a maximum of 4 weeks after) the end of 48 weeks of IMP treatment or ET (after at least 24 weeks of IMP treatment), may provide additional evidence of treatment effect on potential predictors of renal outcome. Modification of markers will be evaluated and compared between treatment groups: including (but not limited to) glomerular deposition of IgG, IgA, Gd-IgA1 (if assay is available) and C3, C4, the MEST parameters and renal parenchyma expression of BLyS and APRIL.

7.7.2 Vaccine Immunization Titers

In order to examine the impact of atacicept treatment on vaccine immunization titers, antibody titers to selected pneumococcal antigens, tetanus toxoid and diphtheria toxoid will be measured via blood samples at the visits specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B).

7.7.3 Pharmacodynamic Assessments

Blood and urine samples will be collected at the time points specified in Table 1 for Part A or Table 2 for Part B. 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 (eg, eGFR).

7.7.4 Exploratory Endpoints

Storage and analyses of samples will be handled according to the specifications as described in the ICF.

Instructions for the preparation and handling/shipment of the samples are provided in a Manual of Procedures.

7.7.4.1 Circulating Proteins

Blood and urine samples will be collected at the time points specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B). The final list of markers will be based on the available technologies and on the results of other atacicept studies.

Potential associations between drug response (efficacy or safety) and circulating proteins (eg, cytokines, chemokines, and additional autoantibodies) may be evaluated.

7.7.4.2 Gene Expression

Blood and urine samples will be collected at the time points specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B).

The gene expression objectives are to identify potential association of gene expression profiles, before and after atacicept treatment, with drug response, efficacy and safety.

7.7.4.3 Pharmacogenetics

Analyses are planned to identify potential associations of genetic variations with safety events, drug response, and treatment efficacy.

All subjects who are enrolled in the study will be eligible to participate in an optional PGx analysis (except subjects in countries where collection of PGx samples is not allowed). The analysis will be performed in eligible subjects from blood samples taken preferably prior to study therapy. Participation is optional and a specific PGx ICF will have to be signed by the subjects who choose to participate.

The results of the genetic analysis are for research purposes only. The results of the genetic tests will not be made available to the subject, members of the subject's family, the subject's personal physician, or other third parties, except as specified below.

Unless otherwise required by law or by regulatory authorities for the purpose of verifying information obtained from this study, only the Sponsor's authorized personnel and agents will have access to the confidential genetic data. The results of the PGx part of the study may be submitted to the regulatory authorities and governmental agencies in countries where the IMP may be considered for approval; however, the subject will be identified by study number and subject number only. The subject will not be identifiable in reports or publications resulting from this study.

7.7.4.4 Immune cell subsets by Flow Cytometry Analysis (at Selected Sites Only)

Blood samples for immune cell subset by flow cytometry analyses will be collected at the time points specified in the Schedule of Assessments (Table 1 for Part A or Table 2 for Part B).

Total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and PCs, PBs, and NK cells may be measured. This assessment will be carried out only on samples derived from selected clinical centers.

8 Statistics

8.1 Sample Size

Sample size justification for Part A

Part A for this Phase II study is designed to evaluate safety, PK, and PD during the 72-week treatment period with atacicept compared to placebo in subjects with IgAN with persistent proteinuria ≥ 1 mg/mg by UPCR at Screening or within 12 months prior to the Screening Visit, or ≥ 0.75 mg/mg during Screening, while on a stable dose of ACEi and/or ARB (considered optimal by the Investigator). While the sample size of 10 subjects per arm in Part A is deemed sufficient

to capture a treatment effect in terms of safety, PK and PD, it is not based on statistical power since no hypotheses will be tested. Particularly, based on observations of Week 24 data for the 75mg atacicept arm in the ADDRESS II study, this sample size will support the detection of a treatment effect in IgA (40% with standard deviation (SD) 20%) with 98% power, or a treatment effect in IgG (25% with SD 20%) with 75% power, both for a two-sided Fisher's exact test with 5% type 1 error. The PK-PD relationship will be explored as data permit.

Sample size justification for Part B

The primary endpoint of Part B is the percent change from baseline in proteinuria at Week 48 (based on UPCR from 24-hour urine collection). The dose-response of the primary endpoint will be analyzed using the dose-finding method Multiple Comparison Procedures with Modeling Techniques (MCP-Mod) (Bretz 2005). The advantage of MCP-Mod is to combine multiple comparison and modeling techniques in choosing the appropriate dose response curve from several pre-defined candidate parametric models while preserving the family-wise error rate for the study. Additionally, for a chosen dose-response curve, MCP-Mod allows to estimate the minimum effective dose (MED) and the target dose (TD) based on pre-defined criteria. In this study, the MED is the smallest dose demonstrating a proteinuria decrease of at least 20% from baseline over placebo; the TD is the closest dose demonstrating a proteinuria decrease of at least 40% from baseline over placebo.

The sample size is planned to primarily support the dose-response testing via MCP-Mod method and calculated using the R package Dose Finding (Version 0.9-11, Date: 2014-02-11).

The following 4 parametric models are considered for dose-response: E_{max}, Linear, Logistic, and Quadratic. "Figure a" in Figure 3 shows the pre-specified dose-response curve of each model. The pre-specified dose-response models are chosen based on the prior dose-response information obtained from previous studies of atacicept in other immunology indications, eg, RA and SLE, where E_{max} or Linear dose-response were suggested. Logistic and Quadratic models are added to account for model uncertainty.

In the dose-response models, the maximum effect size assumption of 40% on proteinuria reduction over placebo is based indirectly from the observed significant PD effect of atacicept on IgG and IgA in the clinical studies conducted of other indications such as SLE and RA, and expecting the strong PD effect would translate into the treatment effect on proteinuria. The assumption is also indirectly supported by external evidence of anti-BLyS agent (blisibimod) in a 24-week treatment study for SLE patient showing blisibimod significantly reduced proteinuria in a subgroup of SLE patients whose baseline proteinuria > 1-6 g/day (baseline mean 1.8-2.0 g/day) (Petri 2012; Furie 2012). In a post-hoc analysis it showed that at Week 24, the pooled blisibimod doses (3 dosing regimens) resulted in a mean reduction in proteinuria of 0.73 g/day (-35.0%) compared to 0.24g/day (-5.1%) in the pooled placebo group ($p = 0.045$, $n = 21$-22 per group); and the reduction in proteinuria in the highest dose (200 mg QW) was 0.96 g/day (-50.1%) compared with an increase of 0.16g/day (+17.7%) in the matched placebo group ($n = 5$-8 per group).

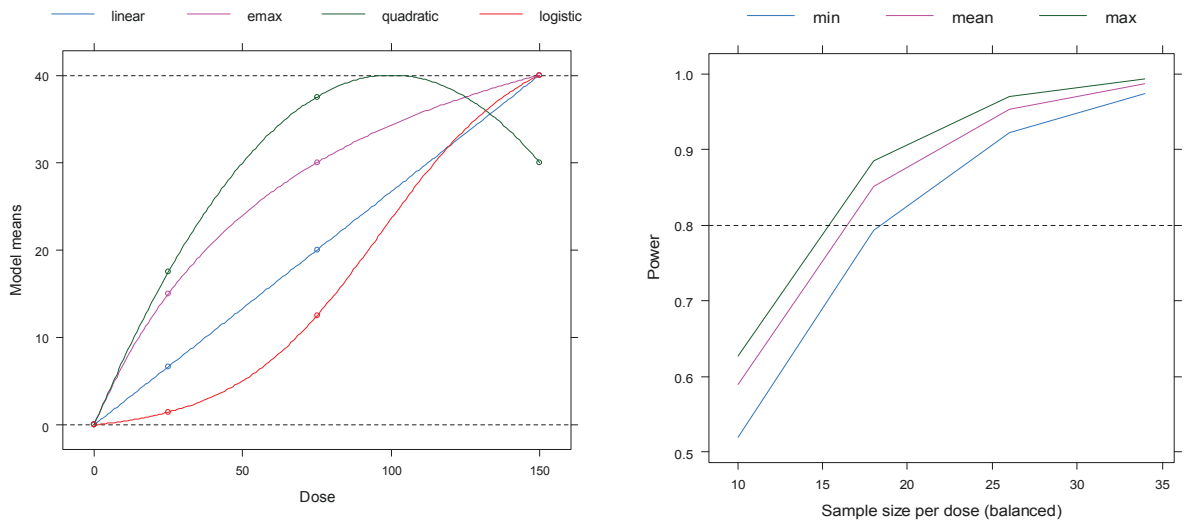
The standard deviation (SD) for proteinuria percent change from baseline is indirectly estimated based on the blisibimod data. The SD of 40% is assumed for sample size planning.

Given the effect size and SD assumptions, it is estimated that 20 evaluable subjects per arm for an equal randomization ratio will provide at least 80% power to demonstrate a statistically significant dose-response at the 2-sided 5% alpha level. Evaluable subjects in Part B are define as subjects who have proteinuria values (based on UPCR from 24-hour urine collection) for both baseline and Week 48. Taking into account 20% non-evaluable subjects by Week 156, the planned total sample size is thus 100 subjects (~25 subjects per arm) randomized to placebo, atacicept 25 mg, atacicept 75 mg, and atacicept 150 mg.

The loss in power associated with misspecification of the parameters in the dose-response model is often found to be negligible for reasonable candidate models (Bornkamp 2009). "Figure b" in Figure 3 displays a relationship between power and sample size for the dose-response models used in this study. For a given sample size per dose, it shows the minimum, average, and maximum power achieved from the 4 dose-response models.

Figure 3 Dose-response Models and Sample Size and Power Calculations

Figure a. Dose-response models *Figure b. Sample size and Power*



8.2 Randomization

The randomization ratio will be adjusted such that the 4 treatment arms will be approximately balanced when a total of 60 subjects are randomized with ~15 subjects per arm at the time of interim futility analysis (when at least 60 subjects have completed 24 weeks of treatment), and so that the final sample size is ~25 subjects per arm (total n = 100 subjects) to receive placebo, atacicept 25 mg, 75 mg or 150 mg. Randomization will be stratified according to the following stratification factors: baseline proteinuria (UPCR < 2 mg/mg vs ≥ 2 mg/mg, based on the Screening 24-hour urine collection) and race (Asian vs non-Asian). Randomization will be conducted in permuted blocks.

Subjects will be randomized by a central IWRS randomization provider. Additional technical and logistical information related to randomization and treatment group assignment can be found in Section 6.3.

8.3 Endpoints

8.3.1 Part A

Primary Endpoint

- AEs, AESI, AEs leading to discontinuation, SAE, and AEs leading to death

Secondary Endpoints

- Serum atacicept concentrations at pre-specified time points (Additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects [~ 6 subjects per treatment group])
- Change from baseline levels (as defined in) of Ig classes (IgG, IgA, and IgM) (g/L) at pre-specified time points
- Change from baseline in serum Gd-IgA1 levels at pre-specified time points, if corresponding assay is available
- Change from baseline in serum complement C3 and C4 levels at pre-specified time points
- Change from baseline in immune cell subsets by flow cytometry analysis at pre-specified time points
- Change in urine immuno-electrophoresis pattern and quantitative analysis of urinary IgG, IgA and IgM levels at pre-specified time points
- Anti-drug antibody assessment at pre-specified time points
- Clinically significant vital signs, ECGs and laboratory assessments

Other Endpoints

- Change from baseline in proteinuria at pre-specified time points, determined by 4 different assessments:
    - Total protein (g/day) by 24-hour urine collection
    - UPCR (mg/mg) by 24-hour urine collection
    - UPCR (mg/mg) by spot urine collection
    - UACR (mg/mg) by spot urine collection
- Complete clinical remission at each time point. Complete clinical remission is defined as having UPCR < 0.3 mg/mg and urine Red Blood Cells < 5/high power field by spot urine over, at minimum, a 24-week period.
- Complete proteinuria remission at each time point. Complete proteinuria remission is defined as UPCR < 0.3 mg/mg by spot urine

- Disease remission at each time point. Disease remission is defined as having UPCR < 0.2 mg/mg by spot urine and reduction of eGFR < 5 mL/min/1.73m^2 from the baseline level (Rauen, 2015)
- Complete renal response at each time point. Complete renal response is defined as having UPCR < 0.3 mg/mg by spot urine and ≤ 10% reduction of eGFR from the baseline level
- Partial renal response at each time point. Partial renal response is defined as having UPCR with > 50% reduction by spot urine and ≤ 25% reduction of eGFR from the baseline level
- Progressive kidney failure at each time point. Progressive kidney failure is defined as having ≥ 40% reduction of eGFR from the baseline level, the development of ESRD (ie, a need for maintenance dialysis or kidney transplantation), or death due to kidney disease (Lv 2017)
- Change from baseline in eGFR at pre-specified time points through Week 72
- Change from baseline in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid at pre-specified time points.

Exploratory Endpoints

- Correlation of serum BLyS and APRIL, baseline and change from baseline (if assay is available), with clinical response and/or safety
- Correlation of exploratory markers (eg, genetic variants [gene expression profiles, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety
- Scoring of renal tissues by immunohistochemistry using the Oxford-MEST classification of IgAN: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T).
- Glomerular IgG, IgA, Gd-IgA1, C3 and C4 deposition; measured by immunohistochemistry and/or immunofluorescence. BLyS and APRIL, expression in renal tissues
- Correlation of above histopathology parameters with clinical response (ie, proteinuria, eGFR) and/or safety

8.3.2 Part B

Primary Endpoint

- Percent change in proteinuria from baseline at Week 48 (based on UPCR derived from 24-hour urine collections). The baseline value will be determined by the average of the values at Screening and Day 1 for UPCR.

Secondary Endpoints

- Proportion of subjects with UPCR < 1 mg/mg and ≥ 25% decrease from baseline (taken from the 24-hour urine collection) with stable eGFR (with < 15% reduction from the baseline level) at Week 48

- Change from baseline in eGFR at Week 156
- AEs, AESI, AEs leading to discontinuation, SAE, AEs leading to death
- Clinically significant vital signs, ECGs and laboratory assessments

Other Endpoints

- For each of the following endpoints, proteinuria will be determined by 4 different assessments:
    1. Total protein (g/day) by 24-hour urine collection
    2. UPCR (mg/mg) by 24-hour urine collection
    3. UPCR (mg/mg) by spot urine collection
    4. UACR (mg/mg) by spot urine collection
    - Proportion of subjects with ≥ 25% decrease from baseline in proteinuria and to less than 1 (g/day for total protein or mg/mg for) with stable estimated glomerular filtration rate (eGFR) (with < 15% reduction compared to baseline level) at pre-specified time points
    - Proportion of subjects with ≥ 50% decrease in proteinuria with stable eGFR (with < 15% reduction compared to baseline level) at pre-specified time points
    - Proportion of subjects with proteinuria < 0.5 (g/day for total protein or mg/mg for UPCR) at pre-specified time points
    - Proportion of subjects with time-averaged proteinuria < 1 (g/day for total protein or mg/mg for UPCR) at pre-specified time points. Time averaged proteinuria is defined as the average proteinuria over a 24-week time window. At Week 156, time averaged proteinuria will also be computed as the average proteinuria over the 156-week treatment period
    - Change from baseline in proteinuria at pre-specified time points
- Complete clinical remission at each time point. Complete clinical remission is defined as having UPCR < 0.3 mg/mg and urine Red Blood Cells <5/high power field by spot urine over, at minimum, a 24-week period.
- Complete proteinuria remission at each time point. Complete proteinuria remission is defined as UPCR < 0.3 mg/mg by spot urine
- Disease remission at each time point. Disease remission is defined as having UPCR < 0.2 mg/mg by spot urine and reduction of eGFR < 5 mL/min/1.73m^2 from the baseline level (Rauen, 2015)
- Complete renal response at each time point. Complete renal response is defined as having UPCR < 0.3 mg/mg by spot urine and ≤ 10% reduction of eGFR from the baseline level
- Partial renal response at each time point. Partial renal response is defined as having UPCR with > 50% reduction by spot urine and ≤ 25% reduction of eGFR from the baseline level

- Progressive kidney failure at each time point. Progressive kidney failure is defined as having ≥ 40% reduction of eGFR from the baseline level, the development of ESRD (ie, a need for maintenance dialysis or kidney transplantation), or death due to kidney disease (Lv 2017)
- Poor renal outcome, defined as at least one of the following criteria: ≥ 30% decrease in eGFR (sustained for at least 4 weeks), ESRD (eGFR ≤ 15 mL/min/1.73m^2, dialysis, or renal transplant), or who died from renal or cardiovascular causes up to and including Week 156; in addition, the proportion of subjects with individual components of this composite endpoint.
- Change from baseline in eGFR at pre-specified time points
- Serum atacicept concentrations at pre-specified time points (Additional PK sampling will be done on Days 2 and/or 3 in a subgroup of study subjects [~6 subjects per treatment group])
- Change from baseline levels of Ig classes (IgG, IgA, and IgM) (g/L) at pre-specified time points
- Change from baseline in serum Gd-IgA1 levels at pre-specified time points, if corresponding assay is available
- Change from baseline in serum complement C3 and C4 levels at pre-specified time points
- Change from baseline in immune cell subsets by flow cytometry analysis at pre-specified time points
- Change in urine immuno-electrophoresis pattern and quantitative analysis of urinary IgG, IgA and IgM levels at pre-specified time points
- Change from baseline in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid at pre-specified time points
- Anti-drug antibody assessment at pre-specified time points.

Exploratory Endpoints

- Correlation of serum BLyS and APRIL (Day 1 as baseline and change from baseline, if assay is available) with clinical response and/or safety
- Correlation of exploratory markers (eg, genetic variants [gene expression profiles, immune cell subsets by flow cytometry, and circulating protein profiles) with clinical response (ie, proteinuria, eGFR) and/or safety (AEs, laboratory assessments)
- Scoring of renal tissues by immunohistochemistry using the Oxford-MEST classification of IgAN: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T).
- Glomerular IgG, IgA, Gd-IgA1, C3 and C4 deposition; measured by immunohistochemistry and/or immunofluorescence. BLyS and APRIL (if assay is available) expression in renal tissues
- Correlation of above histopathology parameters with clinical response (ie, proteinuria, eGFR) and/or safety

8.4 Analysis Sets

For purposes of analysis, the following populations are defined:

Table 7 Analysis Sets

Population	Description
Enrolled	All participants who sign informed consent
Intent-to-treat	The Intent-to-treat (ITT) population consists of all randomized subjects.
Modified Intent-To-Treat	The modified intent-to-treat (mITT) population is defined as all randomized subjects who have received at least 1 dose of the IMP.
Per-Protocol	The PP population consists of all patients in the mITT population who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the Statistical Analysis Plan (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.
Safety	The safety population consists of all randomized subjects who receive at least 1 dose of IMP and have at least one post-dose assessment. The safety population is the analysis population for the safety endpoints.
Pharmacokinetic	The PK population consists of all randomized subjects without protocol deviations affecting PK who were administered at least 1 dose of the IMP and have at least one evaluable PK sample. All PK evaluations (eg, descriptive statistics) will be based on this analysis set.

Subjects in the ITT, mITT and PP populations will be analyzed according to their randomized treatment and subjects in the safety and PK population will be analyzed according to the actual treatment received during the study. The dose-response analysis will be performed using all evaluable subjects at Week 48 in the mITT population. The primary efficacy analysis will be performed using the mITT population. Evaluable subjects in Part B are define as subjects who have proteinuria values (based on UPCR from 24-hour urine collection) for both baseline and Week 48.

8.4.1 Subgroups

Analysis of efficacy variables may also be performed on subgroups of interest and will be outlined in the Statistical Analytical Plan (SAP).

8.5 Description of Statistical Analyses

Analyses, where indicated below, will be performed depending on whether or not Part B of the study is activated. If Part B is activated, the primary analysis (Week 48 analysis) is the basis of statistical inference for hypothesis testing, while analyses at Weeks 96 and 156 will support long-term treatment evidence for safety and efficacy.

- Interim analysis (Part A): may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other

biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team.

- Interim futility analysis (Part B): performed by an independent statistical center after 60 randomized subjects (60% of total subjects) have completed 24 weeks of treatment. The proteinuria and other biomarker changes from baseline at Week 24 will be evaluated for futility by the IDMC and the Sponsor's internal unblinded Firewall team. Kidney biopsy results from these subjects will also be reviewed to determine the need for collecting kidney biopsy samples for the remainder of the study. The criteria for the decision based on the futility analysis will be detailed in the IDMC charter/SAP.
- Week 48 analysis (primary analysis) (Part A or Part B): performed after all randomized subjects have completed the scheduled Week 48 Visit or have discontinued from study. After the Week 48 analysis, the sites and subjects remain blinded while the trial is ongoing.
- Week 96 analysis (Part B): performed after all randomized subjects have completed the scheduled Week 96 Visit or have discontinued from study.
- Week 156 analysis (Part B): performed after all randomized subjects have completed the scheduled Week 156 Visit or have discontinued from study.
- Final analysis (Part A or Part B): will be performed after all randomized subjects have completed the Safety FU Period or have discontinued the study.

8.5.1 General Considerations

A detailed SAP will be finalized and approved prior to the database lock for the Week 48 analysis.

Continuous variables will be summarized descriptively using the number of observations, means, SD, median, 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 (eg, on some occasions, percentages may be calculated out of the total number of subjects with available data at a particular time point).

All tests of treatment effects will be conducted at a 2-sided α-level of 0.05. P-values and the 95% confidence intervals will be presented where applicable.

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings or country findings will be considered if necessary. For those measures that are analyzed using change from baseline scores, observed scores may also be presented descriptively.

Any changes in the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other changes to the planned data analysis that does not require a protocol amendment will be described in the SAP and the Clinical Trial Report. Additional exploratory analyses will be conducted as deemed appropriate.

8.5.2 Analyses of Part A

As indicated above, the primary analyses at Week 48 of Part A will be performed only if Part B is not activated. If performed, analysis of all endpoints will be descriptive in nature. Summary tables with descriptive statistics will be presented for all endpoints. Box plots, spaghetti plots, and scatter plots may also be created to present the data over time and to explore correlation between endpoints. P-values may be presented as nominal. Particularly, continuous variables may be compared between treatment groups by the Wilcoxon-Mann-Whitney test, categorical variables may be compared between treatment groups by Fisher's test or the Wilcoxon-Mann-Whitney test. The Pearson correlation coefficient may be presented in scatter plots.

8.5.3 Analysis of Primary Endpoint of Part B

The primary endpoint is the percent change in proteinuria from baseline at Week 48 (based on UPCR from 24-hour urine collection). The baseline value will be determined by the average of the values at Screening and Day 1 for UPCR by 24-hour urine collection.

Dose response hypothesis testing

The null hypothesis is

H0: There is no dose-response in percent change in proteinuria between atacicept doses compared to placebo

The alternative hypothesis is

H1: There is a dose-response in the percent change in proteinuria between atacicept doses compared to placebo

The dose-response of the primary endpoint will be analyzed for all evaluable subjects at Week 48 using the dose-finding method MCP-Mod (Bretz, 2005) combining multiple comparison and modeling techniques in choosing the appropriate dose response curve from several pre-defined candidate parametric models while preserving the family wise error rate for the study.

The following 4 parametric models are considered for dose-response: E_{max}, Linear, Logistic, and Quadratic.

If the null hypothesis of dose-response is rejected at the 2-sided 5% alpha level, the MED (ie the lowest dose demonstrating a proteinuria decrease of at least 20% from baseline over placebo) and the TD (ie, the lowest dose demonstrating a proteinuria decrease of at least 40% from baseline over placebo) of atacicept in the range of 25 and 150 mg can be estimated from the dose-response model.

Estimating treatment effect

The proteinuria percent change from baseline will be analyzed for mITT subjects using a mixed effects model for repeated measures including treatment and visit as fixed effects, baseline

proteinuria, baseline eGFR, and race (Asian vs non-Asian) as covariates, treatment by visit as the interaction term. Additional baseline covariates will be explored in the modeling including body weight, age, and baseline BLyS and APRIL levels. All cumulative data collected up to Week 156 will be used. Missing data will be assumed missing-at-random (MAR). The treatment effects at Weeks 24, 48, 96 and 156 for each active dose compared to placebo will be evaluated with appropriate contrasts (difference in least squares mean). Sensitivity analysis will be performed to check the assumptions and the robustness of the results. For example, this will include analyses of subjects with Day 1 UPCR > 1 mg/mg.

8.5.4 Analysis of Key Secondary Endpoints for Part B

- The proportion of subjects with UPCR < 1 mg/mg and ≥ 25% decrease from baseline (taken from the 24-hour urine collection) with stable eGFR (< 15% reduction from the baseline level) at Week 48 will be analyzed for mITT subjects using a logistic regression model including treatment as fixed effect, baseline proteinuria, baseline eGFR, and race (Asian vs non-Asian) as covariates. The non-evaluable subjects will be imputed as non-responders in the analysis. The treatment effect at Weeks 24, 48, 96, and 156 will be estimated in the corresponding logistic regression models.

- The change from baseline in eGFR at Week 156: The treatment effect at Week 156 for each active dose compared to placebo will be evaluated from the Mixed Effects Model for Repeated Measures specified in the primary endpoint analysis with appropriate contrasts (difference in least squares mean), including baseline eGFR, baseline proteinuria, race (Asian vs non-Asian) and age as covariates.

- The annual rate of eGFR decline from baseline will be analyzed using random coefficient regression (random slopes and intercepts) model. Additional analysis of eGFR will be performed to take into account the proteinuria change from baseline as a time dependent covariate.

- The eGFR analysis will include all eGFR data collected up to Week 156 at the time of analysis.

- The proportion of subjects with any AEs, AESI, AEs leading to discontinuation, SAEs, AEs leading to death: the differences between each active dose group and the placebo group and their 95% confidence interval (wherever appropriate) will be presented. Additionally, the p-values from Fisher's exact test will be obtained for AESI.

8.5.5 Analysis of Other Endpoints for Part B

All other endpoints of Part B will be summarized as described in Section 8.3.2 and Section 8.5.6.2, and any inferential statistics will be detailed in the SAP. Associations between some of these endpoints with clinical responses to atacicept treatment, particularly changes from baseline in proteinuria and eGFR, may be explored.

8.5.6 Analysis of Safety and Other Endpoints

Values for all safety variables will be listed by subject and time point. Where appropriate, safety variables will be summarized using descriptive statistics. Descriptive statistics for quantitative variables will include: number of available observations, mean, median, lower quartile (Q1), upper quartile (Q3), minimum, maximum, and SD.

Descriptive statistics for qualitative variables will include frequency counts and percentages.

8.5.6.1 Adverse Events

AEs 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. TEAEs are defined as AEs with onset dates occurring on or after the date of the first dose up to 24 weeks after the date of last dose to include the FU period. Frequency counts and percentages will be presented for subjects with at least 1 TEAE within each MedDRA System Organ Class (SOC) and MedDRA Preferred Term PT), by treatment group. TEAEs will also be summarized by relationship to study treatment and by severity within each treatment group, and by pre-defined AEs of special interest.

The analysis of AEs will follow a systematic approach for statistical analysis based on a 3-Tier approach proposed by Crowe et al (2009):

- Tier-1 includes AEs considered as important identified or potential risk from the clinical development of atacicept. For this study, the Tier-1 AEs include the AESIs (infections, cardiac failure, cardiac ischemic events, hypersensitivity reactions [including angioedema], and ISRs). The proportion of subjects experiencing the Tier-1 AEs will be compared between the treatment groups by hypothesis tests using Fisher's Exact test, and further statistical analysis will be performed to quantify the risk. Multiplicity will not be adjusted for the pre-specified hypothesis test.
- The main purpose of AE analyses in Tier-2 is screening for safety signals in non-rare AEs respecting multiplicity adjustment with control over false positive and false negative findings. Tier-2 includes all AEs common enough to generate a statistically significant difference between at least 2 groups. A suitable threshold depending on the number of subjects will be specified in the SAP. There is no pre-specified hypothesis test. Statistical analysis will be performed to quantify the difference and identify potential safety signals.
- All other AEs not pre-specified for hypothesis testing in Tier-1 and too rare for Tier-2 will be addressed in Tier-3 for which only descriptive analysis will be performed. They can be further analyzed in the context of the pooled data with other atacicept studies, in order not to omit potential findings even when considered too rare in this study for signal detection.

8.5.6.2 Clinical Laboratory Test Values, Vital Signs, and ECG Parameters

By-subject listings of clinical laboratory data, vital signs, and ECG data will include indications of values that are outside the reference ranges, and values that are clinically significant. Shift tables describing out-of-reference range shifts and summary statistics of central tendency will be

provided for clinical laboratory test results, vital signs, and ECGs evaluated by independent cardiologists from baseline to last visit, as appropriate and by treatment group.

8.5.6.3 Other Safety Variables

All other safety variables (eg, injection site assessments) will be summarized, as appropriate, with descriptive statistics by treatment group and assessment time point.

ISRs will be defined using terms from the ISRs High Level Term per MedDRA. The number and percentage of subjects will be summarized by severity and by treatment group.

8.5.6.4 Pharmacodynamics

Results of PD endpoints will be summarized by treatment group. The change in proportion of subjects with protective antibody titers to tetanus toxoid, diphtheria toxoid, and selected pneumococcal antigens will be summarized by descriptive statistics by treatment group and by time point (if applicable).

8.5.6.5 Treatment Compliance

Treatment compliance will be assessed in terms of the percentage of the actual doses taken relative to the number of scheduled doses. Treatment compliance will be used to characterize the subjects and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group by means of descriptive statistics (number of observed values, mean, SD, median, Q1, Q3, minimum, and maximum).

8.6 Interim and Additional Planned Analyses

An interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team. Details of the potential interim analysis for Part A will be detailed in the SAP.

If Part B is activated, there is one interim futility analysis planned prior to the primary analysis. The interim futility analysis will be performed by the Unblinded Firewall Team when the first 60 randomized subjects have completed 24 weeks of treatment, with approximately 15 subjects in each arm. The proteinuria and other biomarker changes from baseline will be evaluated and results will be reviewed by the IDMC for futility. The purpose of the futility analysis is to stop the study early when all atacicept doses are unlikely to meet the study primary objective. The futility criteria will be pre-specified confidentially in the IDMC charter/SAP. An Unblinded Firewall Team, composed of senior members from the Sponsor's departments in Clinical, Safety, Biostatistics, and Quantitative Pharmacology, will also review the data and make the final decision regarding the continuation of the study. In order to preserve the integrity of the primary analysis, members of the Unblinded Firewall Team will not be further involved in the conduct and analysis of the study until unblinding of the study for the primary analysis. A Firewall Charter will be established prior to the interim futility analysis to govern the process. There is no pre-specified boundary for

efficacy, therefore there is no alpha spending for the interim analysis. An interim futility analysis plan will be developed and approved prior to the interim futility analysis.

For Part A or Part B, the Week 48 analysis is the primary analysis of the study to be performed by the Sponsor/CRO staff. The Week 48 analysis (primary analysis) for Part A will only be performed if Part B is not activated and after all randomized subjects have completed the scheduled Week 48 visit of Part A or have discontinued from the study. The Week-48 primary analysis for Part B will be performed only if Part B is activated and after all randomized subjects have completed the scheduled Week 48 Visit of Part B or have discontinued from the study. After the primary analysis, study subjects and sites will remain blinded. The primary analysis results will be generated on the aggregate group level and reviewed by a restricted group to limit initial dissemination. Subject level listings will not be automatically generated in order to restrict the access of individual treatment information. In particular situations, individual listings may be generated for regulatory interactions. Such listings will be restricted from access by the clinical trial operation team. It is acknowledged that in special cases, such as the safety analysis involving rare events, it is possible that the treatment code for an individual subject may be revealed during the review of aggregate output. It is considered as a small and acceptable risk. The key endpoints of proteinuria, eGFR, and PD parameters are objective laboratory measures thus least affected by any subjective bias.

The sites and subjects remain blinded until the end of the study. If Part B is activated, additional analyses are planned when all randomized subjects have completed the scheduled Week 96 and Week 156 visits or have discontinued from the study, respectively. The access of individual treatment information will be controlled to not impact the study conduct. The final database will be locked after all subjects have completed the 24-week safety FU or have prematurely discontinued from the study. A final safety FU analysis will be performed.

8.7 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be formed to monitor interim safety on a regular basis to ensure ongoing surveillance of subject safety in this trial and will also be responsible to monitor both safety and efficacy for the futility analysis. The IDMC will consist of at least the following core members: 2 nephrologists and 1 biostatistician. The IDMC will also review interim safety data from the placebo and 25 mg and 75 mg atacicept treatment arms once at least 5 subjects in each arm have had at least 12 weeks of treatment, in order to make a determination on whether opening enrollment in the atacicept 150 mg arm is recommended. In addition, the IDMC will monitor and make recommendations for adjusting the DFR criteria, should the need arise.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, the Japanese ministerial ordinance on GCP, and any other applicable

regulations. The Investigator must ensure that only subjects who have given informed consent are included in the study.

According to US Code of Federal Regulations Part 54.2 (e), for studies conducted in any country that could result in a product submission to the US FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical studies" by the FDA), the Investigator and all sub investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the study and for 12 months following completion of the study.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

With the cooperation of the Sponsor, and in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator will prepare the informed consent form and other written information to be used in obtaining informed consent from the study subjects. The Sponsor should provide the Investigator with documents/information necessary for preparing the aforementioned written information and cooperate with the Investigator to prepare it. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject of all pertinent aspects of the study orally as well as in writing. The language used in the aforementioned oral and written information about the study must be fully and readily understandable to lay persons.

Before consent may be obtained, the Investigator should provide the prospective subject (or the prospective subject's legally acceptable representative if applicable) with ample time and opportunity to inquire about details of the clinical trial and to decide whether or not to participate in the study. In such cases, the Investigator or the study collaborator giving supplementary explanation should answer all questions about the study to the satisfaction of the prospective subject or legally acceptable representative.

If permitted by national regulations, a person other than the Investigator may inform the subject about the study and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator. The study collaborator giving supplementary explanation, where applicable, should sign, seal and date the informed consent form.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each study subject and obtain new written consent for continued participation in the study. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

As this study includes optional PGx examinations, including and collection and storage of biological samples, a separate PGx ICF will be required.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the study as well as in the clinical trial database. All subject data collected in the study will be stored under the appropriate subject number. Only the Investigator will be able to link study data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Storage and analyses of samples will be handled according to the specifications as described in the ICF.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during study participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to 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 provided on the Emergency Medical Support card may include the process for emergency unblinding.

Investigators who are already aware of the CTP and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

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

In cases where the Investigator is not available, the Sponsor has made appropriate provisions to contact a CRO/Sponsor physician or designee. This includes the provision of a 24-hour contact number at a call center, whereby healthcare providers will be given access to the appropriate CRO/Sponsor physician. The CRO/Sponsor physician will assist the healthcare provider in a medical emergency by providing information, advice and assistance relating to the study and the IMP. The CRO/Sponsor physician is not responsible or required for potential emergency unblinding, but should be notified as per Section 6.10 if emergency unblinding is to take place or has occurred, and may provide information if requested regarding the study and IMP.

9.5 Clinical trial Insurance and Compensation to Subjects

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

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 will meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Study Master File at Sponsor or designated organization.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the study, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the study in accordance with national regulations and requirements.

The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site based on favorable opinion/approval from the concerned IRB.

Plans for any substantial amendments to the clinical trial will also be submitted to the concerned IRB before they are implemented (see Section 10.5). Relevant safety information will be submitted to the IRB during the course of the study in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Study Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for further eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely fashion. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that all study data are entered in a timely manner into the eCRF provided by the CRO, in accordance with the Sponsor's data standards. It is the Investigator's responsibility to ensure the accuracy of all data entered in the eCRFs.

Study data will be entered into a validated database provided by the CRO's Data Management group. In addition, the CRO's Data Management group is responsible for data processing, in accordance with the CRO's Data Management SOPs and associated procedures agreed between the Sponsor and CRO. Database lock will occur once quality control procedures, and QA procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the study. This file will contain the available demographic and medical information for the subject listed below and should be as complete as possible. It must be possible to identify each subject from their subject file. In particular, the following data should be available in this file:

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in the CTP
- All AEs

- Date that the subject left the study including any reason for early withdrawal from the study or IMP (if applicable).

In addition, all documents containing source data must be filed. This includes, but is not limited to, original printouts of data recorded or generated by automated instruments, eg, ECG recordings, laboratory value listings, and Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan images. Such documents must at least bear the Subject ID Number and the date when the procedure was performed. This information should be printed by the instrument used to perform the assessment or measurement. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be performed as necessary, and the documentation should be signed and dated by the Investigator.

For data that may be recorded directly in the eCRF such as a subject questionnaire, there will be no record in the original subject file, ie, the data entered in the eCRF will be considered source data. Refer to the Manual of Operations for details of all subject data in the eCRF that are to be considered source data.

Electronic subject files will be printed whenever the Study Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File and a Manual of Operations. These will contain all the study documents necessary for the conduct of the study and will be updated and completed as necessary throughout the study. The Investigator Site File must be available for review by the Study Monitor, and must be ready for Sponsor audit, as well as for inspection by Health Authorities during and after the study. It must also be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator (In Japan, a record retainer designated by the Head of the study site) should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and any other applicable regulations. The Study Monitor will perform visits to the study site at regular intervals.

The CTP, each step of the data capture procedure, and the handling of the data, including the final CSR, will be subject to independent QA activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Sponsor's QA unit or of a designated organization, as well as Health Authorities, must be permitted to inspect all study related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMPs and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical trial Protocol

Changes to the final CTP will be documented in written protocol amendments. Major (substantive, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB (In Japan: through the Head of the study site) for approval or favorable opinion. In such cases, the amendment will be implemented only after (in Japan: written approval from the Head of the study site based on) approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the study requires additional informed consent prior to implementation, following the process as described in Section 9.2.

10.6 Clinical trial Report and Publication Policy

10.6.1 Clinical trial Report

After completion of the study, a CSR will be written by the Sponsor (or designee) in consultation with the CI following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all study sites. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor prior to submission. The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on Clinical trials.gov is planned and will occur 12 months after the last study visit of the final study subject or another appropriate date to meet applicable requirements.

11 References Cited in the Text

Anthera Provides Clinical Program Updates for Blisibimod and Sollpura. [globe newswire]. Hayward, CA: June 28, 2016. http://investor.anthera.com/releasedetail.cfm?releaseid=977464 Accessed September 27, 2016.

Barbour SJ, Espino-Hernandez G, Reich HN, et al, for the Oxford Derivation, North American Validation and VALIGA Consortia. The MEST score provides earlier risk prediction in lgA nephropathy. Kidney International (2016) 89:167–75.

Barratt J, Feehally J. IgA Nephropathy. J Am Soc Nephrol 2005; 16(7):2088–97.

Bartosik LP, Lajoie G, Sugar L et al. Predicting progression in IgA nephropathy. Am J Kidney Dis. 2001; 38(4):728–35.

Berthoux F, Suzuki H, Thibaudin L. et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. J Am Soc Nephr, vol. 23, no. 9, pp. 1579–1587, 2012.

Berthoux F, Mohey H, Laurent B et al. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol 2011; 22(4):752–61.

Bornkamp B, Pinheiro J, Bretz F. MCPMod: An R package for the design and analysis of dose-finding studies. Journal of Statistical Software 2009; 29(7): 1-23.

Bretz F, Pinheiro J, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 2005; 61:738–48.

Castigli E, Scott S, Dedeoglu F et al. Impaired IgA class switching in APRIL-deficient mice. Proc Natl Acad Sci USA 2004; 101(11):3903–8.

Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009; 76:534-45.

Chapter 10: Immunoglobulin A nephropathy. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl 2012, 2:209.

Cheng A, Kang Y, Chen Z et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomized, double-blind, placebo-controlled study. Lancet 2009; 10(1):25–34.

Cohen SB, Emery P, Greenwald MW et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III study evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54(9):2793-806.

Coppo R, Troyanov S, Camilla R, et al. The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. Kidney Int. 2010; 77:921-7.

Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials. 2009; 6:430-40.

Czerkinsky C, Koopman WJ, Jackson S, et al. Circulating immune complexes and immunoglobulin A rheumatoid factor in patients with mesangial immunoglobulin A nephropathies. J Clin Invest 1986; 77(6):1931–8.

D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis 2000; 36(2):227–37.

Descamps-Latscha B, Witko-Sarsat V, Nguyen-Khoa T, et al. Early prediction of IgA nephropathy progression: proteinuria and AOPP are strong prognostic markers. Kidney Int 2004; 66(4):1606-12.

Dillon SR, Gross JA, Ansell SM et al. An APRIL to remember: novel TNF ligands as therapeutic targets. Nat Rev Drug Discov 2006; 5:235–46.

Dillon SR et al. B-lymphocyte stimulator/a proliferation-inducing ligand heterotrimers are elevated in the sera of patients with autoimmune disease and are neutralized by atacicept and B-cell maturation antigen-immunoglobulin. Arthritis Res Ther 2010; 12:R48.

Donadio JV, Grande JP. IgA nephropathy. N Engl J Med 2002 Sep 5; 347(10):738–48.

Floege J, Eitner F. Current therapy for IgA nephropathy. J Am Soc Nephrol 2011; 22(10):1785-94.

Furie R, Scheinberg M, Leon G et al. Blisibimod, an inhibitor of B-cell activating factor, in patients with moderate-to-severe Systemic Lupus Erythematosus. Ann Rheum Dis 2012; 72(Supple):95.

Ginsberg JM, Chang BS, Matarese RA, et al. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med. 1983 22;309(25):1543-6.

Gross JA, Johnston J, Mudri S et al. TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. Nature 2000; 404:995–9.

Gross JA, Dillon SR, Mudri S et al. TACI-Ig neutralizes molecules critical for B-cell development and autoimmune disease: Impaired B-cell maturation in mice lacking BLyS. Immunity 2001; 15:289–302.

Hahne M, Kataoka T, Schroter M. et al. APRIL, a new ligand of the tumor necrosis factor family, stimulates tumor cell growth. J Exp Med 1998; 188:1185–90.

Hotta K, Fukasawa Y, Akimoto M et al. Tonsillectomy ameliorates histological damage of recurrent immunoglobulin A nephropathy after kidney transplantation. Nephrology 2013; Dec 18(12):808–12.

Huard B, McKee T, Bosshard C et al. APRIL secreted by neutrophils binds to heparan sulfate proteoglycans to create plasma cell niches in human mucosa. J Clin Invest 2008; 118(8):2887–95.

International Society of Nephrology. Kidney Disease - Improving Global Outcomes. J Int Soc Nephrol 2012.

Kim YG, Alvarez M, Suzuki H et al. Pathogenic role of a proliferation-inducing ligand (APRIL) in murine IgA Nephropathy. PLoS One 2015; 10(9):e0137044.

Kiryluk K, Li Y, Sanna-Cherchi S, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet 2012; 8(6):e1002765.

Kumar D, Chang R, Sun CC et al. IgA Nephropathy is associated with elevated levels of renal BAFF and APRIL. American Society of Nephrology Scientific Meeting. 2016; Abstract 4553.

Lee H, Kim DK, Oh KH et al. Mortality of IgA nephropathy patients: a single center experience over 30 years. PLoS One. 2012; 7(12):e51225.

Li LS, Liu Zh. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004; Sep 66(3):920–3.

Liu LL, Wang LN, Jiang Y et al. Tonsillectomy for IgA nephropathy: a meta-analysis. Am H Kidney Dis 2015; Jan 65(1): 80–7.

Lv J, Zhang H, Wong MG et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA Nephropathy. TESTING Study Group. JAMA. 2017 Aug; 318(5):432-42.

Lv J, Xu D, Perkovic V et al. Corticosteroid therapy in IgA nephropathy. J Am Soc Nephrol 2012; 23(6):1108–16.

Mackun P, Wilson S. Population distribution and Change: 2000 to 2010, 2010 Census Briefs. U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau.

Matsuo S, Imai E, Horio M et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009 Jun; 53(6):982-92.

Matuosovic K, Novak J, Yanagihara T et al. IgA-containing immune complexes in the urine of IgA nephropathy patients. Nephrol Dial Transplant. 2006; 21(9):2478–84.

Merrill JT, Burgos-Vargas R, Westhovens R et al. The efficacy and safety of atacicept in patents with non-life threatening manifestations of systemic lupus erythematosus: Results of a twelve-month, multicenter, exploratory phase IIb, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010; 62:3077-87.

Moore PA, Belvedere O, Orr A et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science 1999; 285:260–3.

Moreaux J, Sprynski AC, Dillon SR et al. APRIL and TACI interact with syndecan-1 on the surface of multiple myeloma cells to form an essential survival loop. Eur J Haematol 2009; 83(2):119–29.

Moriyama T, Tanaka K, Iwasaki C et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014; 9(3):e91756.

Novak J, Julian BA, Tomana M, et al. IgA glycosylation and IgA immune complexes in the pathogenesis of IgA nephropathy. Semin Nephrol 2008; 28(1):78–87.

NYHA. The criteria committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown & Co; 1994: 253-6.

Odendahl M, Jacobi A, Hansen A et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. J Immunol 2000; 165:5970–79.

Petri MA, Furie RA, Ramiterre E et al. The subcutaneous BAFF inhibitor, blisibimod, significantly reduces proteinuria in subjects with moderate-to-severe systemic lupus erythematosus. Poster presented at the Asian Lupus Summit. November 23-29 2012, Manila, Philippines.

Pozzi C, Bolasco PG, Fogazzi GB et al. Corticosteroids in IgA Nephropathy: a randomized controlled study. Lancet. 1999; 353 (1956):883–7.

Praga M, Gutierrez E, Gonzalez E et al. J Am Soc Nephrol. 2003; 14 (6):1578–83.

Rauen T, Eitner F, Fitzner C et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med 2015; 373:2225-36.

Reich HN, Troyanov S, Scholey JW et al. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007; 18(12):3177–83.

Reid S, Cawthon PM, Craig JC et al. Non-immunosuppressive treatment for IgA nephropathy. Cochrane Database Syst Rev 2011(3): CD003962.

Roberts ISD, Cook HT, Troyanov S, et al. A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney International 2009 76, 546–556.

Roschke V, Sosnovtseva S, Ward CD et al. BLyS and APRIL form biologically active heterotrimers that are expressed in patients with systemic immune-based rheumatic diseases. J Immunol 2002; 169:4314–21.

Ruggenentti P, Cravedi P, Chianca A et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol 2012; Aug 23 (8):1416–25.

Rychlik I, Jancova E, Tesar V et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000. Nephrol Dial Transplant. 2004; Dec 19(12):3040–9.

Schiemann B, Gommerman JL, Vora K et al. An essential role for BAFF in the normal development of B-cells through a BCMA-independent pathway. Science 2001; 293(5537):2111-4.

Schneider P. The role of APRIL and BAFF in lymphocyte activation. Curr Opin Immunol 2005; 17(3):282–9.

Schneider P, MacKay F, Steiner V et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B-cell growth. J Exp Med 1999; 189:1747–56.

Shin DH, Lim BJ, Han IM, et al. Glomerular IgG deposition predicts renal outcome in patients with IgA nephropathy. Mod Pathol. 2016 Jul;29(7):743-52.

Suzuki H, Fan R, Zhang Z, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest 2009; 119(6):1668–77.

Suzuki Y, Matsuzaki K, Suzuki H et al. Serum levels of galactose-deficient immunoglobulin (Ig) A1 and related immune complex are associated with disease activity of IgA nephropathy. Clin Exp Nephrol 2014; Jan 30.

Suzuki Y, Matsuzaki K, Suzuki H et al. Proposal of remission criteria for IgA nephropathy. Clin Exp Nephrol 2013; 18:481–6.

Table B7. Prevalence of reported ESRD, by primary diagnosis, 2011. U.S. Renal Data System 2013 Annual Data Report, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

Table A7. Incidence of reported ESRD, by primary diagnosis, 2007-2011 combined. U.S. Renal Data System 2013 Annual Data Report, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

Tahtinen S, Kaikkonen S, Merisalo-Soikkeli M et al. Favorable alteration of tumor microenvironment by immunomodulatory cytokines for efficient T-cell therapy in solid tumors. PlosOne. 2015; 10(6):e0131242.

Tomana M, Matousovic K, Julian BA, et al. Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. Kidney Int 1997; 52(2):509–16.

Varfolomeev E, Kischkel F, Martin F et al. APRIL-deficient mice have normal immune system development. Mol Cell Biol 2004; 24:997-1006.

Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med 2013 Jun 20; 368(25):2402–14.

Xin G, Shi W, Xu L et al. Serum BAFF is elevated in patients with IgA nephropathy and associated with clinical and histopathological features. J Nephrol 2013; 26(4):683-90.

Zhai YL, Zhu L, Shi SF et al. Increased APRIL Expression induces IgA1 aberrant glycosylation in IgA Nephropathy. Medicine (Baltimore). 2016 Mar; 95(11):e3099.

Zhou YH, Tang LG, Guo SL et al. Steroids in the treatment of IgA nephropathy to the improvement of renal survival: a systematic review and meta-analysis. PlosOne. 2011; 6(4):e18788.

12 Appendices

Appendix I: Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
IND Number	122,043
EudraCT Number	2016-002262-31
Clinical trial Protocol Date Version	27 November 2018 / Version 5.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD _____ 30 November 2018

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research and Development Institute Inc.
Address:	45A Middlesex Turnpike, Billerica, MA 01821, US
Telephone number:	PPD
E-mail address:	PPD

Signature Page – Coordinating Investigator

Study Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
IND Number	122,043
EudraCT Number	2016-002262-31
Clinical trial Protocol Date Version	27 November 2018 / Version 5.0

I approve the design of the clinical trial and I understand and will conduct the study according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Signature Page – Coordinating Investigator

Study Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
IND Number	122,043
EudraCT Number	2016-002262-31
Clinical trial Protocol Date Version	27 November 2018 / Version 5.0

I approve the desig PPD rial and I understand and will conduct the study according to the clinical trial pproved protocol amendments, International Council for Harmonization G actice (Topic E6) and all applicable Health Authority requirements and r

PPD

PPD

Signature Date of Signature

PPD

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Signature Page – Coordinating Investigator

Study Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
IND Number	122,043
EudraCT Number	2016-002262-31
Clinical trial Protocol Date Version	27 November 2018 / Version 5.0

I approve the design of the clinical trial and I understand and will conduct the study according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Signature Page – Principal Investigator

Study Title	A Phase II, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in IgA Nephropathy
IND Number	122,043
EudraCT Number	2016-002262-31
Clinical trial Protocol Date Version	27 November 2018 / Version 5.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Inc.
Address:	45 A Middlesex Turnpike, Billerica MA 01821, US
Telephone number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research and Development Institute Inc
Address:	45B Middlesex Turnpike, Billerica, MA 01821, US
Telephone number:	PPD
E-mail address:	PPD

Appendix II: Protocol Amendments and List of Changes

Previous Protocol Amendments

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1.0	Y	27 May 2016	Global	N
2.0	Y	20 October 2016	Global	N
3.0	Y	15 September 2017	Global	N
4.0	Y	27 November 2018	Global	Y

Amendment #4

Global amendment effective: 27 November 2018

Rationale

To remove mention of needle gauge.

To include and provide a description of an interim analysis to inform the Sponsor decision with regards to Part A of the study.

Administrative and Editorial Changes

- The change in Medical Responsible from PPD to PPD was documented.
- The change in Sponsor Responsible Persons not named on the cover page was documented:
  - PPD , to PPD
  - PPD to PPD
- The name change of the global CRO (PPD are now known as PPD) was documented.
- Minor corrections were made to grammar and other text in the protocol.

Major Scientific Changes

Noted in the table below.

Comparison with Clinical Trial Protocol Version 4.0, 15 September 2017 (Amendment No.3)

Change	Section	Page	Previous Wording	New Wording	Rationale
Specification of needle gauge removed	6.6 Packaging and Labeling of the Investigational Medicinal Product	69	Atacicept and placebo will be supplied to the investigational site in prefilled 1 mL glass syringes with 29 gauge needles.	Atacicept and placebo will be supplied to the investigational site in prefilled 1 mL glass syringes ~~with 29 gauge needles~~.	Provision of atacicept and placebo is not limited to 29 gauge needles.
Text describing potential interim analysis of Part A	Synopsis: Methodology	12	…by an Independent Data Monitoring Committee (IDMC). Following recommendation by the IDMC and decision by the Sponsor, enrollment may be opened for Part B…	…by an Independent Data Monitoring Committee (IDMC). **After IDMC recommendation, an interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team.** Following recommendation by the IDMC and decision by the Sponsor, enrollment may be opened for Part B…	Interim analysis of Part A is required to inform Sponsor decision with regards to Part A of the study.
	Synopsis: Planned Analysis	19	Not applicable	**Interim analysis (Part A): may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team.**	
	Figure 1	42	Not applicable	Potential interim analysis of Part A included in diagram.	

	Section 5.1 Overall Study Design and Plan	43	A review of cumulative safety data will be conducted after data from at least 5 subjects per arm have received at least 12 weeks of IMP treatment in Part A. Part B will be activated based on IDMC recommendation and Sponsor's decision. Primary analysis will be at week 48 if Part B is not activated.	A review of cumulative safety data will be conducted after data from at least 5 subjects per arm have received at least 12 weeks of IMP treatment in Part A. ~~Part B will be activated based on IDMC recommendation and Sponsor's decision.~~ **After IDMC recommendation, an interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team. Following recommendation by the IDMC and decision by the Sponsor, enrollment may be opened for Part B.** Primary analysis will be at week 48 if Part B is not activated.	
	Section 5.1.1 Study Periods	44	Part A of the study will begin with 3 treatment arms. Subjects will be randomized in a ratio of 1:1:1 to receive placebo, atacicept 25 mg, or atacicept 75 mg, given by SC injection once weekly. If Part B is not activated, then only Part A will be conducted.	Part A of the study will begin with 3 treatment arms. Subjects will be randomized in a ratio of 1:1:1 to receive placebo, atacicept 25 mg, or atacicept 75 mg, given by SC injection once weekly. If Part B is not activated, then only Part A will be conducted. **An interim analysis may be performed, after ~ 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision (see Section 5.1 and Section 8.6).**	

	Section 6.10 Blinding	72	An Unblinded Firewall Team, composed of senior members from the Sponsor's departments in Clinical, Safety, Quantitative Pharmacology, and Biostatistics, will be unblinded for the planned interim futility analysis (if Part B is activated) after at least 60 subjects have completed the treatment period through Week 24	An Unblinded Firewall Team, composed of senior members from the Sponsor's departments in Clinical, Safety, Quantitative Pharmacology, and Biostatistics, will be unblinded for ~~the~~ **planned interim analyses, including one performed after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision, and the** interim futility analysis (if Part B is activated) which will be performed after at least 60 subjects have completed the treatment period through Week 24.	
	Section 8.5	111/ 112	Not applicable	**Interim analysis (Part A): may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team.**	
	Section 8.6	116	Not applicable	**An interim analysis (Part A) may be performed, after approximately 15 randomized subjects have completed 24 weeks of treatment, to inform the Sponsor decision. Proteinuria and other biomarkers (eg, IgA and Gd-IgA1) may be evaluated by the Sponsor's internal Unblinded Firewall team. Details of the potential interim analysis for Part A will be detailed in the SAP.**	

Appendix III: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent Failure rate of <1% per year when used consistently and correctly.

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining 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 participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment